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THE EFFECT OF MICROMETRIC PROPERTIES AND SPECIFIC GRAVITY MEASUREMENT METHODS ON PHARMACEUTICAL RAW MATERIALS: A REVIEW

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ABSTRACT

Background: Tablet preparations consist of active substance compositions with or without additional substances (excipients). Micrometric properties are taken into consideration in the development of solid formulations because they can play a role in formulating formulations to obtain optimal therapeutic targets and ranges to form products that can be fully developed. In selecting a tablet manufacturing method, namely the direct compression method, it is very necessary to have a substance that has good flowability and compressibility. **Objective:** In this study, observations were made on the poor micrometric properties in order to increase the specific gravity of the particles used so that an optimal drug formulation is obtained. **Methods:** The writing method used is a comparative method by collecting various sources obtained from research journals from 2014-2024. **Results:** Observations of micrometric properties can increase along with modifications to substances or compounds, namely by using the carboxymethylation, crystallization, and agglomeration methods. **Conclusion:** Pharmaceutical raw materials that have poor micrometric properties can be improved by modifying them either through carboxymethylation, crystallization, or agglomeration processes. So that it can reduce the Carr index and increase the Hausner ratio of the material, then the specific gravity test provides information about the purity of the compound.

Keywords: Agglomeration; Carboxymethylation; Crystallization; Micrometric; Specific gravity;.

INTRODUCTION

Tablets are solid preparations with an active ingredient composition with or without additional ingredients (excipients)[1]. Excipients are inert substances added to active ingredients to help in the manufacturing process to maintain the stability of a product. They can be in the form of disintegrants, binders, glidants, striations, antioxidants, absorbents, flavors, dyes, and even preservatives[21]. Active ingredients or API (Active Pharmaceutical Ingredients) are substances that provide pharmacological activity in the treatment, prevention, and healing process and can modify the physiological functions of the body[3].

Tablet manufacturing is divided into three methods, namely, direct compression method, wet granulation, and dry

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granulation. The direct compression method is the most commonly used in the tablet manufacturing process because the process is simple, the equipment and labor are minimal, and the processing time is fast, which can reduce production costs[27]. An important factor in choosing the direct compression method is the flow properties and compressibility of the active ingredients to be used[24]. Micrometric is a technology related to small particles, especially particle size. In the pharmaceutical field, particle size is related to the stability and release of drugs from the dosage form and can help in determining the dispersion system of pharmaceutical preparations[7].

Micrometric are considered in the development of solid dose formulations used in their physical, mechanical, and chemical processes because they can play a role in formulating formulations to obtain optimal therapeutic targets and ranges to form products that can be fully developed. For example, in the manufacture of tablets that can be compressed directly, the particle size range is 100-200 µm, and the optimal particle size range for chewable tablets is 20-50 µm. Knowledge of the effect of particle size and particle size distribution of API (Active Pharmaceutical Ingredients) and excipients is useful for dealing with the manufacture of tablets and capsules. Control of particle size and particle size distribution has an impact on the flowability, weight uniformity, weight variation, and dissolution rate that affect the bioavailability of drugs in body fluids[15]. Specific gravity is a comparison between the mass of a solid substance and the mass of water at certain temperature and volume conditions. Specific gravity testing can use a pycnometer[1]. Compressed specific gravity is the weight of the sample divided by the volume of the sample. The difference in specific gravity in all granules can be caused by differences in the size of the granule particles, which result in differences in the space between particles. True specific gravity is the weight of the sample divided by the volume of the sample without any interparticle space and intraparticle space caused by differences in the amount of space between particles and intraparticle space owned by each granule[14]. One of the factors that affect specific gravity is temperature; namely, at high temperatures, the test compound can experience evaporation, and at low temperatures, the compound will experience a freezing process that is difficult to calculate[24]. Based on the background above, this literature study was conducted so that it can be used in carrying out research related to the influence of micrometric properties and methods for measuring the specific gravity of pharmaceutical raw materials.

METHODS

The writing method used to conduct this article review was a comparative method, which was collected from various sources obtained from research journals. The literature review was carried out by searching for articles through journal databases such as Google Scholar, PubMed, Science Direct, MDPI, and NCBI with the keywords "micrometric Properties and specific gravity." The author determines several inclusion criteria. Namely, the articles reviewed are full text, discuss the effect of micrometric properties and specific gravity measurement methods on pharmaceutical raw materials, were in English and Indonesian, and were obtained from articles from the last 10 years (2014-2024). The quality assessment study of the candidate articles used is based on the Scopus ranking or accreditation and impact factor value.

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RESULTS AND DISCUSSION

Poor Micrometric properties of drug particles will result in difficulties in the formulation and manufacturing process of drugs, especially in solid preparations. To achieve good micrometric properties, several methods have been developed for improvement, such as carboxymethylation, crystallization, and agglomeration methods[5].

Based on the USP (United States Pharmacopeia) criteria, good Micrometric properties that cause good flow must have a Hausner ratio <1.18 and a Carr index <15%. At the same time, the angle of repose value is also not more than 30-350 so that the flow can be accepted and can flow freely[17]. Hausner ratio and Carr index tests are used to measure the flowability and compression ability of a granule with parameters of actual density and compressed density[17].

Carr's index is an indirect measure of various powder characteristics, namely bulk density, size and shape, surface area, water content, and material cohesion[12]. So the compressibility index (Carr index) refers to the ability of the granule to remain compact under pressure.

Table 1. Study Characteristics

No	Author (Year)	Title	Journal
1.	Paramakrishnan, N., Jha, S., & Kumar. (2016).	Effect of carboxymethylation on physicochemical, Micrometrics, and release characteristics of *Kyllinga nemoralis* starch.	International Journal of Biological Macromoleculs
2.	Kedia, K. & Wairkar, S. (2019).	Improved Micrometrics, packing properties and compressibility of high dose drug, Cycloserine, by spherical crystallization.	Powder Technology
3.	Dalvadi, H., Parmar, K., & Yadav, S. (2019).	Spherical agglomeration to improve dissolution and Micrometric properties of an anticancer drug, Bicalutamide.	Drug Development and Industrial Pharmacy
4.	Islam, M.S. & Pathan, M.S.I. (2017).	Improving Micrometric properties of Ibuprofen: an agglomeration approach.	Bangladesh Pharmaceutical Journal
5.	Himawan, A., Djide, N.J.N., Mujahid, M., Lukita, A.D.I., Arjuna, A., & Aliyah. (2019).	physicochemical and Micrometrics properties of ketoprofen-tartaric acid binary system.	Journal of Physics: Conference Series
6.	Latifah, F., Taufiq, H., & Fitriyana, N.M. (2020).	Uji antioksidan dan karakterisasi minyak atsiri dari kulit jeruk purut (Citrus hystrix D.C)	Journal of Pharmaceutical Science and Clinical Research
7.	Suharyanisa., Marpaung, J.K., Purba, I.E., & Simahara, B. (2022).	Pengujian efek diuretik infusa daun kope (Coffea arabica L.) pada tikus putih jantan galur Wistar.	MEDFARM: Jurnal Farmasi Dan Kesehatan.
8.	Royyan, M.Y.I., Trisnawati, A., & Sudarni, D.H.A. (2024).	Pemisahan minyak atsiri dari daun kemuning menggunakan metode Microwave Hydrodistillation (MHD).	Jurnal Kimia (Journal of Chemical)
9.	Suryani, M., Marpaung, J.K., Suharyanisa., & Lumbantoruan, M. (2023).	Pengujian potensi diuretik infusa daun bangun-bangun (Plectranthus amboinicus (Lour. Spreng) yang diujikan pada tikus jantan (Rattus norvegicus Berkenhout) galur Wistar.	Jurnal Ilmu Kesehatan dan Gizi
10.	Desnita, E., Rasyadi, Y., & Nanda, A.D. (2024).	Aktivitas roll on minyak atsiri aromaterapi daun kemangi (Ocimum sanctum L.) sebagai antiinflamasi.	Jurnal Farmasi Indonesia

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Table 2. Literature Reviewing Micrometric Measurement Methods

No	Journal Author (Year) and Title	Material	Methods	Study Results
1.	Paramakrishnan, N., Jha, S., & Kumar. (2016). Effect of carboxymethylation on physicochemical, Micrometrics, and release characteristics of *Kyllinga nemoralis* starch.	*Kyilinga nemoralis* carboxymethyl starch	Starch from *Kyilinga nemoralis* rhizome was extracted and modified by adding monochloroacetic acid and then its degree of substitution was determined. Furthermore, the solubility and Micrometrics tests of carboxymethyl starch were carried out by measuring its mass density, powder flow, angle of repose, and porosity. Tablets were made using carboxymethyl starch by the wet granule method.	Carboxymethyl starch samples experienced an increase in the degree of carboxymethylation, thus reducing the Carr index below 18% and increasing the flowability of the sample. The increase in the angle of repose that experienced carboxymethylation, followed by an increase in the degree of substitution, indicated good compressibility. Micrometric results showed that carboxymethylated starch was more suitable in the form of an adjuvant than its original form because of its better flowability.
2.	Kedia, K. & Wairkar, S. (2019). Improved Micrometrics, packing properties and compressibility of high dose drug, Cycloserine, by spherical crystallization.	Cycloserine (second line anti tuberculosis)	Cycloserine exhibits very poor Micrometric and compression characteristics so compression with spherical crystallization was performed to evaluate its Micrometric characteristics by measuring the angle of repose, Hausner ratio and Carr index.	There was an increase in the Hausner ratio parameter to 1.123 and the Carr index to 12.35% after the crystallization process. Both parameters indicate an increase in compression behavior, namely the agglomerate has better compressibility than the original drug. The angle of repose after the crystallization process also experienced a very good increase, namely 28.92ÿ to agglomerate so that it is useful in the manufacture of high-dose Cycloserine drugs.
3.	Dalvadi, H., Parmar, K., & Yadav, S. (2019). Spherical agglomeration to improve dissolution and Micrometric properties of an anticancer drug, Bicalutamide.	Bicatulamide (anticancer drugs)	Bicatulamide has limitations in dissolution rate, bioavailability, and poor Micrometric properties, so research was conducted to optimize its Micrometric properties by crystallization. The	There was a decrease in the Carr index value compared to the pure drug, indicating that its flowability and compressibility increased in the agglomerate form. The resulting Hausner ratio also showed better

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No	Journal Author (Year) and Title	Material	Methods	Study Results
			parameters observed were flow properties by determining the angle of repose, Carr index, and Hausner ratio.	flow characteristics than the original drug. The modified Bicalutamide agglomerate showed increased drug dissolution properties and compressibility, indicating an increase in the physical and mechanical properties of the drug.
4.	Islam, M.S. & Pathan, M.S.I. (2017). Improving Micrometric properties of Ibuprofen: an agglomeration approach.	Ibuprofen (NSAIDs)	Ibuprofen has a problem in solubility because it has low flow and compressibility properties so that severe sticking to the molding tool during compression is generally occurred. As a result, research was conducted on the manufacture of ibuprofen agglomerates to produce improved Micrometric properties better than untreated drug crystals.	The Carr index decreased so that the compressibility value increased due to the conversion into ibuprofen agglomerates. The Hausner ratio also gave a very good value and there was a decrease in the angle of repose value so that it showed better flow properties compared to the pure drug. In this study, the Micrometric properties of ibuprofen were successfully developed using the pseudo-emulsion solvent diffusion method so that the study can be continued to determine the stability of other solid properties in the suitability of this agglomerate.
5.	Himawan, A., Djide, N.J.N., Mujahid, M., Lukita, A.D.I., Arjuna, A., & Aliyah. (2019). physicochemical and Micrometrics properties of ketoprofen-tartaric acid binary system.	Ketoprofen (NSAIDs)	Ketoprofen has limitations in topical and parenteral formulations, so a study was conducted by making Ketoporfen cocrystals with tartaric acid. Furthermore, observations of Micrometric properties were carried out by observing the flow rate and angle of repose using the Haussner ratio, Carr index, porosity, and elasticity.	Ketoprofen-tartarate showed greater improvement in Micrometric properties compared to ketoprofen with angle of repose of 25.30, Carr index of 16.67, Haussner ratio of 1.2, and porosity of 61.7%. The improvement in Micrometric properties of ketoprofen-tartarate powder contributed to better flow into the mold.

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Table 3. Studies Specific to Gravity Measurement Methods

No	Author (Year) and Title	Material	Methods	Study Results
1.	Latifah, F., Taufiq, H., & Fitriyana, N.M. (2020). Antioxidant test and characterization of essential oil from kaffir lime peel (*Citrus hystrix* D.C)	Kaffir Lime Peel Essential Oil	Distillation was carried out on fresh kaffir lime peel to obtain its essential oil by adding anhydrous Na2SO4 to reduce the water content. Furthermore, characterization was carried out on the essential oil by testing its specific gravity using a pycnometer.	The reference parameter to compare the suitability of the specific gravity of the essential oil of kaffir lime peel is by looking at the specific gravity of the kaffir lime leaf oil because it is still in the same taxonomy. The specific gravity of the essential oil of kaffir lime peel is 0.84029 g/ml which is said to be standardized because it is still within the reference parameter range of 0.837 - 0.845 g/ml. The heavier the concentration of the molecules of the compounds that make up the essential oil and its double bonds, the higher the specific gravity.
2.	Suharyanisa., Marpaung, J.K., Purba, I.E., & Simahara, B. (2022). Testing the diuretic effect of infusion of kope leaves (*Coffea arabica* L.) on male white Wistar rats.	Urine of male white rats after administration of coffee leaf infusion as a diuretic effect	Making coffee leaf infusion with 3 variations of dose concentration, namely 10%, 20%, and 40%. Then given to mice that were fasted for 10 hours and the volume of urine excretion was recorded every 1 hour for up to 6 hours. The specific gravity of urine was measured to see the diuretic effect shown.	Specific gravity reflects the presence of dissolved substances in the urine. The best specific gravity of urine was in group V, which was 5.030 ± 0.12, which was given a dose of 40% comparable to furosemide affecting the specific gravity of male white mice. The low specific gravity of the average indicates a low level of urine concentration because the test animals did not receive feed for 10 hours before treatment and 6 hours of testing so that the levels of dissolved substances usually obtained from feed also became less.
3.	Royyan, M.Y.I., Trisnawati, A., & Sudarni, D.H.A. (2024). Separation of essential oils from kemuning leaves using the *Microwave Hydrodistillation* (MHD) method.	Kemuning Leaf Essential Oil	Determination of the specific gravity characteristics of kemuning leaf essential oil using a pycnometer.	The process of extracting essential oils from kemuning leaves using the microwave hydrodistillation (MHD) method is then carried out by separating the mixture of water and essential oils slowly until oil is obtained using anhydrous sodium sulfate so that water can be

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				released. Then a specific gravity characteristic test is carried out. The average specific gravity of kemuning leaf essential oil is 0.8106 g/ml.
4.	Suryani, M., Marpaung, J.K., Suharyanisa., & Lumbantoruan, M. (2023). Testing the diuretic potential of bangun-bangun leaf infusion (*Plectranthus amboinicus* (Lour. Spreng) which was tested on male rats (Rattus norvegicus Berkenhout) Wistar strain.	Urine of male rats after infusion of bangun-bangun leaves as a potential diuretic	Making bangun-bangun leaf infusion with 3 concentration variations, namely 10%, 20%, and 40%. Then given to white mice that were fasted for 10 hours but still given water. The specific gravity of urine was measured by comparing the weight of the urine weighed with the volume of urine measured.	The best urine specific gravity was in group IV, which was 6.813±0.048, so it was concluded that a 40% dose of bangun-bangun leaf infusion had an effect comparable to the diuretic effect of furosemide.
5.	Desnita, E., Rasyadi, Y., & Nanda, A.D. (2024). The activity of roll on aromatherapy essential oil of basil leaves (*Ocimum sanctum* L.) as an anti-inflammatory.	Basil leaf essential oil (*Ocimum sanctum* L.)	Preparation of basil leaf essential oil then put into the roll on making formula. Specific gravity testing using a pycnometer using a volume of 10 ml.	The measurement of specific gravity aims to determine the density of aromatherapy roll-on preparations and to test the purity of drug compounds in liquid form. The specific gravity of each concentration of 15%, 20%, and 25% basil leaf essential oil is 0.700; 0.783; and 0.760.

The shape, density, and size of the granule greatly affect compressibility[14]. The Carr index showing a value of up to 20 indicates that the formulation is well accepted[12].

Table 4. Compressibility index

% Carr Index	Flow Type
5-15	Very good
12-16	Good
18-21	Quite good
23-35-	Bad
35-38	Very bad
>40	Extremely bad

Hausner ratio is the ratio between tapped density and bulk density as an index of internal friction of cohesive powder[12]. If the Hausner ratio value is <1.25, it indicates good flow properties, while if it is>1.25, it indicates poor flow properties[20].

Porosity is the empty space between particles in the granule, which can explain the solubility of the granule in the solvent. The greater the porosity value, the smaller the contact between particles, and the faster the dispersion speed becomes, so that there is an increase in volume between particles[14].

The angle of repose is used as a parameter to compare the physical properties of the mixture of granules or powders, which can be calculated by the contingent of the height of the cone formed by the powder or granule, then the large angle that forms it will be obtained. The range of the angle of repose that indicates

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good flow properties or good granule quality is 28-420[6].

Based on the research of Paramakrishnan et al. (2016) in Table 1, the modified Kyilinga nemoralis carboxymethyl starch sample experienced a decrease in the Carr index below 18%, so it can be estimated that the compressibility of the carboxymethyl starch has increased.

Based on the research of Kedia and Wairkar (2019) in Table 1, the Hausner ratio increased to 1.123, and the Carr index increased to 12.35% after the Cycloserine crystallization process. Both parameters indicate an increase in compression behavior. Namely, the agglomerate has better compressibility than the original drug. Thus, Cycloserine crystallization is useful in the manufacture of high-dose Cycloserine drugs.

Based on the research of Dalvadi et al. (2019) in Table 1, the decrease in the Carr index value and the increase in the Hausner ratio value of the Bicalutamide agglomerate compared to the pure drug indicate that its flowability and compressibility have increased. The modified Bicalutamide agglomerate shows an increase in drug dissolution properties and compressibility, thus indicating an increase in the physical and mechanical properties of the drug.

Based on the research of Islam and Pathan (2017) in Table 1, the Carr Index decreased, the angle of repose decreased, and the Hausner ratio gave a very good value so that the compressibility value increased due to the conversion into ibuprofen agglomerates compared to the pure drug.

Based on the research of Himawan et al. (2019) in Table 1, Ketoprofen-tartrate showed a greater increase in Micrometric properties compared to ketoprofen with an angle of repose of 25.30, a Carr index of 16.67, a Haussner ratio of 1.2, and a porosity of 61.7%, thus contributing to better flow into the mold.

The specific gravity of a substance is influenced by the temperature, volume, pressure, concentration, and viscosity of the substance[4]. Based on the research of Latifah et al. (2020) in Table 2, the specific gravity of the essential oil of kaffir lime peel is 0.84029 g/ml, which is said to be standardized because it is still within the reference parameter range of 0.837 - 0.845 g/ml. There are three main components of the essential oil of kaffir lime peel, namely β-pinene (1 double bond), limonene (2 double bonds), and sabinene (1 double bond), so the specific gravity value is higher. The heavier the concentration of the molecules of the compounds that make up the essential oil and its double bonds, the higher the specific gravity.

Based on research by Suharyanisa et al. (2022) in Table 2, the best specific gravity of urine was in group V, which was 5.030 ± 0.12, which was given a dose of 40% comparable to furosemide affecting the specific gravity of male white mice. Specific gravity reflects the presence of substances dissolved in the urine.

Based on research by Royyan et al. (2024) in Table 2, the process of extracting essential oils from kemuning leaves using the microwave hydrodistillation (MHD) method and testing the characteristics of specific gravity. The average specific gravity of kemuning leaf essential oil was 0.8106 g / ml.

Based on research by Suryani et al. (2023) in Table 2, the best urine specific gravity was in group IV, which was 6.813 ± 0.048, so it was concluded that a dose of 40% bangun-bangun leaf infusion had an effect comparable to the diuretic effect of furosemide.

Based on research by Desnita et al. (2024) in Table 2, the specific gravity of each concentration of 15%, 20%, and 25% basil leaf essential oil was 0.700; 0.783; and 0.760. The measurement of specific

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gravity aims to determine the density of the aromatherapy roll-on preparation and to test the purity of the drug compound in liquid form.

In the carboxymethylation process, perfect homogeneity is required so that the dispersion rate of drug particles can be increased, but the carboxymethylation process can provide a negative charge on the cellulose used [7]. The use of the agglomeration method can improve the Micrometric properties of a particle, such as the flow rate of the particle, but the agglomeration process has not been widely used in the pharmaceutical industry because of possible problems in controlling the production parameters of agglomerates [15]. Crystallization is the process of forming crystals that are separated from their solution so that they can become homogeneous solid particles. Crystallization is commonly used in the pharmaceutical industry because approximately 90% of active pharmaceutical ingredients are synthesized as crystal forms. The methods in the crystallization process are very diverse, such as mixed suspension mixed product removal (MSMPR) crystallizers and tubular or plug flow crystallizers (PFC): laminar-flow tubular crystallizers (LFTC), coiled flow inverter (CFI) crystallizers, segmented/slug flow crystallizers, and continuous oscillatory baffled crystallizers (COBC). However, some of the crystallization methods used have several drawbacks, such as increased production and maintenance costs, inconsistency of the products produced, and crystallization that can change over time[19].

CONCLUSION

Pharmaceutical raw materials that have poor micrometric properties can be improved by modifying them either through carboxymethylation, crystallization, or agglomeration processes. The results can reduce the Carr index and increase the Hausner ratio of the material. Then, the specific gravity test provides information on the ratio of solids to water at certain temperature and volume conditions so that it is useful in testing the purity of the compound.

CONFLICT OF INTEREST

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