

ODT PRODUCT QUALITY MANAGEMENT ON THE EXAMPLE OF AUTOMATIC CONTROL OF TABLET WEIGHT UNIFORMITY

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Purpose: The aim of the work was to present the automation of the mass measurement process as a factor that can significantly affect the quality and speed of analyzes in pharmaceutical industry.

Design/methodology/approach: In this study, two methods were presented for testing the mass uniformity of tablets whose weight ranged from 13 mg to 2580 mg. The first method involved determining the weight of 20 randomly selected tablets of pharmaceutical preparations by statically measuring the weight of these tablets. In the second method, an automatic tablet feeder type PA-04/H was used, in which, as a result of vibration, successive tablets were automatically moved via a special chute onto the weighing pan.

Findings: No significant differences were found in the weight measurements performed by the manual and automatic methods. The largest differences were noted at the 0.5% level. All tablets tested met the United States Pharmacopeia requirements for their mass uniformity. For orally disintegrating tablets, the largest percentage deviations in weight from the mean value were -4.47% for tablet F6, -4.26%, for tablet F1 and 3.31% for tablet F2. The differences in accuracy and precision between the automatic and manual methods were insignificant.

Research limitations/implications: Mass measurement by the manual method is one of the most frequently performed measurements in the laboratory. The final result from this measurement method may be subject to error caused, for example, by human error, i.e. reading, writing or calculation error. For this reason, process automation is increasingly being used, which eliminates the possibility of error to a large extent.

Practical implications: The automation of weight measurement reduces the effort required for product inspection. Thus, it can be an important factor in the process of optimization and product quality management.

Originality/value: The description of the research method and its results can be a valuable guideline for people who deal with product quality control in the pharmaceutical industry. It has been shown that automation to be effective does not have to be complicated but well designed.

Keywords: mass, measurement, mass uniformity, tablets, accuracy, weighing, time management.

Category of the paper: Research paper.

1. Introduction

The production of tablets is a rather complex process with quite a high level of risk (EMA/CHMP/ICH/24235/2006) in which quality must be maintained at a constantly high level, hence the aim to have quality built into the product - Quality by Design (Schmitt, 2018; Snee, 2016; Anushka et al., 2012; Kishor et al., 2022; Pritam, Shubham, 2022). The compressing technologies in use today (Van der Haven et al., 2022; Abouzeid et al., 2014; Baroutaji et al., 2017) ensure maximum line efficiency while maintaining the relevant properties of the medical formulation. The key to achieving and maintaining both is to optimize the compressing process (Ganesh et al., 2012; Mohit et al., 2021; Antonyuk et al., 2010) taking into account the specific characteristics of the tablet (its size, composition, drug release rate) and the capabilities and limitations of the compressing system. One of the important parameters of each tablet is its mass, which is de facto the sum of all the components that make up its matrix.

One of the popular types of tablets today are polymeric matrix tablets with a controlled release rate of the drug substance, which ensures a constant concentration in the patient's blood (Sangmun et al., 2011; Raghuram et al., 2003; Katzhendler et al., 2000; Levina, Rajabi-Siahboomi, 2004; Viridén et al., 2010). In this solution, the rate of drug release can be modified by additives such as hypromellose - a semi-synthetic cellulose derivative (HPMC) that can account for approximately 20-40% of the tablet weight (The Dow Chemical Company, 2000). Another novel tablet form is tablet that disintegrate in the mouth referred to as Oro-Dispersible Tablets (ODTs) (Teaima et al., 2022; Sipos et al., 2017; Etman et al., 2014; Mohammadali et al., 2021). The small size of ODTs and the rapid disintegration of the drug in the patient's mouth of about 30 seconds (Guidance for Industry-Orally Disintegrating Tablets, 2008) or a few minutes (European Pharmacopoeia, 2019) is an excellent example of personalisation in medicine dedicated to paediatric and geriatric patients and in cases of dysphagia. It should be noted that the rapid disintegration of ODTs (Mohammadali et al., 2021) in contact with the patient's saliva allows the appropriate dose of the drug to be applied also on the move without having to sip the drug with water, which is undoubtedly their advantage. Thanks to its small size, ODTs are a discreet and effective form of medication for patients with chronic diseases who need to take their medication frequently and systematically. From a medical point of view, the speed of action of ODTs is important, which is desirable in cases of migraine, severe pain or diarrhoea. Regardless of the type of tablet, the weight of each tablet must be within certain limits (US Pharmacopoeia, 2011; European Pharmacopoeia..., 2019). On the one hand,

the uniformity of tablet mass over the production cycle is a normative requirement that must be met so that a production batch can be considered compliant. On the other hand, the tablet mass drifts observed in a production run are an indicator for process control (VanDrie, 2007), where uniformity of filling of the tablet die cavity is important. This is a complex process, the efficiency of which depends on the flowability, cohesion and particle size of the powder mixture. The parameters of the process equipment are also important in this regard. The aim of the study was to see if the introduction of automation in mass measurement has a significant effect on the accuracy of determining the uniformity of tablet mass. In the study, the authors also wanted to indicate that the search for alternative, simple methods can be one of the factors that fits into the model of proper time management not only of personnel, but also of performing a specific analysis.

2. Material and methods

The material in the study consisted of 10 selected pharmaceutical preparations including six ODT-type preparations two lozenges and two swallowable preparations. Twenty tablets of each pharmaceutical preparation were used for the study by conducting tests for each tablet separately. The characteristics of the formulations are shown in Table 1. From a metrological point of view, the size of the tested products and thus their weight was important. As the weight increases, significant differences can be expected between the manual and automatic measurements, mainly due to the impact that occurs when a tablet is dropped from a certain height onto the weighing pan, as was the case when measuring the weight of tablets using Method II.

Table 1.
Characteristics of tablets tested for mass uniformity

Sample	Active substance	Type	Indication for use	Manufacturer
F1	desloratadinum	ODT	allergies	Adamed Pharma, Poland
F2	desloratadinum			US Pharmacia, Poland
F3	meloxicamum		pain, inflammation	Hasco-Lek S.A., Poland
F4	2 mg Loperamidi hydrochloridum		diarrhoea	McNeil Healthcare, Ireland
F5	Melatonin		sleep problems	Olimp Laboratories, Poland
F6	Folate Quatrefolic		support of the immune system	Medimes, Poland
F7*	chlorquinaldolum 2 mg	lozenges	bacterial infections of the throat, mouth	Bausch Health Ireland Limited, Ireland
F8*	alcohol 1.2 mg, 2.4-dichlorobenzyllicus, 0.6 mg amylometacresolum			Reckitt Benckiser S.A., Poland

Cont. table 1.

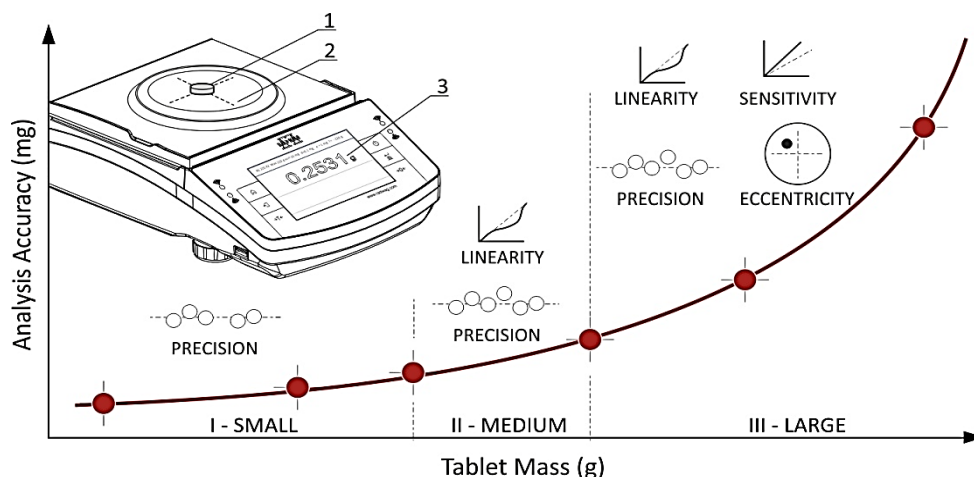
F9*	lutein 24 mg	oral tablets	improving vision	Aflofarm Polska Sp. z o.o., Poland
F10*	choline, L-aspartate, L-ornithine, extracts of artichoke, holly, chicory, holly		improve liver function and maintain normal fat and homocysteine metabolism	Teva, Poland

Legend: F1-F10 means symbols of tested pharmaceutical preparations; * dietary supplements.

2.1. Methods I – manual

The weight of each of the 20 tablets was determined by manual weighing by gently placing it with a pencil on the balance pan. An analytical balance AS 220.X2 manufactured by Radwag Wagi Elektroniczne, Radom, Poland, was used for the weight measurements; the elementary scale division for the weight measurement was 0.1 mg. The repeatability of the readings for tablet mass measurements was 0.06 mg, which was in accordance with the data provided by the balance manufacturer regarding the repeatability of readings when the sample mass is no more than 5 % of the balance maximum load.

The metrological relationships associated with manual mass measurement affecting the accuracy of tablet mass determination are shown in Figure 1.



Legend: 1 – weighted tablet, 2 – weighing pan, 3 – weighing result.

Figure 1. Manual weighing process - weighing accuracy depending on the size of the tablet weight.

In the first weighing range when the weight of the tablet was less than 5% of the maximum load of the balance, the accuracy of the weight measurement depended only on the precision of the measurement. For stable operating conditions in the temperature range, the measurement precision was very good (had a low value) because there were no impacts during weighing when the tablet was placed on the weighing pan. In the second and third weighing ranges, the accuracy of the weight measurement is further influenced by other metrological factors such as sensitivity, linearity and centricity of the balance. The sensitivity of the balance before the test was adjusted by internal adjustment of the balance. Performing the adjustment meant that the linearity characteristics of the balance were correct. Centricity deviations can be significant for the measurements carried out when the object to be weighed is placed off-centre on the pan.

The tablets were placed in the centre of the pan. The weight of the tablets tested ranged from 13 mg to 2580 mg. It was therefore assumed that the error in determining their weight was only affected by the precision of the measurements as stated by the manufacturer. The effects of sensitivity, linearity and centricity of the balance were considered negligible.

From the results obtained, the mean tablet weight was calculated and the percentage of tablet weight variation relative to the mean value was checked. The acceptable limits of variation in tablet weight (US Pharmacopeia, 2011; European Pharmacopoeia..., 2019) depending on the mean value are shown in Table 2.

Table 2.

Tablet weight uniformity - allowable percentage deviations in tablet weight according to the United States Pharmacopeia

Average tablet weights	Percentage deviation	Number of tablets
$m \leq 80$ mg	± 10.0 ± 20.0	Minimum 18 units. Max. 2 pcs.
$80 \text{ mg} < m \leq 250$ mg	± 7.5 ± 15.0	Minimum 18 units. Max. 2 pcs.
$m > 250$ mg	± 5.0 ± 10.0	Minimum 18 units. Max. 2 pcs.

The percentage deviation of each tablet was calculated according to the formula below:

$$Deviation (\%) = \frac{|\bar{m} - m_i|}{\bar{m}} * 100 \% \quad (1)$$

where:

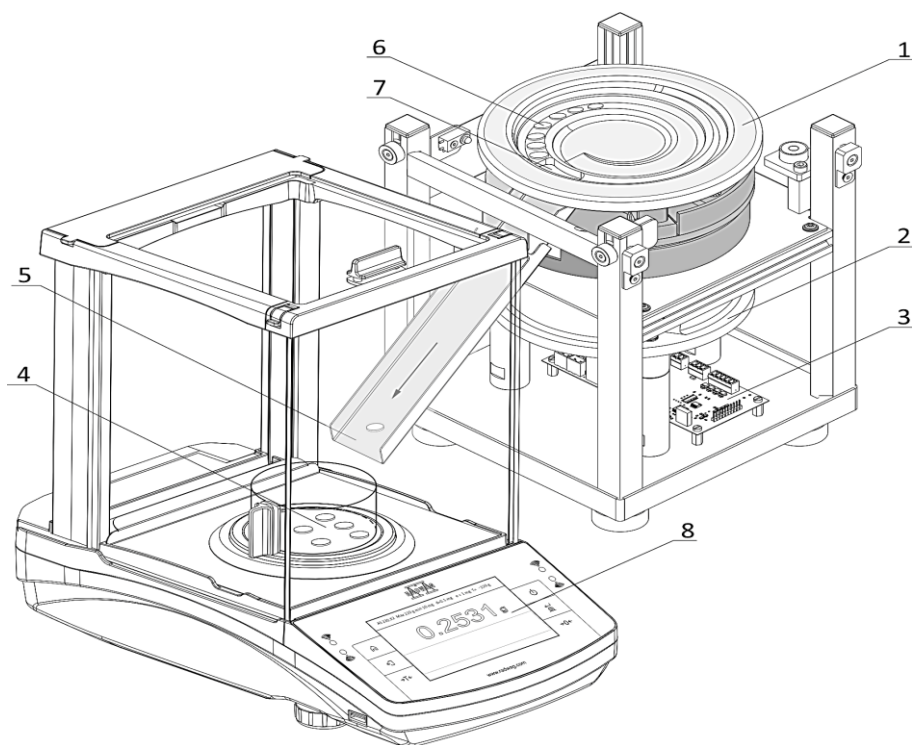
\bar{m} - average tablet weight,

m_i - weight of the next tablet.

2.2. Method II - automatic

In the automatic method, a PA-04/H automatic feeder produced by Radwag Wagi Elektroniczne, Radom, Poland and an AS 220.X2 analytical balance were used (Figure 2). The tablets subjected to the weight test (6) were placed in the vibrating feeder (1). The spiral plane of the feeder was slightly inclined towards the drop hole (7), so that when the vibration of the feeder (1) was activated, an orderly array of tablets (6) was obtained, which automatically shuffled into the drop hole (7). The presence of a tablet in the drop hole was registered by a detector, which temporarily switched off the vibration of the device. The tablet was then transported via the discharge chute (5) to the weighing vessel (4). The AS 220.X2 balance recorded the weight of the tablet (8) and then zeroed the display so that the next measurement was taken from the exact zero state. Once the weight of the tablet had been recorded by the scale, the feeder received a signal back that it was ready for the next weighing and restarted the vibration of the tablet feeder (1). Such a measurement cycle was cycled for a series of 20 measurements of each tablet. At the end of the series of measurements, the balance display

showed the result of the test, i.e. the average value of the tablet weight and the deviation of the weight of each tablet from the average value.



Legend: 1 – vibrating feeder, 2 – base of vibrating feeder, 3 – control system of device operation, 4 – weighing pan with tablet container, 5 – drain chute, 6 – tablets, 7 – drop opening with tablet detector, 8 – weighing result.

Figure 2. Automatic feeder PA-04/H with scale AS 220.X2.

The PA-04/H vibration feeder allowed the vibration intensity to be adjusted from a low value to a high value, which was used when testing ODT tablets, mainly due to their small size. The accuracy of the automatic method used to test the mass uniformity of the tablets was determined by comparing the mass measurements obtained using this method with the results that were obtained using the manual method.

3. Results for precision and accuracy of tablet weight measurements

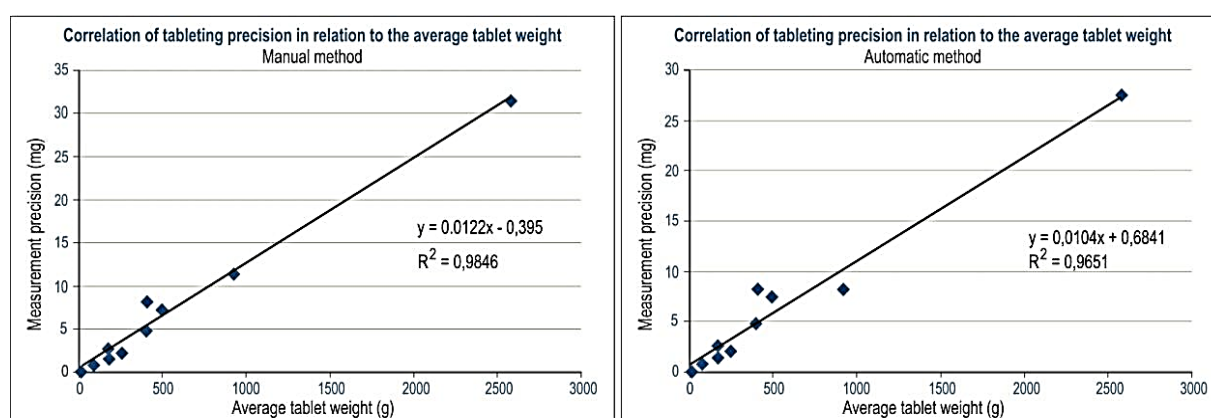
The hygroscopicity of ODT tablets is a desirable feature due to their rapid disintegration in the patient's mouth, but on the other hand, it is a factor that can affect the accuracy of mass measurement (ISO 5725-6, 2002). For this reason, the weight of each tablet was determined immediately after removal from the pack using both manual and automated methods. The average weight of each tablet, the precision of the tablet device defined by the standard deviation and the accuracy of the automatic method weight measurements are shown in Table 3.

Table 3.*Mass of tablets (accuracy and precision of the automatic method)*

Sample	M1 - method manual AS 220.X2	M2 - method automatic PA-04/H + AS 220.X2	Difference M2-M1
	$\bar{x} \text{ (mg)} \pm S \text{ (mg)}$		%
F1	171.69 ± 2.73	171.57 ± 2.73	0.07
F2	85.32 ± 0.93	84.77 ± 0.90	0.53
F3	253.98 ± 2.25	253.47 ± 2.22	0.20
F4	13.30 ± 0.13	13.37 ± 0.15	0.49
F5	176.22 ± 1.62	176.37 ± 1.55	0.09
F6	407.76 ± 8.23	408.20 ± 8.20	0.11
F7*	400.14 ± 4.88	400.45 ± 4.94	0.08
F8*	2580.01 ± 31.55	2579.71 ± 27.52	0.01
F9*	918.14 ± 11.47	919.13 ± 8.34	0.11
F10*	494.69 ± 7.27	493.86 ± 7.50	0.17

Legend: F1-F10 means symbols of tested pharmaceutical preparations; * dietary supplements.

There were no significant differences in the accuracy of tablet weight measurements between the manual and automatic methods. The greatest discrepancy of approximately 0.50% between the measurements obtained by the manual and automatic methods was recorded for tablets F2 and F4 (ODT preparations), where the weight of these tablets was determined as 85 mg and 13 mg, respectively. It should be noted that the accuracy of the determination of the average tablet mass value is significantly affected by the precision of the measurements. In this case, the precision of the tablet weight measurements was not a measure of the repeatability of the balance readings, i.e. the ability to indicate the same measurements for the same object, but was a measure of the repeatability of the tablet machine used in the production cycle. It was found that as the average tablet weight increased, the discrepancy in tablet weight within a batch increased significantly, which may indicate a feature of the processes used during compressing (Partheniadis et al., 2022; Peciar et al., 2016). The relationship of tablet weight disparity to average tablet weight is shown in Figure 3.

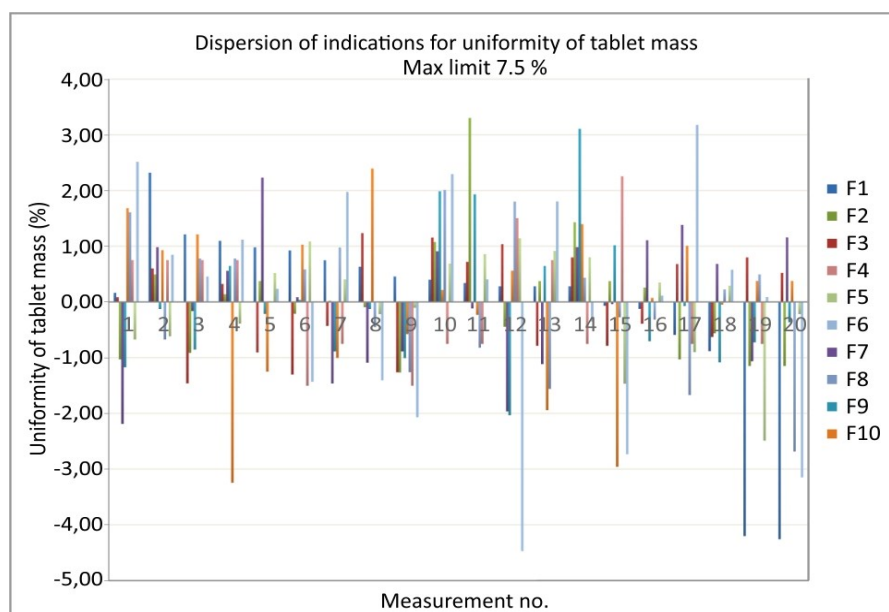
**Figure 3.** Mass uniformity in the compressing process - mass measurement precision.

The values of the r-Pearson correlation coefficients, i.e. the linear relationship between the mean tablet weight and tablet precision, were 0.99 and 0.98, indicating a significantly strong linear relationship between the value of the mean tablet weight and the discrepancy between their weights in the series. It was found that the use of an automated method during tablet

weighing did not introduce significant distortions - the coefficient of determination R^2 , a measure of the fit of the linear regression model, was 0.98 and 0.96 for the methods used, respectively.

3.1. Test results for assessing the uniformity of tablet mass

Based on the percentage deviation of the weight of each tablet relative to its average weight, it was concluded that the weight uniformity requirement shown in Table 2 was met. A graphical interpretation of these relationships for the manual weighing method in which the AS 220.X2 balance was used is presented in Figure 4.



Legend: F1-F10 means symbols of tested pharmaceutical preparations.

Figure 4. Scatter of readings for tablet mass uniformity.

The largest weight percentage deviations from the mean values were noted for tablets F6 (- 4.47%) and F1 (- 4.26%). It should be noted that the maximum allowable limit for percentage deviations in mass was 10% for tablet F6 and 7.5 % for tablet F1. The observed percentage mass deviations were therefore considered to be insignificant. For most tablets, the mass uniformity was in the range of 1-2%, which was an acceptable result within the required limits (US Pharmacopeia, 2011; European Pharmacopoeia..., 2019). Table 4 shows the mean value of the percentage deviations from a series of 20 weighings of each tablet type and the precision of the determination of this value, which was a measure of the scatter that characterised the series of measurements. The scatter of the series of measurements was defined by the value of the standard deviation, and its value was used to estimate whether the tablet under test met the weight uniformity requirements (Table 2). On the other hand, these values were used to compare the accuracy and precision of the measurements of the automatic and manual methods. No significant differences were found in the accuracy as well as the precision of the analysis carried out, regardless of which method was used.

Table 4.*Mass uniformity of tablets - manual and automatic method*

Sample	Average mass	Precision and max. deviation masses of tablets		Max. normative limit for mass uniformity
		manual method	automatic method	
	\bar{x} (mg)	$\overline{\Delta m}$ (%) \pm S (%)		m (%)
F1	171.69	1.01 \pm 1.60	1.00 \pm 1.59	7.5
F2	85.32	0.79 \pm 1.09	0.78 \pm 1.05	7.5
F3	253.98	0.80 \pm 0.89	0.74 \pm 0.87	10
F4	13.30	0.76 \pm 0.98	0.81 \pm 1.12	20
F5	176.22	0.71 \pm 0.92	0.67 \pm 0.88	7.5
F6	407.76	1.56 \pm 2.02	1.56 \pm 2.01	10
F7*	400.14	1.01 \pm 1.22	1.02 \pm 1.23	10
F8*	2580.01	0.97 \pm 1.22	0.87 \pm 1.07	10
F9*	918.14	0.94 \pm 1.25	0.70 \pm 0.91	10
F10*	494.69	1.13 \pm 1.48	1.20 \pm 1.52	10

Legend: F1-F10 means symbols of tested pharmaceutical preparations, * dietary supplements.

4. Conclusions

The difference in tablet masses in a production run is the result of inaccuracies in the technological methods and equipment used. From a technological point of view, it can be stated that factors such as powder flow, speed of the compressing machine, pressure applied during pressing and the type of machines used for compressing are important. The size and distribution of particles in the compression process are also important. Determining the mass uniformity and, in fact, the mass discrepancy of tablets in a production run by gravimetric mass measurement is the fastest, simplest and cheapest method. It is adaptable to any laboratory with minimal operator input and qualification. Manual mass measurement performed using analytical (0.1 mg) and semi-microanalytical (0.01 mg) balances requires stable operating conditions and tablet mass information is usually recorded manually. This mode of operation is prone to errors due to the so-called human factor and the method of data digitisation. The introduction of automation in the tablet mass uniformity testing method saves time and makes the process much more ergonomic. The study concluded that manual and automatic methods can be used interchangeably without losing the accuracy of the analysis. Today, the aim is to automate many processes in pharmacy, and observing and controlling the process remotely significantly increases safety and supervision of the control and production process. The PA-04/H automatic feeder fits into this trend as a small component of any pharmaceutical company's GLP/GMP system.

In summary, the introduction of the automatic mass measurement method using the PA-04/H vibrating feeder reduces analysis time while maintaining parameters such as precision and measurement accuracy. Its implementation in the pharmaceutical industry, in the authors' opinion, is a valid, convenient alternative to this type of measurement.

Thus, this method is part of effective time management which, to a large extent, allows you to optimally use the potential of the company in a consistent pursuit of the desired goal.

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