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Determining Compression Pressure for Amlodipine Nicotinate Floating Tablet Production

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Abstract:

The aim of this study was to determine the optimal pressure value for production of amlodipine nicotinate floating tablets through direct compression. The range of pressure values was determined using Heckels equation, and tablets were produced using the values from this range. Characteristic features of the tablets, i.e. floating time and buoyancy lag time were experimentally assessed. As the result, the optimal pressure for production of amlodipine nicotinate tablets was established.

Key words: Amlodipine nicotinate, direct compression, floating tablets, pressure value**.**

INTRODUCTION

Scientific research in order to development of effective, high-quality, stable and safe drugs are relevant and most important in the theory and practice of drugs production. The development of drugs should be given high priority to the qualitative and quantitative composition of excipients. The selection of excipients is carried out taking into account properties of the active substance, the required properties of the future dosage form and the selected technology for producing the drug.

The main methods for producing tablets are direct compression and compression using granulation. Granulation can be dry and wet. [1]. The most universal is the method of wet granulation because it allows you to get the mass for tableting with the necessary technological properties. Meanwhile, the dosage of the drug and the technological properties of the active pharmaceutical substance do not significantly affect the effectiveness of granulation [2]. However, the wet granulation method is expensive and time consuming in comparison with the method of direct compression. In addition, the number of critical parameters increases with wet granulation, which means that the risk of producing a poor-quality drug increases [3].

The direct compression method is more profitable in terms of direct production costs: there are no additional technological stages, and in terms of effects on the substance: the active pharmaceutical substance is not exposed to excessive moisture or organic solvents, temperature, overpressure and other factors [4]. This makes the direct compression method more attractive for tablet production. Tablet composite for direct compression should have a number of technological properties: good flowability (at least 5-6 g/s), high compressibility (at least 70 - 100 N), optimal bulk density (at least 0.4 - 0.5 g/ml), low angle of repose (no more than 40º).

Also, porosity readings are used for further calculation of the coefficients Carr's (at least 20%) and Hasner (no more than 1.26). A high Carr's coefficient indicates a good compressibility of the substance powder, while a Hasner coefficient determines the flowability of the powder [5].

Scientific research to find the optimal technology for obtaining a tablet dosage form is carried out at the stage of pharmaceutical development, and at the stage of industrial production of a drug in order to optimize technology. In a simplified aspect, the goal of modeling the pressing process is to derive an equation by which it is possible to predict the ability to compress various substances and to design formulations of tabletted composition by calculation [6]. Hekkel's mathematical model was used to determine the optimal pressing pressure of tablet composition, which allows predicting the compressibility by comparing the geometric characteristics of a curve constructed by the Hekkel equation and its angle of inclination. The substance has more plastic properties if the curve segment is smaller and the angle of inclination is larger, which means that it is pressed at lower pressure to form a strong tablet. [7,8]. Hekkel's mathematical model is described by the equation:

$$ln\frac{1}{1-pf} = mP + b$$

where the constants b and m are determined analytically on the segment intersection point and angle extrapolated linear region of the curve $ln\frac{1}{1-pf}$ ~P respectively.

Hekkel's model takes into account the ratio of the elastic and plastic properties of the material, for this reason it is the most adequate and applicable for most pharmaceutical substances and excipients.

MATERIALS AND METHODS

Amlodipine Nicotinate - it is an active substance, a white amorphous powder with a weak specific smell and bitter taste. The substance is slightly soluble in water, soluble in methanol and ethanol [9]. The substance was obtained by LLC «PIK-Pharma Chem» as an experimental series.

As auxiliary substances, Hydroxypropyl methylcellulose, carbopol, sodium starch glycolate and microcrystalline cellulose were used as matrix-forming components, magnesium stearate and aerosil as lubricants and antifriction substances, and sodium hydrogen carbonate as a blowing agent.

Powder density was determined using a pycnometer. Weighed on an analytical balance with an accuracy of 0.02 mg. The material was crushed, dried at 105 ° C, and sieved through a sieve with a hole diameter of 0.2 mm. The definition was reduced to finding V fluid displaced by a known m powder from a vessel of a certain volume (pycnometer).

m_1 – powder mass (approximately 3.0 g);

m_2 – mass of a pycnometer with liquid (o-xylene) filled up to risks;

m_3 – the mass of the pycnometer with a sample of the detected powder and o-xylene filled to risks;

m_4 – weight of xylene displaced;

ρ_x – density of o-xylene (0.880 g /cm^3).

$$m_3 + m_4 = m_1 + m_2$$

$$m_4 = m_1 + m_2 - m_3$$

$$V_f = \frac{m_1 + m_2 - m_3}{\rho_x}$$

$$\rho_{pa} = \frac{\rho_x m_1}{(m_1 + m_2 - m_3)}$$

Evaluated the degree of flowability of the powder using the ErwekaGTL device according to the method described in Russia State Pharmacopoeia 13 (XIII) (GMP «1.4.2.0016.15 the degree of flowability of powders»).

The appearance of the tablets was determined organoleptically and using measuring instruments.

Porosity was determined by the formula:

$Ps = (1-P/\rho) * 100\%$,

where Ps – porosity in %,

P – bulk density in g /cm^3,

ρ – density in g /cm^3.

The linear approximation method (least squares method) was used to process the obtained data.

The flotation time was estimated as follows: a tablet was dropped into a glass containing an acidic solution with a pH of 1.7, and the time during which the tablet was floated was estimated using a stopwatch.

Result and discussion

Amlodipine nicotinate is a powder with low flowability, small bulk mass, high residual humidity, with particles differing in shape and size.

Since the amount of substance per 1 tablet is small (10 mg per 500 mg tablet), the problem of low flowability can be eliminated by introducing excipients with good flowability in sufficient quantities.

It was decided to use the production of LP by direct pressing, since this method allows to reduce the number of technological operations and minimize the risks in production.

In the process of work, model compositions were selected to study the influence of pressure value, the component ratio of which is indicated in Table 1.

Table 1. The investigated compounds.

Components	Number of composition					
	1	2	3	4	5	6
Amlodipine nicotinate	10,0	10,0	10,0	10,0	10,0	10,0
Hydroxypropyl methylcellulose	100,0	-	-	75,0	-	-
Carbopol	-	100,0	-	-	75,0	-
Sodium starch glycolate	-	-	100,0	-	-	75,0
Microcrystalline cellulose	307,5	-	307,5	332,5	332,5	332,5
Sodium hydrogen carbonate	77,3	77,3	77,3	77,3	77,3	77,3
Magnesium stearate	2,6	2,6	2,6	2,6	2,6	2,6
Aerosil	2,6	2,6	2,6	2,6	2,6	2,6
Tablet mass	500,0	500,0	500,0	500,0	500,0	500,0

Table 2. The calculated coefficients for the Heckel equation.

A	k	Da	Db	1/k, кН
0,3712 ± 1,1232	0,0065 ± 0,01114	1,98	1,34	15,3846

Table 3. Dependence of the lag phase on pressing pressure, sec.

Number of composition	Pressure pressing, kN		
	10 kN	15 kN	20 kN
1	18±3	23±5	40±8
2	26±4	39±8	61±10
3	8±2	15±4	22±6
4	24±6	30±7	56±8
5	27±8	35±6	48±7
6	21±6	24±5	47±7

Table 4. Dependence of the flotation time of the pressing pressure, min.

Number of composition	Pressure pressing, kN		
	10 kN	15 kN	20 kN
1	450±22,5	483±24,15	543±27,15
2	424±21,2	459±22,95	521±26,05
3	5±0,1	5±0,1	7±0,35
4	323±16,15	394±19,7	447±22,35
5	315±15,75	352±17,6	423±22,15
6	12±0,6	15±0,15	22±1,1

Figure 1. Dependence of pressing pressure

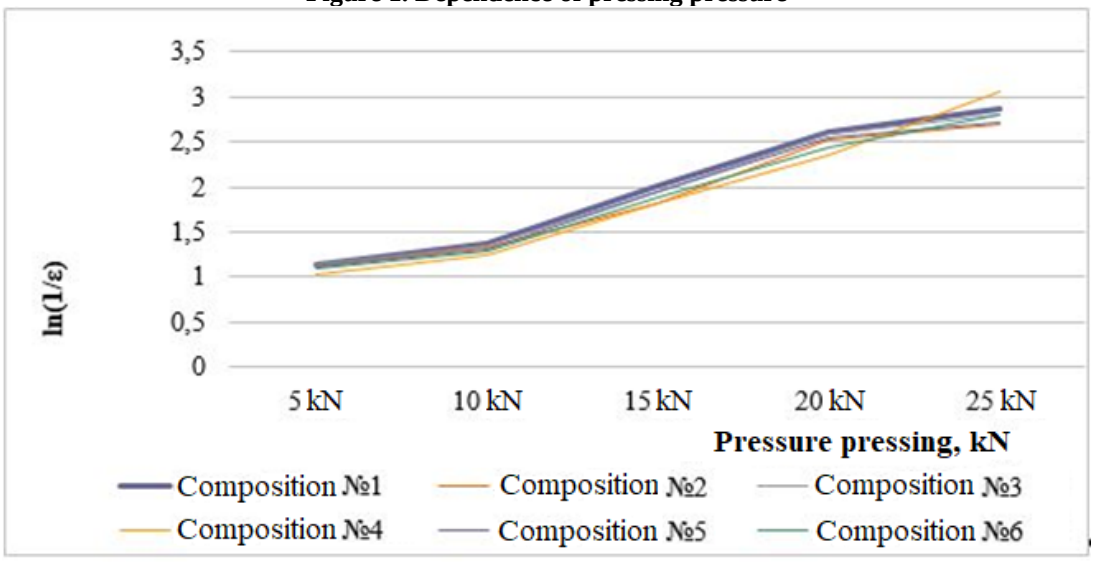


Figure 2. The graph of the dependence of the pressing pressure on the natural logarithm of the porosity of the tablets.

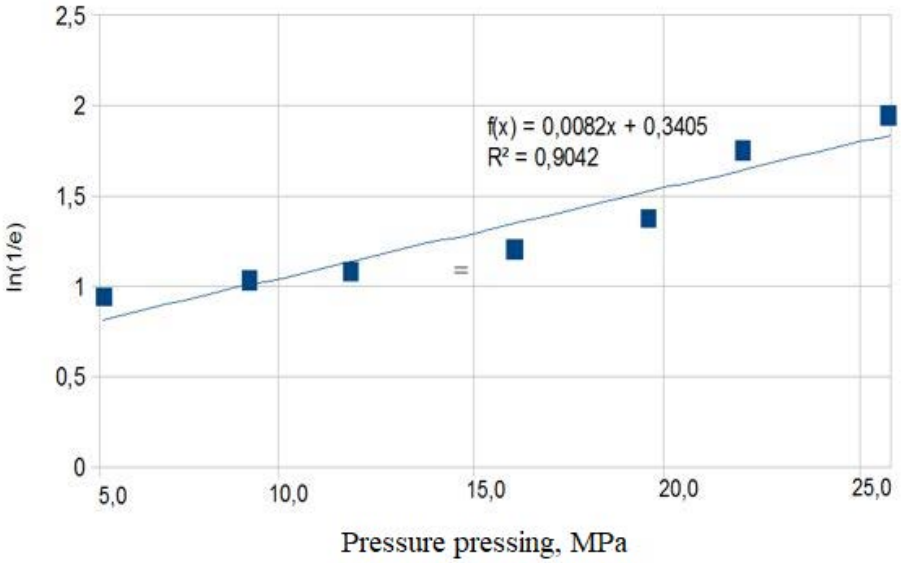


Figure 3. Dependence of the lag phase on pressing pressure.

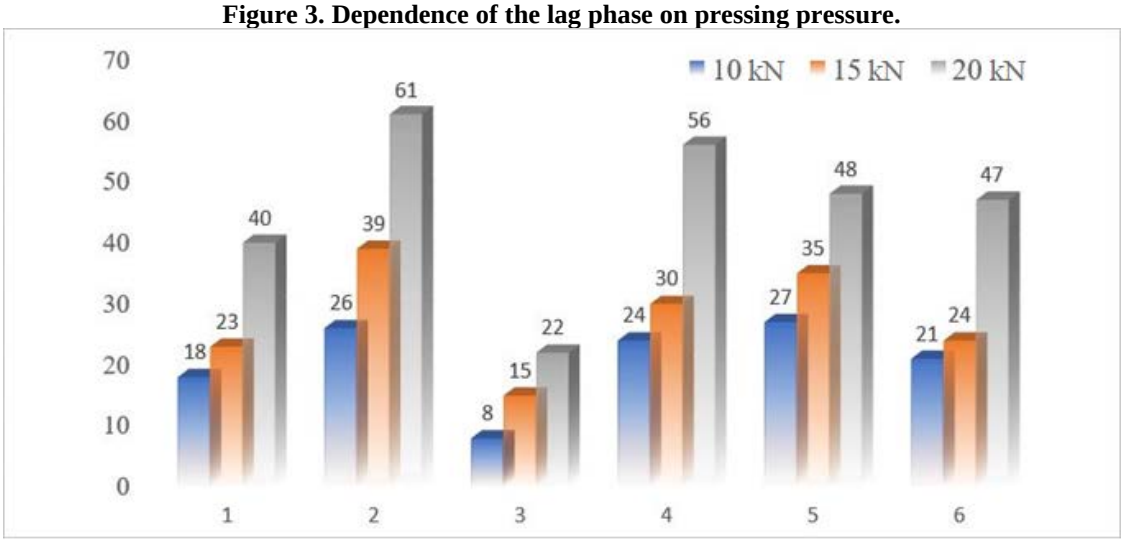
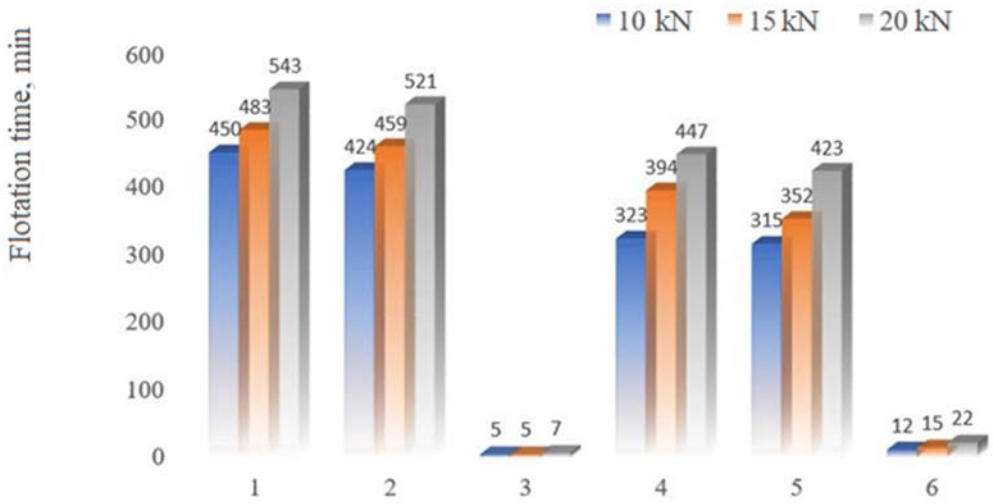


Figure 4. Dependence of flotation time on pressing pressure.



The tablet mass was prepared by mixing in the laboratory mixer MP-6 powders (MultiPharma, Italy) for 15 minutes of all pre-sidered ingredients. Next, the resulting mixture was dusted with magnesium stearate for 2 minutes. The density of the tablet mass is 1.28 g / cm^3. Pressing of the tablet mass was carried out on the rotary tablet press (Cambcavi C&C 800) with gradual overlapping of pressure value, with an exposure time of 20 s and a relaxation time of 15 min. The value of pressing range has been selected from 5 to 25 kN.
For tablets obtained at a pressure within the selected range in increments of 5 kN, the values of the coefficients of the Heckel equation were measured:
- tablet height (cm),
- tablet mass (g),
- density (g /cm^3),
- porosity (ε),
- ln (1/ ε).

On the basis of the received data the graph was constructed (Fig. 1) which reflects the dependence of ln(1/ε) on the pressure value. The graph shows that for all the compositions presented, the Heckel equation was performed without a large variation in deviations.
An analysis of the coefficients of the Haeckel equation indicates that a growth of pressure value increased the mechanical compressive strength. At pressure value below 10 kN, insufficiently strong tablets were obtained. Raising of the pressure value more than 20 kN increased the strength of the tablets.
The data obtained as a result of the experiment were processed by the linear approximation method (least squares method), as a result of which the equation y = bx + a was transformed as follows:
y = (0,0065 ± 0,01114) x + 0,3712 ± 1,1232
Confidence probability - 0.95
Number of measurements - 7
Student's coefficient - t = 2.37
Absolute errors: for a - Δa = ± 1.1232
for b - Δb = ± 0.01114
Correlation coefficient — 0,9042
f(x) = 0,0065x + 0,3712
R^2 = 0,9042
According to the data obtained, a graph of the pressure value dependence on the natural logarithm of the porosity of the tablets was plotted (figure 2).
Graph (Fig. 2), built on the Heckel equation, describes the processes occurring with the tablet mass under pressure application, as well as the pressing mechanism (fragmentation or plastic deformation) during tableting. The slope of the linear portion of the graph of the Heckel equation has high values in the case of plastic deformation during compression and low values-in the case of fragmentation. The reciprocal of 1 / k is the optimal pressure value, which is characterized by particle deformation.
According to the analysis of the data obtained, fragmentation prevails in the pressing process, as evidenced by a sufficiently high value of the coefficient A (table 2). Db values are less than Da values, indicating particle redistribution during the pressing process
The straight section of the graph is located in the range of pressure values from 10 to 20 kN. It can also be assumed that the optimal pressure value to produce tablets is 15 kN.
Data from literature the main criteria for quality indicators of flotation systems of LV delivery are lag-phase and flotation time [10]. These indicators were studied for tablets obtained at pressure value 10, 15 and 20 kN.
The following diagrams and tables show the dependence of the lag phase and flotation time on the pressure value in the range from 10 to 20 kN.

CONCLUSIONS

From tables 3 and 4 and figures 3 and 4 it can be seen that the lag phase and flotation time increase with increasing pressure. These parameters are limiting for flotation tablets, compositions 3 and 6, which showed a short flotation time, will be excluded from the study. For other samples, the pressure range of 10 to 20 kN is optimal.
It is necessary to conduct a study of dissolution profiles to narrow this range.

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