PharmacologyOnLine

Archives • 2021 • vol.3 • 927-936

IMPACT OF QUANTITATIVE FACTORS ON PHARMACO-TECHNOLOGICAL PROPERTIES OF TABLETS WITH THICK EXTRACT OF *PRIMULA DENTICULATA* SMITH

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Abstract

The method of random balance was used in the research process. The influence of six quantitative factors on the pharmaco-technological properties of powder masses and on the main indicators of tablet quality was studied. The optimal ratio of excipients in the composition of tablets was established. The study found that the flowability of the powder mixture depended to a large extent on the amount of croscarmellose sodium and Neusilin US 2 – with increasing of which the tablet mass flowed faster. Also, the quantity of these excipients in the tablets significantly affected their resistance to abrasion. With a decrease in croscarmellose sodium and Neusilin US 2, the study rate improved. The most significant effect on the resistance to crushing of tablets was the increase in the quantity of Prosolv 90 and the decrease in the quantity of colloidal anhydrous silica, as a result of which the tablets became stronger. In the study of the disintegration period, it was found that reducing the compression pressure (40 kg*s/cm^2) and increasing the quantity of croscarmellose sodium in the tablets improved their disintegration.

In the process of research, the desirability function was used as a generalized indicator of the quality of powder mixtures and tablets. Also, the results of research allowed optimizing the composition of tablets.

Keywords: *Primula denticulata* Smith, thick extract, croscarmellose sodium, colloidal anhydrous silica, Neusilin US 2, Prosolv 90

Introduction

Recently, there is a tendency to prescribe herbal medicines in modern medicine, despite significant advances in the development of synthetic drugs for the treatment of many diseases [1-4].

An important task of modern pharmaceutical science is the research of medicinal plants in terms of studying their biologically active substances and establishing the pharmacological activity of the obtained substances in order to further develop new drugs. There is a tendency to expand the range of finished drugs every year in the pharmaceutical market [5, 6].

The popularity of drugs containing biologically active substances from plants is high, despite the annual increase in the number of new medicines of synthetic origin, which often model the biologically active substances of plants [7-12]. Pharmacotherapy increasingly takes into importance the centuries-old experience of folk medicine with the application of phytopreparations [13-15]. Increasing demand for herbal medicines around the world is an incentive to develop new, effective herbal medicines in various dosage forms. The plant medicines are well tolerable, often used in the fight against many diseases, and have minor side effects [16-20].

We obtained a thick extract of primula denticulata and determined the quantitative content of biologically active substances (hydroxycinnamic acids, phenolic compounds, flavonoids), established anti-inflammatory, expectorant, and antibacterial activity of primula denticulata [21-24]. These properties are the result of the availability of different groups of biologically active compounds [25, 26].

At the previous stage of the study, the qualitative composition of excipients was studied and selected, the use of which allowed obtaining a solid dosage form (tablets) with satisfactory pharmaco-technological properties [27].

The aim of our research is to study the optimal ratio of excipients in the composition of tablets, as well as the impact of their quantity on the technological properties of powder masses and quality indicators of tablets.

The experiment plan is designed to reduce the total number of experiments, but at the same time to be able to thoroughly analyze the data of the experiment and obtain reliable results, which cannot always be achieved with the help of a subjective approach [28].

Methods

Tablets with thick extract of primula denticulata were obtained by the classical method of wet granulation. Thick extract of primula denticulata was used as a moisturizing solution. The tablets were developed at the Department of Pharmacy Management, Economics and Technology (I. Horbachevsky Ternopil National Medical University) [29].

The method of random balance was used to determine the amount and feasibility of the quantity of all pre-selected excipients [30], which studied the six quantitative factors at the top and bottom levels. This method makes it possible to optimize the composition of tablets with plant extracts [31, 32]. Quantitative factors and their levels are given in Table. 1.

Additionally, it was decided to investigate the effect of compression force and optimize the average weight of the tablets.

Taking into account the plan of the experiment, granular (powder) mass was prepared for tableting and the technological properties (flowability, Hausner ratio, bulk density, abrasion of tablets, tablets resistance to crushing, disintegration time of tablets, desirability function) of mixtures and tablets were studied [33, 34].

In cases where the total weight of excipients was less than the calculated, Avicel PH-105 was administered in addition to the composition of the mixture.

The plan and results of the study of tablets based on primula denticulata thick extract are shown in Table 2.

The obtained results of the study were analyzed and scatter plots were constructed. The difference between the mean values in the diagram was expressed in medians.

Results and Discussion

The greatest impact on the bulk density of the mass for tableting has a factor of x_1 (average weight of tablet), when increasing to 0.65 g, the bulk density increases. x_4 (quantity of colloidal anhydrous silica) and x_6 (quantity of Prosolv 90) also have a significant impact on the research indicator. Bulk density increases when studying these factors at the lower level. As the quantity of x_5 (Neusilin US 2) and x_3 (croscarmellose sodium) increases, this figure also increases.

The results of the study of the flowability (Fig. 1) showed that significantly affected this indicator x_3 (quantity of croscarmellose sodium) and x_5 (quantity of Neusilin US 2), with increasing of which the flowability improved. Also, the flowability improved when decreasing x_4 (quantity of colloidal anhydrous silica) and x_6 (quantity of Prosolv 90) in the composition of the powder mass.

Based on the scattering diagram, it was established that x_6 (quantity of Prosolv 90) had the greatest impact on the Hausner ratio with the increase of which in the composition of the tablets the value of the research indicator deteriorated. x_1 (average weight of tablets) also had a significant effect on the ratio. When studying the average mass at the upper level, the Hausner ratio improves and is 1.021.

The influence of the other three factors is manifested to the least extent – with increasing x_4 (quantity of colloidal anhydrous silica), x_5 (quantity of Neusilin US 2) the studied indicator improves and on the contrary worsens with increasing x_3 (quantity of croscarmellose sodium).

The factors x_3 (quantity of croscarmellose sodium) and x_5 (quantity of Neusilin US 2) had the greatest influence on the tablets resistance to abrasion (Fig. 2). By reducing the content of which resistance to abrasion improves in the composition of the studied tablets. Factors had a less significant effect on the tablets resistance to abrasion: x_1 (average weight of tablets), x_2 (compression pressure), x_4 (quantity of colloidal anhydrous silica). With increasing average weight, compression force and decreasing colloidal anhydrous silica content, the resistance to abrasion of the test tablets improves.

The study of tablets of primula denticulata thick extract on the resistance to crushing of tablets (Fig. 3) found that in all experimental series, the value of this indicator exceeded 100 N, which is twice the limit value according to the State Pharmacopeia of Ukraine [33].

Factors x_4 (quantity of colloidal anhydrous silica) and x_6 (quantity of Prosolv 90) had a significant effect on resistance to crushing of tablets. As the quantity of Prosolv 90 increased and the quantity of colloidal anhydrous silicon dioxide in the tablets decreased, their strength increased. The resistance to crushing of tablets also improved if the factor x_3 (quantity of croscarmellose sodium) was studied at the lower level.

Factors x_1 (average weight of tablets) and x_5 (quantity of Neusilin US 2) within the studied intervals have almost no effect on the studied indicator.

Also, a study of the impact of quantitative factors on the disintegration of tablets of primula denticulata thick extract was conducted.

As can be seen from Fig. 4, the disintegration time of tablets of primula denticulata thick extract is in the range of 2 to 5 minutes.

Analysis of the obtained results showed that with a decrease in compression force (40 kg*s/cm^2, factor x_2) and administration to the composition of tablets (up to 15%) of croscarmellose sodium (factor x_3), the disintegration time of model tablets accelerated to 2 minutes.

Factors x_1 (average weight of tablets), x_4 (quantity of colloidal anhydrous silica), x_5 (quantity of Neusilin US 2), and x_6 (quantity of Prosolv 90) have a less significant effect on the disintegration time of tablets. As the x_4 (colloidal anhydrous silica) and x_5 (Neusilin US 2) contents increased, the disintegration process improved. Conversely, with increasing x_1 (average weight of tablets) and x_6 (Prosolv 90 content), this figure deteriorated.

After analyzing the results, we can conclude that the research factors (x_1, x_2, x_3, x_4, x_5, x_6) affect the indicators in different ways. It will be advisable to

use a generalized indicator – the function of desirability. To generalize the indicators, the obtained results were translated into dimensionless quantities using the desirability function and the medians were built on their basis (Fig. 5). The influence of the studied quantitative factors on the generalized indicator was established by the magnitude and direction of medians.

It was found that factors x_1 (average weight of tablets) and x_4 (quantity of colloidal anhydrous silica) in the composition of tablets based on primula denticulata thick extract had the most significant influence on the desirability function., The values of most of the studied indicators improve as the average weight of tablets increases and the quantity of colloidal anhydrous silicon dioxide decreases.

The factor x_5 (quantity of Neusilin US 2) had also a significant impact on most indicators. When studying this factor at the lower level, most of the pharmaco-technological properties of the tablet mass and the main quality indicators of tablets are improved. Other factors have little effect on the generalized indicator.

Conclusions

Based on the method of random balance, the impact of the quantity of excipients in the composition of the tablet mass and tablets of primula denticulata thick extract on their properties was established:

- when a decrease in the average weight of tablets (factor x_1) their disintegration process and flowability improved. Given that the disintegration is a more important indicator of quality, and the value of bulk density for tableting, the resistance to crushing of tablets is satisfactory, it was decided that the optimal average weight of tablets based on primula denticulata extract was 0.6 g.

- when increasing the compression pressure (factor x_2) force to 80 kg*s/cm^2 the strength of the tablets improves (abrasion, resistance to crushing), but the disintegration time deteriorates. Since the strength of the tablets, both resistance to abrasion and resistance to crushing are within acceptable limits, it is advisable to press at a force of 40 kg*s/cm^2.

- the flowability mass for tableting and the process of disintegration of tablets improve when increasing the quantity of croscarmellose sodium (factor x_3) in the composition of tablets from 5 to 15%. The optimal quantity of this excipient in the composition of tablets based on primula denticulata thick extract leaves is 15%.

- when studying Neusilin US 2 (factor x_5) at the upper level the flowability improves the process of disintegration of tablets, the bulk density increases.

- the amount of Prosolv 90 (factor x_6) in the optimal composition of the tablets was decided to administer 1 %.

The optimal amounts of the investigated excipients in the composition of tablets based on primula denticulata thick extract were established: thick extract of *Primula denticulata* Smith. - 0.3 g, Avicel PH – 105 - 0.174 g, Croscarmellose sodium - 0.09 g, Prosolv 90 - 0.006 g, Neusilin US 2 - 0.03 g.

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Table 1. Quantitative factors and their levels, which were studied in the development of tablets based on thick extract of *Primula denticulata* Smith.

Factors	Levels of factor	
	Lower level «-»	Upper level «+»
x_1 – average weight, g	0.6	0.65
x_2 – compression pressure, kg*s/cm^2	40	80
x_3 – quantity of croscarmellose sodium, %	5	15
x_4 – quantity of colloidal anhydrous silica, %	3	5
x_5 – quantity of Neusilin US 2, %	3	5
x_6 – quantity of Prosolv 90, %	0.5	1

Table 2. Planning matrix of the experiment and the results of mass studies for tableting and tablets based on primula denticulata thick extract

No. formula	x_1	x_2	x_3	x_4	x_5	x_6	y_1	y_2	y_3	y_4	y_5	y_6	D
1	-	-	-	+	+	+	3.907	1.023	0.470	0.250	124	2	0.50
2	-	+	-	+	-	+	3.330	1.064	0.456	0.042	409	7	0.43
3	+	-	-	-	-	-	3.522	1.021	0.481	0.078	125	2	0.62
4	+	+	-	-	+	-	2.801	1.010	0.507	0.077	277	7	0.58
5	-	-	+	+	-	-	2.756	1.020	0.440	0.250	126	1	0.51
6	-	+	+	-	+	+	2.409	1.110	0.458	0.043	205	2	0.46
7	+	-	+	+	+	-	1.886	1.020	0.503	1.045	58	2	0.42
8	+	+	+	-	-	+	2.770	1.034	0.568	0.150	202	3	0.88

Notes: y_1 – flowability, g/s;
y_2 – Hausner ratio;
y_3 – bulk density, g/cm^3;
y_4 – abrasion of tablets, %;
y_5 – tablets resistance to crushing, N;
y_6 – disintegration, min;
D – desirability function.

Figure 1. Scattering diagram of the study results of the influence of quantitative factors on the flowability

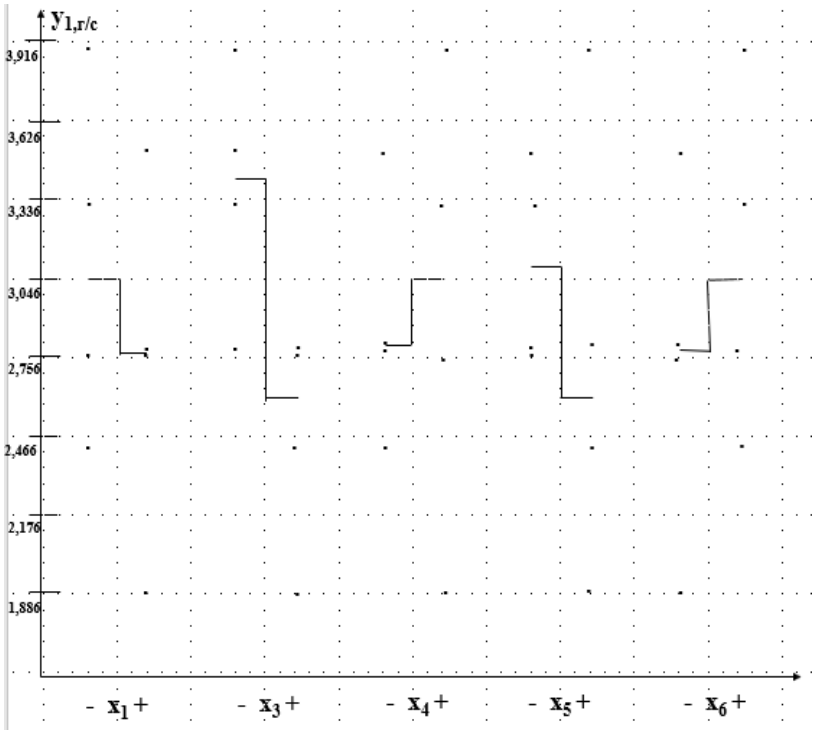

Figure 2. Scattering diagram of the study results of the influence of quantitative factors on the abrasion of tablets

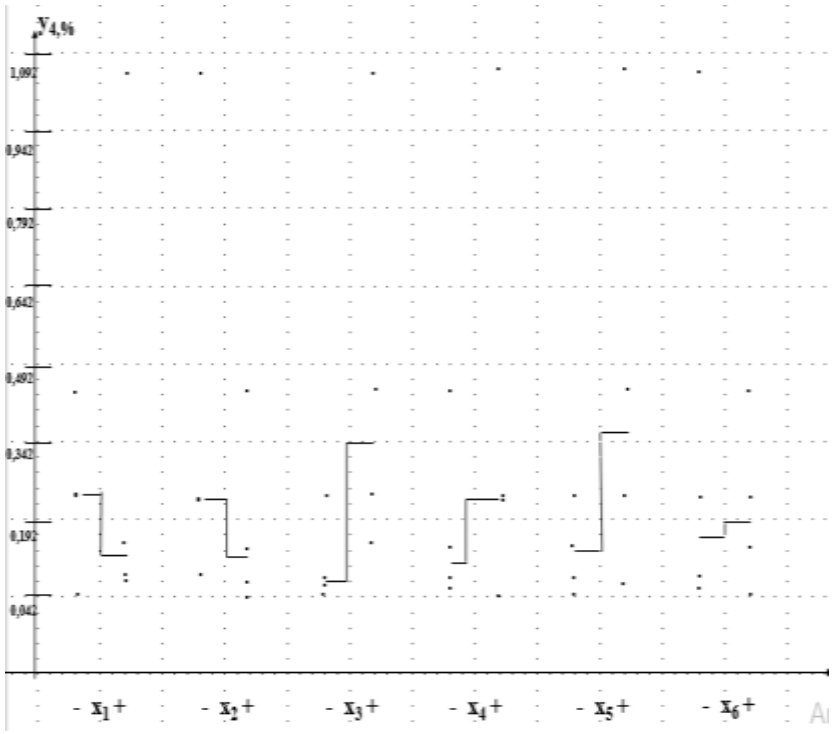

Figure 3. Scattering diagram of the study results of the influence of quantitative factors on the tablets resistance to crushing

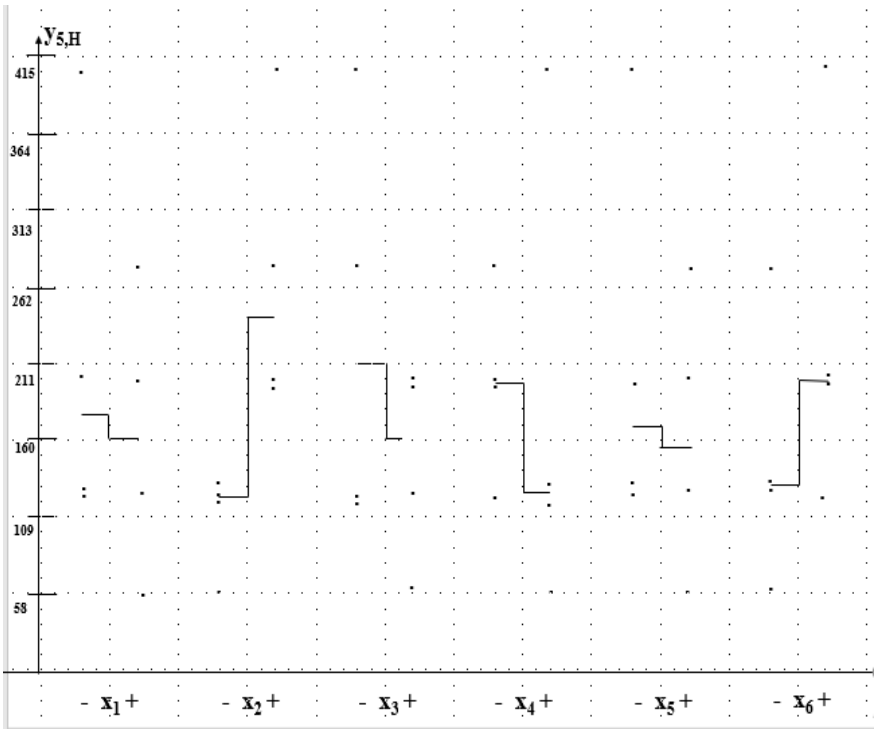

Figure 4. Scattering diagram of the study results of the influence of quantitative factors on the disintegration of tablets