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STUDY OF THE INFLUENCE OF QUALITATIVE FACTORS ON THE PHARMACO-TECHNOLOGICAL PARAMETERS OF GRANULAR MASSES WITH PLANT EXTRACT HAVING EXPECTORANT PROPERTIES

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Abstract

The aim of the work. Study of the influence of qualitative factors (excipients), such as fillers, disintegrants, sorbents, and lubricants on the pharmaco-technological performance of granular masses with plant extract having expectorant properties.

Methods. Using one of the methods of mathematical planning, namely a four-factor plan based on the Greco-Latin square, the effect of sixteen excipients on the pharmacological and technological properties of granular masses with a thick extract of *Primula denticulata* Smith. was studied. Excipients were divided into four groups of four substances each. The following indicators of granulate quality were studied: flowability, Hausner ratio, bulk density.

Results. Studies conducted using mathematical planning of the experiment showed that the flowability of granular masses depended to a large extent on the content of disintegrants. The granular mixture containing sodium croscarmellose scattered the fastest. Disintegrants also had the greatest effect on bulk density. With the use of potato starch, this figure increased. The Hausner ratio was most significantly influenced by the introduction of fillers, so the best result was obtained when using Avicel PH - 105.

Conclusions. The influence of 16 excipients on the pharmaco-technological indicators of the quality of granular masses with a thick extract of *Primula denticulata* Smith., which has expectorant properties, was established.

Keywords: granular masses, pharmaco-technological parameters, mathematical planning, extract, *Primula denticulata* Smith.

Introduction

In recent years, herbal medicines have become extremely popular in the pharmacotherapy of many diseases, despite significant advances in the development of synthetic drugs [1-4]. The appearance of synthetic drugs, which mostly simulate the biologically active substances of plants, has not reduced the role of herbal drugs [5].

According to WHO statistics, up to 80 % of the world's population prefers drugs of natural origin [6]. There is a tendency to expand the range of drugs every year in the pharmaceutical market [7, 8]. The interest in the use of medicinal plants and drugs derived from them is due to the fact that when properly dosed, they are almost low-toxic, without significant side effects, relatively affordable, effective, and in some cases due to the complex action have no competitors [9-13].

Significant resources, availability of raw materials, the possibility of cultivation make plant raw materials a promising object of study in order to develop new herbal medicines. Herbal medicines have a wide range of pharmacological action. It is possible to use them for the treatment of many diseases due to many biologically active substances with different pharmacological action contained in them [14-16]. Pharmacotherapy increasingly takes into importance the centuries-old experience of folk medicine with the application of phytopreparations [17-19].

It was previously found that the extract of *Primula denticulata* Smith. has expectorant properties. Therefore, the development of new drugs based on *Primula denticulata* Smith. is relevant.

The aim of the research was to study the effect of qualitative factors on the technological performance of granular masses with a dense extract of *Primula denticulata* Smith.

Methods

A study of the influence of excipients on the pharmaco-technological performance of granular masses with plant extract was performed at the Department of Pharmacy Management, Economics and Technology (I. Horbachevsky Ternopil National Medical University) [20-23].

The powder mass included excipients and a thick extract of *Primula denticulata* Smith. Excipients were of domestic and foreign production. According to the requirements of the State Pharmacopeia of Ukraine, they must ensure compliance with all pharmaco-technological indicators of the quality of tablets [24]. Therefore, sixteen excipients were selected for the experiment [25-32]. All of them were divided into four groups (factors) of four substances (levels) in each. The study was performed using the mathematical planning of the experiment [33, 34].

To study the influence of four factors and their levels on the pharmaco-technological properties of granular masses, 4x4 Greco-Latin square was used [35-37]. The list of excipients (factors) that were studied in the development of granules is shown in Table 1.

For obtaining granulate, the filler (factor A), disintegrant (factor B) and sorbent (factor C) were first loaded and mixed. After obtaining a homogeneous mass, moisturize with a thick extract of *Primula denticulata* Smith. was conducted. The moistened mass was granulated through a sieve with a hole diameter of 4 mm. The wet granulate was dried at a temperature of 40–50 °C. Dry granulation was performed through a sieve with a hole diameter of 1 mm. The dry granulate was dusted with a lubricant (factor D) and examined by the following parameters: flowability of the granulate, Hausner ratio and bulk density.

Flowability was determined using the fixed funnel method. The mixture (±100 g) was poured through the funnel. The time for the mixture to fall through the funnel was used to calculate flowability [24, 38].

Hausner ratio is an indirect index of the ease of the powder flow. It is calculated as the ratio of the tapped density (Dt) to the bulk density (Db). Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25) [24, 38].

Bulk density of the mixture was determined by pouring the mass into the graduated cylinder. The bulk volume (Vb) and weight of the blend (m) were also determined. The bulk density is the ratio of the total mass (m) to the bulk volume [24, 38].

The planning matrix of the experiment and the results of the study of the pharmaco-technological properties of granular masses containing a thick extract of *Primula denticulata* Smith. are shown in Table 2. The results were subjected to analysis of variance. In cases where the experimental value of the F-criterion was higher than the table, conclusions were made about the statistical significance of the studied factor and the results were discussed. In the case where the F-criterion was lower than the table, it was taken into account that there is no difference between the levels of an insignificant factor on the studied indicator [39].

Results

Analysis of variance of experimental data showed that the flowability of the granular mass (y_1) is influenced by all factors. The effect of factors on the studied of a mass quality indicator for tableting can be represented by the following ranked number of advantages: B > A > C > D.

The effect of disintegrants on the flow of the granulate is shown in Figure 1.

It was found that the best value of flow is provided by the use of sodium croscarmellose – 2.33 g/s, which has advantages over sodium starch glycolate – 2.71 g/s, sodium carboxymethyl starch – 2.77 g/s and potato starch – 3.40 g/s.

It was found that among the fillers (factor A) the granular mass, contained Avicel PH – 105, scattered the fastest, the scattering rate was 2.38 g/s. Microcrystalline cellulose 102 and microcrystalline cellulose 200 proved to be slightly worse, while the flow rate of granular mass was 2.69 g/s and 2.75 g/s, respectively, when conducting these microcrystalline cellulose samples. The worst flow was obtained using microcrystalline cellulose 101 (3.39 g/s).

The effect of lubricants on granular mass flow has the following ranked advantages: calcium stearate (2.47 g/s) > Prosolv SMCC HD 90 (2.49 g/s) > sodium lauryl sulfate (2.94 g/s) > magnesium stearate (3.32 g/s).

In studying the effect of sorbents on flowability, it was found that the best value is provided by the use of calcium silicate (2.49 g/s), which is inferior to Neusilin US 2 (2.75 g/s) and Syloid 244 FP (2.84 g/s). The worst results of mass flow for tableting were obtained with the introduction of anhydrous colloidal silica (3.14 g/s).

The influence of the studied factors on the Hausner ratio (y_2) can be represented by the following ranked number of advantages: A > D > C > B. The influence of the most significant factor A, namely fillers, is shown in Figure 2.

The best result was obtained when using Avicel PH – 105, the value of the Hausner ratio was 1.03. Slightly worse results were obtained when administered into the tableting mass microcrystalline cellulose 200 and microcrystalline cellulose 102. The worst value of the studied indicator was obtained using microcrystalline cellulose 101, the value of the Hausner ratio when introducing this brand of microcrystalline cellulose was 1.0745.

After analyzing the effect of lubricants (factor D) on the Hausner ratio, it was found that the best value of the study factor was obtained using magnesium stearate (1.032) and Prosolv SMCC HD 90 (1.034). With the introduction of calcium stearate and sodium lauryl sulfate, the Hausner ratio increased to 1.06 and 1.069, respectively.

The ranked number of benefits of the effect of factor C on the Hausner ratio is as follows: Neusilin US 2 (1.041) > anhydrous colloidal silica (1.044) > calcium silicate (1.047) > Syloid 244 FP (1.063).

It was found that among the disintegrants, the best value of the Hausner ratio is provided by the introduction into the mass for tableting potato starch (1.045) and sodium starch glycolate (1.046). The value of the study factor slightly worsened with the use of sodium croscarmellose (1.05) and sodium carboxymethyl starch (1.055).

After analyzing the results, we found that all test samples have excellent flow and meet the requirements of the State Pharmacopeia of Ukraine [40]. The obtained indicators are in the range from 1.0 to 1.11.

The ranked number of advantages reflecting the influence of qualitative factors on the bulk density of the granulate, based on a thick extract of *Primula denticulata* Smith. (y_3), is as follows: B > A > D > C.

The effect of the most significant factor B, namely disintegrants, on the bulk density of the granular mass is shown in Figure 3.

Among the investigated disintegrants, the highest value of bulk density was provided by potato starch (0.546 g/cm^3), which had an advantage over sodium carboxymethyl starch (0.522 g/cm^3), sodium starch glycolate (0.517 g/cm^3) and sodium croscarmellose (0.420 g/cm^3).

The highest value of bulk density among the fillers was found when introduced into the mass of microcrystalline cellulose 102 (0.541 g/cm^3). The lowest value of the study indicator was obtained when using Avicel PH – 105 (0.465 g/cm^3).

It was found that magnesium stearate (0.542 g/cm^3) provided the highest bulk density of granular mass among lubricants. Masses to which lubricants such as Prosolv SMCC HD 90 (0.496 g/cm^3), calcium stearate (0.485 g/cm^3) and sodium lauryl sulfate (0.484 g/cm^3) were added had a lower bulk density.

The influence of sorbents on bulk density can be represented by the following ranked number of advantages: anhydrous colloidal silica (0.530 g/cm^3) > Neusilin US 2 (0.509 g/cm^3) > Syloid 244 FP (0.498 g/cm^3) > calcium silicate (0.469 g/cm^3).

Conclusions

The conducted studies allowed determining the effect of sixteen excipients on the pharmaco-technological parameters of granular masses with a thick extract of *Primula denticulata* Smith., which has expectorant properties. Pharmaco-technological indicators of granular masses with plant extract and excipients indicate the possibility of obtaining tablets by direct compression.

References

1. Anzina K.M., Gudzenko A.V., Kalko K.O. (2021). Preliminary phytochemical screening and antioxidant activities of the extract of Teucrium chamaedrys L. PharmacologyOnLine, 2, 972-977.
2. Slobodianiuk, L., Budniak, L., Marchyshyn, S., Kostyshyn, L., Zakharchuk, O. (2021). Analysis of carbohydrates in Saponaria officinalis L. using GC/MS method. Pharmacia, 68(2), 339-345. https://doi.org/10.3897/pharmacia.68.e62691
3. Savych, A., Basaraba, R., Muzyka, N., Ilashchuk, P. (2021). Analysis of fatty acid composition content in the plant components of antidiabetic herbal mixture by GC-MS. Pharmacia, 68(2), 433–439. doi: 10.3897/pharmacia.68.e66693
4. Slobodianiuk, L., Budniak, L., Marchyshyn, S., Demydiak, O. (2021). Investigation of the anti-inflammatory effect of the dry extract from the herb of Stachys sieboldii Miq. Pharmacologyonline, 2, 590-597.
5. Slobodianiuk L, Budniak L, Marchyshyn S, Kostyshyn L, Ezhned M (2021) Determination of amino acids content of the Tagetes lucida Cav. by GC/MS. Pharmacia 68(4), 859-867. https://doi.org/10.3897/pharmacia.68.e73325
6. Lecture. Ways to create herbal medicines. Available at: https://nmapo.edu.ua/images /Novosti/30_03_20-21.pdf [Ukrainian]
7. Budniak, L., Slobodianiuk, L., Marchyshyn, S., Klepach, P. (2021). Investigation of the influence of the thick extract of common centaury (Centaurium erythraea Rafn.) herb on the secretory function of the stomach. Pharmacologyonline, 2, 352-360.
8. Djordjevic, S. (2017). From Medicinal Plant Raw Material to Herbal Remedies. https://doi.org/10.5772/66618
9. Savych, A., Marchyshyn, S., Nakonechna, S. (2021). Influence of some herbal mixtures on insulin resistance and glucose tolerance in rats. PharmacologyOnLine, 1, 356–364.
10. Budniak, L., Slobodianiuk, L., Marchyshyn, S., Parashchuk, E. (2021) Determination of carbohydrates in burnet saxifrage (Pimpinella saxifraga L.). Pharmacologyonline, 2, 1374-1382.
11. Savych, A., Marchyshyn, S., Basaraba, R., Kryskiw, L. (2021). Determination of carboxylic acids content in the herbal mixtures by HPLC. ScienceRise:

Pharmaceutical Science, 2(30), 33–39. https://doi.org/10.15587/2519-4852.2021.229132

12. Budniak, L., Slobodianiuk, L., Marchyshyn, S., Ilashchuk, P. (2021). Determination of polysaccharides in Gentiana cruciata L. herb. Pharmacologyonline, 2, 1473-1479.
13. Slobodianiuk, L., Budniak, L., Marchyshyn, S., Berdey, I., Slobodianiuk, O. (2021). Study of the hypoglycemic effect of the extract from the tubers of Stachys sieboldii Miq. Pharmacologyonline, 2, 167-178.
14. Marchyshyn, S., Polonets, O., Savych, A., Nakonechna, S. (2020). Determination of carbohydrates of Chrysanthemum morifolium L. leaves and flowers by GC-MS. Pharmakeftiki Journal, 32(4), 202-212.
15. Shostak, T.A., Kalyniuk, T.G., Hutz N.I. (2014). Aspects of pharmaceutical development of herbal medicines (Literary review). Fitoterapiya. Chasopys, 4, 77-82. [Ukrainian]
16. Feshchenko, H., Marchyshyn, S., Budniak, L., Slobodianiuk, L., Basaraba, R. (2021). Study of antibacterial and antifungal properties of the lyophilized extract of fireweed (Chamaenerion angustifolium L.) herb. Pharmacologyonline, 2, 1464-1472.
17. Budniak, L., Slobodianiuk, L., Marchyshyn, S., Basaraba, R., Banadyga, A. (2021). The antibacterial and antifungal activities of the extract of Gentiana cruciata L. herb. PharmacologyOnLine, 2, 188-197.
18. Marchyshyn, S., Slobodianiuk, L., Budniak, L., Ivasiuk, I. (2021). Hypoglycemic effect of Cyperus esculentus L. tubers extract. Pharmacologyonline, 2, 1383-1392.
19. Huzio, N., Grytsyk, A., Slobodianiuk, L. (2020). Determination of carbohydrates in Agrimonia eupatoria L. herb. ScienceRise: Pharmaceutical Science, 28(6), 35-40. https://doi.org/10.15587/2519-4852.2020.221661.
20. Budniak, L., Slobodianiuk, L., Darzuli, N., Honcharuk, Ya. (2021). The antibacterial activity of the tablets with dry extract of round-leaved wintergreen leaves. Pharmacologyonline 2, 672-679.
21. Darzuli, N., Budniak, L., Hroshovyi, T. (2019). Selected excipients in oral solid dosage form with dry extract of Pyrola rotundifolia L. International Journal of Applied Pharmaceutics, 11, 210-216. https://doi.org/10.22159/ijap.2019v11i6.35282.
22. Budniak, L., Vasenda, M., Slobodianiuk, L. (2021). Determination of flavonoids and hydroxycinnamic acids in tablets with thick extract of Primula denticulata SMITH. PharmacologyOnLine, 2, 1244-1253.
23. Kurylo, Kh., Budniak, L., Volska, A., Zablotskyy, B., Klishch, I. (2020). Influence of phytocompositions on dynamics of change in basic glycemia and glycemia in oral glucose tolerance test in rats with streptozotocin-nicotinamide-induced diabetes mellitus type 2. Georgian medical news, 300(3), 112-116.
24. State Pharmacopoeia of Ukraine. Vol. 2 (2015). Kharkiv: Derzhavne pidpriemstvo. Ukrayinskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv, 1128.
25. Ruban, O.A., Pertsev, I.M., Kutsenko, S.A., Maslii, Yu.S. (2016). Substances in the manufacture of drugs: teaching manual for students of higher education. Kharkiv: Golden Pages, 720.
26. Neusilin® US2. Pharma Excipients. Available at:https://www.pharmaexcipients.com/product/neusilin-us2/
27. Syloid® FP Silica. Pharma Excipients. Available at: https://www.pharmaexcipients.com/wp-content/uploads/attachments/M432_2-Step+Glidant+Mixing+App+Note_Final.pdf?t=1431027268
28. Anhydrous Colloidal Silica. Pharma Excipient – PharmaCentral. Available at: https://pharmacentral.com/product/anhydrous-colloidal-silica-pharmaceutical-excipient/
29. Avicel PH-105. Pharma Excipients. Available at:https://www.pharmaexcipients.com/product/avicel-ph-105/
30. Prosolv® SMCC. JRS Pharma. Available at: https://www.jrspharma.com/pharma_en/products-services/excipients/hfe/prosolv-smcc.php?gclid=Cj0KCQiA_JWOBhDRARIsA

NymNOZ_PBfvxVklJwJGJzm7p0oP5vQq7t0fjii6SevEOlJJtbwCrJug75YaAh3VEALw_wcB

31. Sodium Lauryl Sulfate. Pharma Excipient – Pharmacentral. Available at: https://pharmacentral.com/product/sodium-lauryl-sulfate-pharmaceutical-excipient/
32. Excipients - Meha Chemical. Available at: http://mehachem.com/products/excipients/
33. Hroshovyi, T.A., Martseniuk, V.P., Kucherenko, L.I., Vronska, L.V., Hureieva, S.M. (2008). Matematychne planuvannia eksperymentu pry provedenni naukovykh doslidzhen v farmatsii. Ternopil: Ukrmedknyha, 377.
34. Mathematical planning of experiment in pharmacy. Available at: https://www.pharmencyclopedia.com.ua/article/1348/matematichne-planuvannya-eksperimentu-u-farmacii [Ukrainian]
35. Graeco-Latin square designs. Available at: https://www.itl.nist.gov/div898/handbook/pri/section3/pri3322.htm
36. Latin square and related designs. Available at: https://www.itl.nist.gov/div898/handbook/pri/section3/pri3321.htm
37. Graeco-Latin square. Available at: https://handwiki.org/wiki/Graeco-Latin_square
38. Beck DC. European Pharmacopoeia. 8th ed. Strasbourg Cedex, France: European Directorate for the Quality of Medicines (EDQM). Council of Europe; 2013-2014. p. 4866.
39. Hordiienko, O. I., Hroshovyi T. A. (2019). Investigation of the influence of excipients on pharmaco-technological properties of powder masses with plant extracts and essential oil. Pharmaceutical review, 2, 36-42. https://doi.org/10.11603/2312-0967.2019.2.10248 [Ukrainian]
40. State Pharmacopoeia of Ukraine. Addition 3 (2009). Kharkiv: Derzhavne pidpriemstvo. Ukrayinskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv, 280.

Table 1. Excipients studied in the creation of tablets based on *Primula denticulata* Smith. extract

Factors	Levels of factor
A – fillers	a_1 – Avicel PH – 105 a_2 – microcrystalline cellulose 102 (MCC 102) a_3 – microcrystalline cellulose 101 (MCC 101) a_4 – microcrystalline cellulose 200 (MCC 200)
B – disintegrants	b_1 – sodium carboxymethyl starch b_2 – sodium starch glycolate b_3 – sodium croscarmellose b_4 – potato starch
C – sorbents	c_1 – calcium silicate c_2 – anhydrous colloidal silica c_3 – Neusilin US2 c_4 – Syloid 244 FP
D – lubricants	d_1 – calcium stearate d_2 – magnesium stearate d_3 – Prosolv 90 d_4 – sodium lauryl sulfate

Table 2. Four-factor experiment based on Greco-Latin square and results of mass for tableting study with extract of *Primula denticulata* Smith.

Series No.	*A*	*B*	*C*	*D*	y_1	y_2	y_3
1	a_1	b_1	c_1	d_1	1,989	1,060	0,436
2	a_1	b_2	c_2	d_4	2,651	1,026	0,492
3	a_1	b_3	c_3	d_2	2,444	1,010	0,422
4	a_1	b_4	c_4	d_3	2,442	1,029	0,508
5	a_2	b_1	c_2	d_3	2,760	1,036	0,576
6	a_2	b_2	c_1	d_2	2,538	1,029	0,572
7	a_2	b_3	c_4	d_4	2,699	1,097	0,439
8	a_2	b_4	c_3	d_1	2,801	1,031	0,576
9	a_3	b_1	c_3	d_4	3,177	1,095	0,517
10	a_3	b_2	c_4	d_1	3,073	1,098	0,486
11	a_3	b_3	c_1	d_3	2,181	1,042	0,380
12	a_3	b_4	c_2	d_2	5,137	1,063	0,614
13	a_4	b_1	c_4	d_2	3,162	1,029	0,560
14	a_4	b_2	c_3	d_3	2,581	1,029	0,519
15	a_4	b_3	c_2	d_1	2,014	1,051	0,440
16	a_4	b_4	c_1	d_4	3,238	1,056	0,486

Notes: y_1 – flowability, g/s;
y_2 – Hausner ratio;
y_3 – bulk density, g/cm^3.

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Figure 1. Influence of disintegrants on the granular mass flow

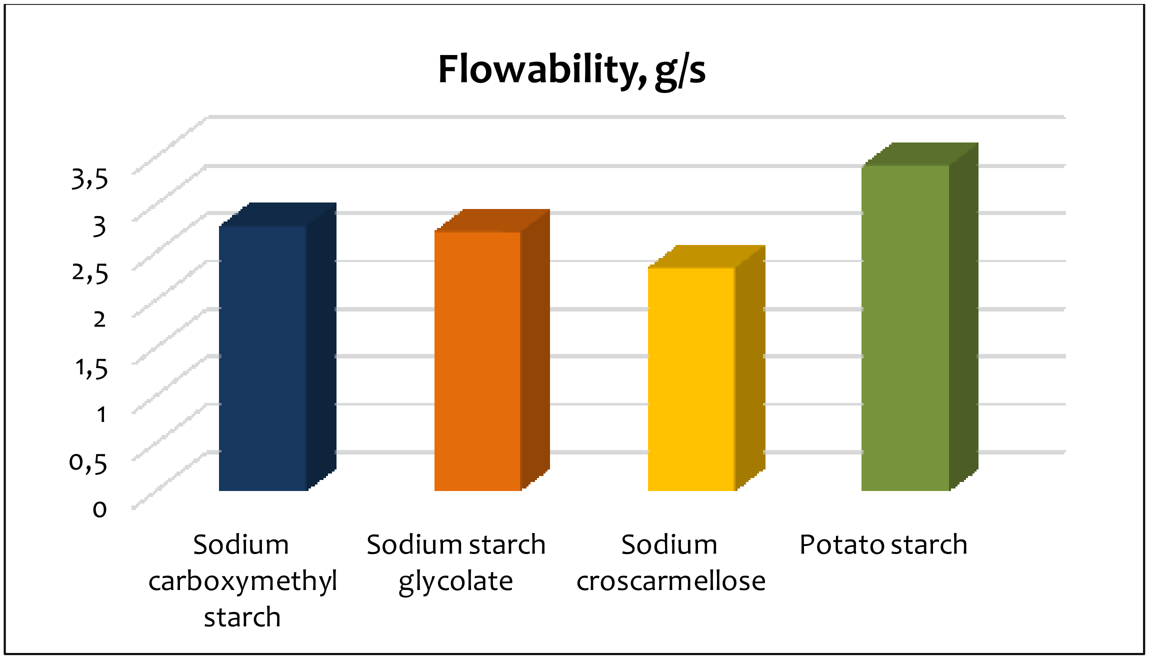

Figure 2. Influence of fillers on the Hausner ratio of granular mass

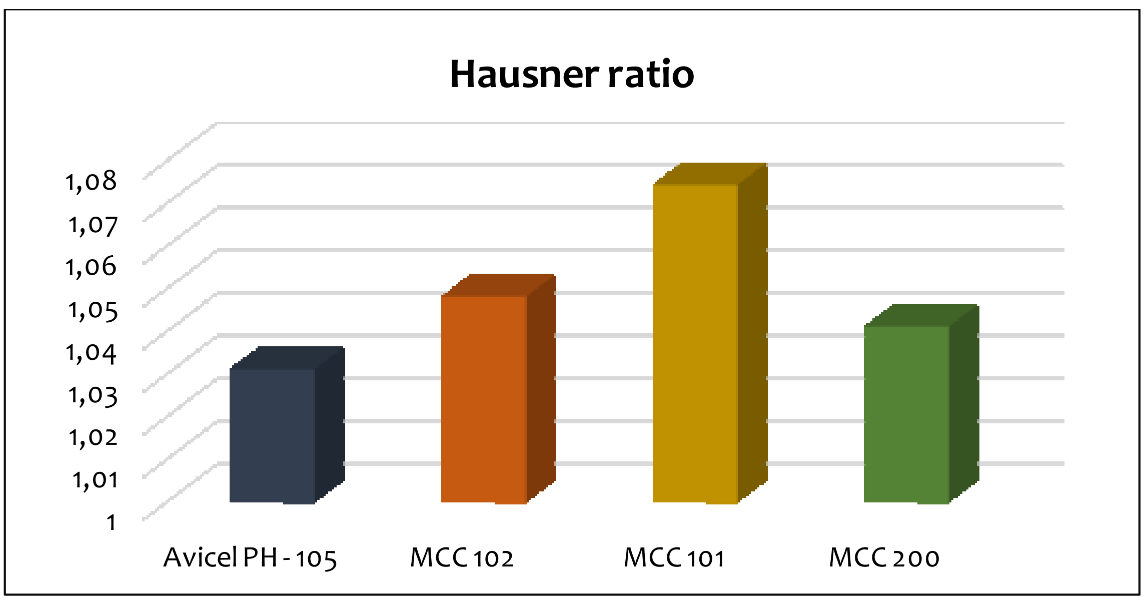

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Figure 3. The effect of disintegrants on the bulk density of granulate