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Study of the effect of excipients on the pharmacotechnological attributes of ribavirin capsules using the random balance method

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Abstract. One of the main stages in the creation of solid pharmaceutical forms is pharmaceutical development, during which the quality, efficacy, and safety of the future drug are established. The selection of biopharmaceutical factors when planning technological research is a critical task in pharmaceutical development, complicated by the need for a comprehensive consideration of all influencing factors. The aim of this work was to investigate and analyse the impact of the quantitative characteristics of excipients on the quality indicators of powder masses and hard capsules containing ribavirin. Mathematical experimental planning was applied, enabling the creation of an optimal composition by identifying the relationships between factors and technological parameters that must ensure the pharmacological action of ribavirin. The random balance method was employed to select optimal excipients for inclusion in the composition of gelatin capsules. Based on the obtained statistical data, scatter diagrams were constructed, where the median magnitude indicated the significance of the factors' influence on the corresponding quality characteristics. The study examined the effect of quantitative factors on the properties of capsule masses and hard capsules with ribavirin, manufactured using wet granulation. It was found that quantitative characteristics at both "high" and "low" levels did not demonstrate a significant effect on indicators such as "Bulk density", "Tapped density" for capsule masses, and "Disintegration" for hard capsules. The greatest influence of excipients on the Hausner ratio (flowability) for powder masses and the uniformity of the capsule content mass was exerted by binding agents such as hydroxypropyl cellulose and povidone. Increased amounts of these binders improved these characteristics. Scatter diagrams showed that the loss in mass during the drying of capsule masses significantly improved with an increased amount of microcrystalline

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cellulose and a reduced content of crospovidone. Factors affecting the "Dissolution" parameter were identified, including an increased amount of croscarmellose sodium and a reduced content of magnesium stearate and povidone

Keywords: direct-acting antiviral drugs; Design of Experiments; bulk density; Hausner ratio; capsule disintegration; capsule dissolution

Introduction

Modern pharmaceutical science is focused on improving the technology for the production of medicinal forms to enhance their pharmacotechnological properties, bioavailability, and stability. Ribavirin, as an effective agent for the treatment of chronic hepatitis C, is widely used in combination therapy regimens; however, the impact of excipients on the quality of its encapsulated forms has not been sufficiently studied. Optimising the composition and technology for the production of ribavirin capsules will improve their technological parameters, increase treatment efficacy, and reduce side effects.

The authors A.V. Volkova & A.A. Nozdrina (2020) noted that, as of 2019, the WHO (World Health Organization) reported 58 million people suffering from the chronic form of HCV (Hepatitis C Virus) HCV, which poses serious medical and social problems and is a global health threat that does not receive sufficient attention. Researcher T.L. Hrydina (2022) highlighted that one of the effective DAAs (Data Authentication Algorithm) DAAs for treating chronic HCV is ribavirin. As noted by V.I. Trykhlib (2020), ribavirin is effective in ribavirin/sofosbuvir combinations (with an Sustained virological response (SVR) rate of 91% in patients without liver cirrhosis).

N.S. Behei & O.V. Tryhubchak (2020) noted that one of the primary stages in creating solid dosage forms is pharmaceutical development, which lays the groundwork for the drug's quality, effectiveness, and safety. A. Singh & C.S. Chauhan (2022) pointed out that pharmaceutical drug development faces numerous regulatory challenges due to inconsistent product quality and the absence of certain product characteristics, leading regulatory authorities worldwide to continually compel pharmaceutical manufacturers to apply systematic tools. I.M. Fukuda *et al*. (2018) highlighted that in this regard, Design of Experiments (DoE) is considered an indispensable tool for enhancing product quality through rational planning and meaningful execution of experiments.

The random balance method is one of the screening designs most frequently used by Ukrainian researchers to study the influence of quantitative characteristics of excipients on the composition being developed. For instance, N. Behei & O. Tryhubchak (2020) investigated the influence of seven factors on amlodipine tablets with enalapril, conducting ten experiments with varying quantitative ratios of active pharmaceutical ingredients. In a study by B.V. Pavliuk *et al*. (2022), the effect of various amounts of 12 excipients on the pharmacotechnological parameters of tablets with lyophilised drone homogenate powder was examined, with 16 experimental series performed using the direct compression method. N.P. Darzuli & T.A. Hroshovyi (2018) analysed the influence of seven factors on the pharmacotechnological properties of powder masses and tablets of sharp-leaved wintergreen extract, conducting eight experiments using direct compression. In the work of M. Vasenda *et al*. (2023), the quantitative effects of six factors on the pharmacotechnological properties of tablets based on walnut septum phytosubstances were examined, with eight experimental series performed using the direct compression method. O.I. Hordiienko & T.A. Hroshovyi (2021) explored the impact of different amounts of 10 excipients on the pharmacotechnological parameters of masses for tableting and tablets containing plant extracts and essential oils, conducting 16 experiments via direct compression.

A review of the scientific literature demonstrated that when using mathematical experiment planning, the random balance method is widely employed to investigate the effects of multiple excipients on the properties of medicinal products. This approach provides a scientific basis for optimising formulations. The aim of the study was to investigate the effect of excipients and their quantity on the pharmacological and technological parameters of capsule masses and hard gelatin capsules containing ribavirin using the random balance method.

Materials and Methods

The study was conducted at Kyiv National University of Technologies and Design, Ukraine. The composition of hard gelatin capsules was developed using ribavirin samples manufactured by Jinan Mingxin Pharmaceutical Co., Ltd., China. The following excipients were used: microcrystalline cellulose (MCC), type 101 (Comprecel® M101D +), polyvinylpolypyrrolidone (PVPP, Kollidon® CL), croscarmellose sodium (Solutab® A), povidone (PVP, Plasdone™ K29/32), hydroxypropyl cellulose (HPC, type L), colloidal anhydrous silica (Aerosil® 200), and magnesium stearate (type LIGAMED MF-2-V). MCC 200 was used as a compensator.

To determine the significance of the quantitative factors, scatter diagrams were constructed, where the x-axis represents the influencing factor and the y-axis represents the evaluation response variable (Revyatskyy & Barchuk, 2019). Each evaluated attribute was visually represented in separate charts as scatter plots based on statistical data processing. The median value visually indicated the dominance of one factor over another, i.e., the significance of the quantitative characteristics of excipients in relation to the critical attributes of ribavirin formulations. The median orientation indicated the direction of this effect.

Physicochemical and pharmacotechnological attributes of the capsule mass and the finished dosage form were

investigated in accordance with the methodology of the State Pharmacopoeia of Ukraine (2015). Hard capsules containing the active pharmaceutical ingredient (API) ribavirin were produced using wet granulation with high-shear mechanical processing (Dipy & Wildfong, 2017). The effect of the quantitative attributes of excipients was investigated. These attributes (excipient quantities) were examined at "low" (–) and "high" (+) levels (Table 1).

***Table 1**. Quantitative factors and their levels studied in the development of hard gelatin capsules with ribavirin*

Factor	Factor levels	
	"Low" (–)	"High" (+)
x_1 – quantity of MCC (Comprecel® M101D+), mg	69.0	74.0
x_2 – quantity of Crospovidone (Kollidon® CL), mg	3.0	6.0
x_3 – quantity of Croscarmellose sodium (Solutab® A), mg	3.0	6.0
x_4 – quantity of Povidone (PlasdoneTM K29/32), mg	3.5	7.0
x_5 – quantity of Hydroxypropyl cellulose (HPC, type L), mg	3.0	6.0
x_6 – quantity of Silica, colloidal anhydrous (Aerosil® 200), mg	1.0	2.0
x_7 – quantity of Magnesium stearate (type LIGAMED MF-2-V), mg	1.5	3.0

***Source:** developed by the authors based on their own research*

The influence of excipients was determined by constructing scatter plots based on the data of pharmacotechnological parameters of the capsule mass and hard gelatin capsules. The random balance method enabled the selection of certain excipients in optimal amounts and the exclusion of those that did not fully meet the pharmacotechnological quality attributes of the capsules (Darzuli & Hroshovyi, 2018). This approach allowed for a reduction in the number of test series.

Results and Discussion

To obtain hard gelatin capsules of ribavirin, the attributes of 25 excipients were preliminarily studied. Based on the results, excipients with the most significant effect on the pharmacotechnological quality attributes of capsules were selected (Shah & Shahzad, 2015). The optimal quality parameters for the capsule mass based on ribavirin as follows: "Bulk density before and after tapping" – 0.57-0.62 g/ml and 0.62-0.70 g/ml, respectively; "Hausner ratio" – 1.12-1.15 (good flowability); "Loss on drying" – 2-3%. The optimal quality parameters for hard gelatin capsules containing the active pharmaceutical ingredient ribavirin are: "Uniformity of capsule content mass" – ± 5.0%; "Disintegration" – no more than 15 minutes; "Dissolution" – at least 85 % of the active substance must dissolve within 15 minutes.

Eight batches were prepared, differing in the quantitative composition ratios of excipients. To achieve a capsule content mass of 300 mg, MCC 200 was used as a compensator during the mixing and powdering operations. It acted as an independent quantitative factor without significant effect on the studied characteristics. The produced powder masses and capsules were analysed for pharmacotechnological attributes in accordance with the requirements of the State Pharmacopoeia of Ukraine (2015). The experimental design and analysis results are presented in Table 2.

***Table 2**.Experimental design and results of studies on hard gelatin capsules with ribavirin*

Batch	x_1	x_2	x_3	x_4	x_5	x_6	x_7	y_1	y_2	y_3	y_4	y_5	y_6	y_7
1	–	+	–	–	+	–	+	0.589	0.689	1.17	3.0	4.6	93	92.8
2	–	+	+	+	+	–	+	0.568	0.647	1.14	3.7	3.6	95	93.2
3	–	+	+	–	–	–	–	0.549	0.659	1.20	4.1	5.2	91	99.6
4	+	–	+	–	–	+	–	0.612	0.704	1.15	2.7	4.2	100	98.5
5	+	–	–	+	–	–	–	0.550	0.655	1.19	2.4	5.0	99	83.7
6	–	+	–	–	–	+	+	0.531	0.627	1.18	3.1	4.8	102	91.1
7	+	–	+	+	+	+	–	0.563	0.636	1.13	2.5	3.3	104	96.0
8	+	–	–	+	+	+	+	0.573	0.653	1.14	2.2	3.5	92	86.4

***Note:** y_1 – Bulk density, g/mL; y_2 – Tapped density, g/mL; y_3 – Hausner ratio (flowability); y_4 – Loss on drying, %; y_5 – Uniformity of capsule content mass, ± %; y_6 – Disintegration time, s; y_7 – Dissolution, % in 15 minutes*
***Source:** developed by the authors' based on their own research*

The results of experimental studies of eight experiments on pharmacotechnological indicators, shown in Table 2, demonstrated the following values: bulk density ranges from 0.531 g/ml to 0.612 g/ml (the best results were obtained in experiments No. 1, No. 4 and No. 8); bulk density after shrinkage – from 0.627 g/ml to 0.704 g/ml (the best results were experiments No. 1, No. 3 and No. 4); Hausner coefficient (characterising the fluidity of the mass for encapsulation) – from 1.13 to 1.20 (the best results were experiments No. 2, No. 7 and No. 8); mass loss during drying – from 2.2% to 4.1% (the best results were experiments No. 5, No. 7 and No. 8); mass uniformity of the capsule contents – from ± 3.3% to 5.2% (the best results were experiments No. 2, No. 7 and No. 8); disintegration – from 91 s to

104 s, which is not a significant difference in the results, making it difficult to single out the best experiments; dissolution – from 83.7% to 99.6% (the best results are experiments No. 3, No. 4 and No. 7). If the experiments are analysed by all indicators together, then experiments No. 4 and No. 7 showed the most optimal results. The effect of quantitative factors on the "Bulk density" attribute (y_1) is shown in the scatter diagram in Figure 1.

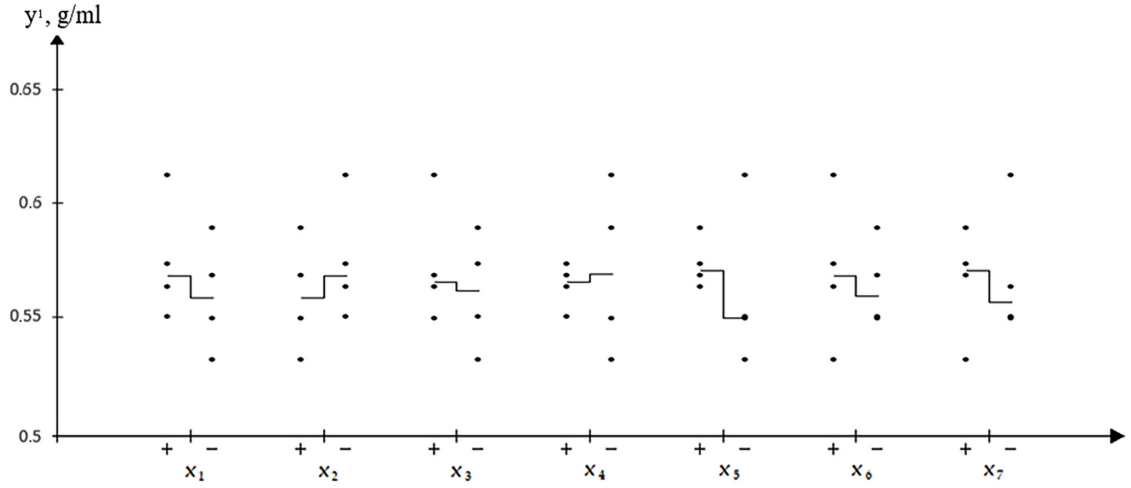

***Figure 1**. Effect of quantitative factors on "Bulk Density" of ribavirin capsule mass*
***Source:** developed by the authors' based on their own research*

The bulk density of the encapsulation mass, determined using the graduated cylinder pouring method, characterises fluidity and flowability and should ensure uniform dosing on the capsule filling machine. Based on the analysis of the scatter diagram of bulk density results, were determined that the binding agent HPC-L (x_5) had a minor effect, while the effects of other excipients were negligible and could be disregarded. When examining the effect of quantitative factors on the "Tapped density" attribute (y_2), the results are presented in the scatter diagram in Figure 2.

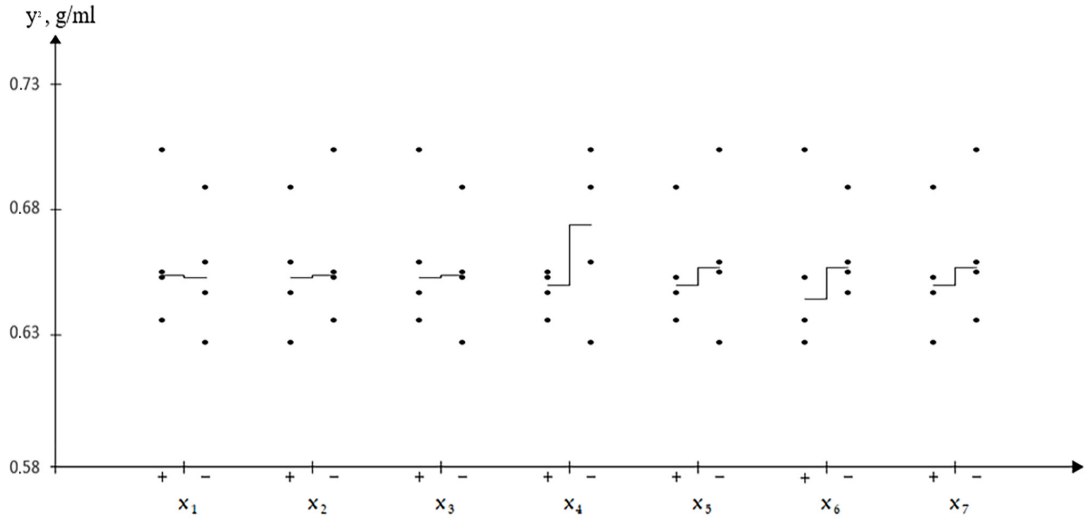

***Figure 2**. Effect of quantitative factors on "Tapped Density" of ribavirin capsule mass*
***Source:** developed by the authors' based on their own research*

Tapped Density is used to calculate the Hausner Ratio that for capsule filling. The results indicated that the binding agent Plasdone™ K29/32 (x_4) and the glidant Aerosil® 200 (x_6) had a minimal effect on this attribute. Other factors did not affect "Tapped density" at all. The scatter diagram in Figure 3 demonstrated that the Hausner Ratio (flowability)(y_3) of ribavirin capsule masses was significantly affected by HPC-L (x_5), with a slightly lower effect from PlasdoneTM K29/32 (x_4). Quantitative characteristics of the following excipients also showed a significant effect: Comprecel® M101D + (x_1), Kollidon® CL (x_2), Solutab® A (x_3), and Aerosil® 200 (x_6). The lubricant magnesium stearate (MF-2-V) (x_7) exhibited a negligible effect.

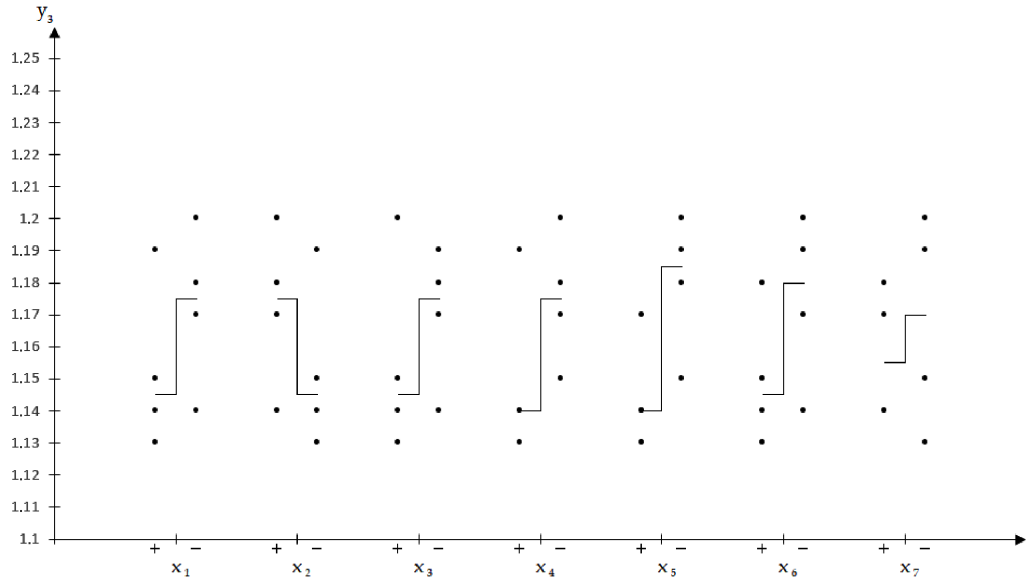

***Figure 3**. Effect of Quantitative Factors on "Hausner Ratio" (flowability) of Ribavirin Capsule Mass*
***Source:** developed by the authors' based on their own research*

Based on the statistical data and median directions, the following results were obtained: increasing the amounts of Comprecel® M101D + (x_1), Solutab® A (x_3), PlasdoneTM K29/32 (x_4), HPC-L (x_5), Aerosil® 200 (x_6) and magnesium stearate (MF-2-V) (x_7) decreased the Hausner Ratio (y_3), improving the flowability of powder masses containing ribavirin; increasing the disintegrant Kollidon® CL (x_2) increased the Hausner Ratio (y_3), reducing the flowability of capsule masses.

The scatter plot data in Figure 4 demonstrated that the "Loss on Drying" attribute (y_4) of the mass for encapsulation is significantly affected by the factors Comprecel® M101D + (x_1) and Kollidon® CL (x_2). Less pronounced effects are observed from Solutab® A (x_3), PlasdoneTM K29/32 (x_4), Aerosil® 200 (x_6), and magnesium stearate (MF-2-V) (x_7). The quantitative factor HPC-L (x_5) has almost no effect on the studied attribute y_4.

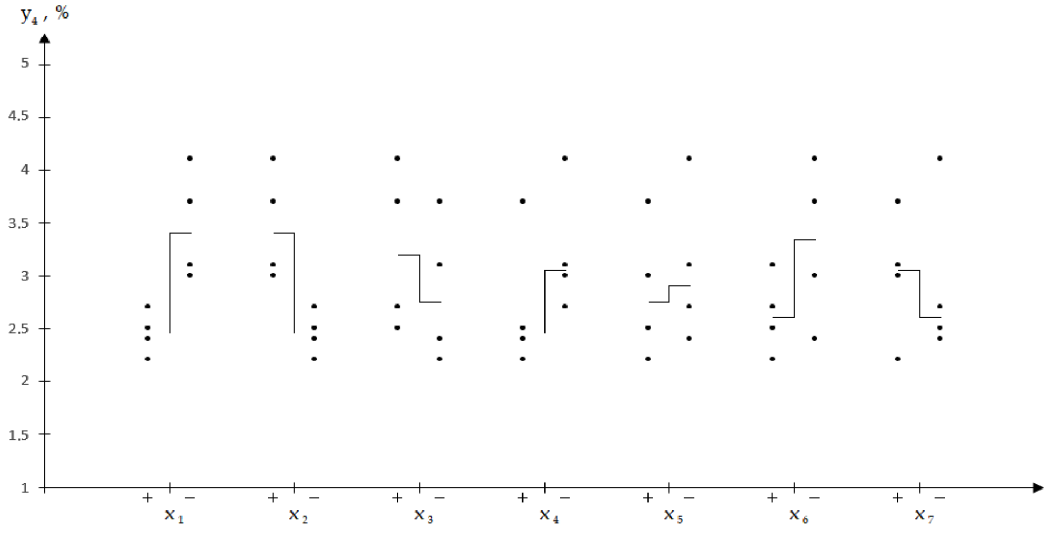

***Figure 4**. Effect of quantitative factors on "Loss on Drying" of ribavirin capsule mass*
***Source:** developed by the authors based on their own research*

Based on the statistical data and the positioning of the medians: increasing the amounts of factors x_2, x_3 and x_7 increased the "Loss on Drying" attribute (y_4), which raised the moisture content in the powder masses containing ribavirin; increasing the amounts of factors x_1, x_4, x_5, and x_6 decreased the "Loss on Drying" attribute (y_4), reducing the moisture content in the capsule masses. Granules were dried to a moisture content within the range of 1.8-2.0%. A moisture content of more than 3.0% in the capsule mass led to material "sticking" in the capsule-filling machine hopper and partial powder adherence to the hopper walls. Therefore, the optimal "Loss on Drying" attribute (y_4)

for capsule masses should range between 2.0% and 3.0%. Based on these data, it is better to avoid combining disintegrants (Kollidon® CL and Solutab® A) and to use smaller amounts of one disintegrant. Additionally, higher quantities of the diluent Comprecel® M101D+, the binder Plasdone™ K29/32, and the glidant Aerosil® 200 should be used.

The effect of quantitative factors on the "Uniformity of Capsule Content Mass" attribute (y_5) is shown in the scatter diagram in Figure 5. According to the requirements of the State Pharmacopoeia of Ukraine, for a capsule content mass of 300 mg with ribavirin, deviation of this attribute should be within ± 7.5%.

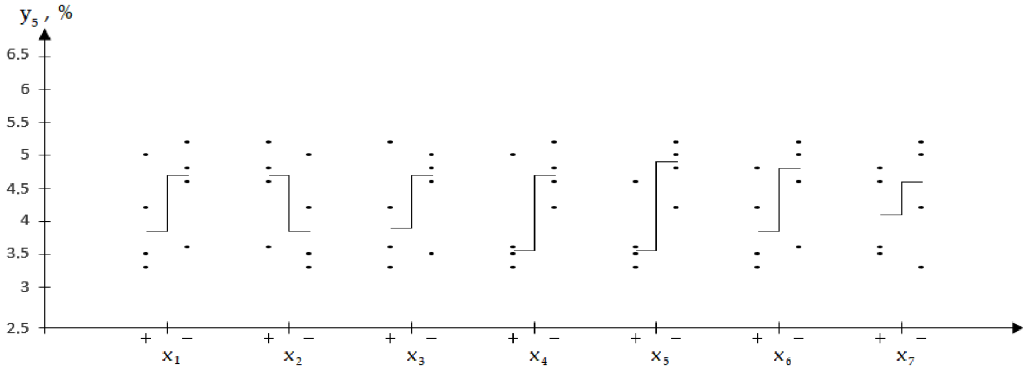

***Figure 5**. Effect of quantitative factors on "Uniformity of Capsule Content Mass" with API ribavirin*
***Source:** developed by the authors based on their own research*

When studying the effect of quantitative factors on the y_5 factor, it was found that the binding agents PlasdoneTM K29/32 (x_4) and HPC-L (x_5) had the greatest effect. Significant but slightly lesser effects were observed for the following excipients: Comprecel® M101D+ (x_1), Kollidon® CL (x_2), Solutab® A (x_3), and Aerosil® 200 (x_6). The lubricant magnesium stearate (MF-2-V) (x_7) had an insignificant effect on the uniformity of capsule content mass with ribavirin.

Based on the statistical data and the orientation of medians, the following results were obtained: increasing the amounts of Comprecel® M101D+ (x_1), Solutab® A (x_3), PlasdoneTM K29/32 (x_4), HPC-L (x_5), Aerosil® 200 (x_6) and magnesium stearate (MF-2-V) (x_7) reduced the deviations between the minimum and maximum values of capsule content mass, thus improving the "Uniformity of Capsule Content Mass" (y_5) attribute for ribavirin. Conversely increasing the disintegrant Kollidon® CL (x_2) increased the deviations between the minimum and maximum values of capsule content mass, thereby deteriorating the "Uniformity of Capsule Content Mass" (y_5).

To reduce deviations, i.e., improve the uniformity of capsule content mass, enhancing the flowability of the capsule mass is necessary. Based on the above data, this can be achieved by increasing the quantities of binding agents (x_4 or x_5), diluent (x_1), and glidants (x_6). Based on the research results none of the selected factors significantly affected the "Disintegration" attribute (y_6), as this attribute depends not on the quantitative characteristics of excipients but on the rate at which the hard gelatin capsule shell breaks down to release its contents.

The graphical data from the scatter diagram in Figure 6 showed that the "Dissolution" attribute (y_7) of hard ribavirin capsules is significantly affected by the disintegrant Solutab® A (x_3). A lesser, but still notable, effect is exerted by Plasdone™ K29/32 (x_4) and the lubricant magnesium stearate (MF-2-V) (x_7). Insignificant effects were observed for the excipients Comprecel® M101D+ (x_1), Kollidon® CL (x_2), and HPC-L (x_5), while the quantitative factor Aerosil® 200 (x_6) had almost no effect on the "Dissolution" attribute (y_7).

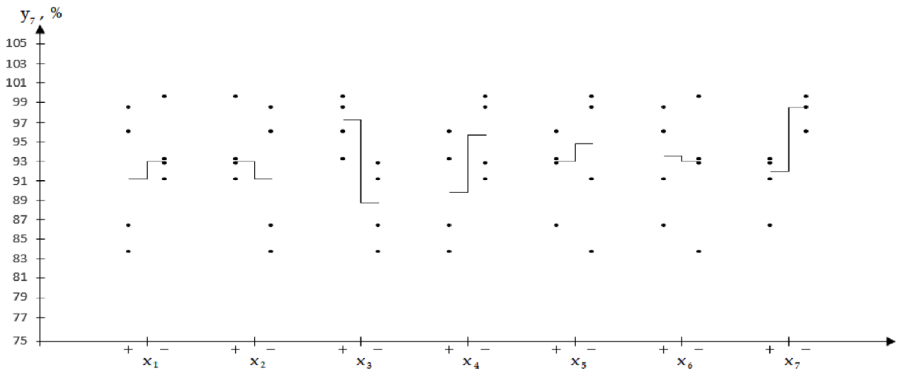

***Figure 6**. Effect of quantitative factors on "Dissolution" of hard capsules with API ribavirin*
***Source:** developed by the authors based on their own research*

Based on statistical data and the positioning of medians: increasing the amounts of x_2, x_3, and x_6 enhanced the "Dissolution" attribute (y_7), accelerating the release of the active substance from the dosage form; Conversely increasing the amounts of x_1, x_4, x_5, and x_7 reduced the "Dissolution" attribute (y_7), slowing down the release of the active substance. V. Loustaud-Ratti *et al*. (2016) highlighted that adding peginterferon to this combination resulted in an SVR rate ranging from 86% to 91% in patients with liver cirrhosis, etc. Ribavirin is primarily used in solid oral dosage forms, including Rebetol®, hard capsules of 200 mg; Ribasphere®, hard capsules of 200 mg, 400 mg, and 600 mg; Copegus®, film-coated tablets of 200 mg, and others.

As noted by R. Samineni *et al.* (2022) ribavirin belongs to Class I of the Biopharmaceutical Classification System (BCS), meaning it refers to highly soluble substances with a high degree of permeability. G.F. Plöger *et al*. (2018) noted that, according to the State Pharmacopoeia of Ukraine, at least 85% of the API must be released within 15 minutes. Researchers O.O. Salii *et al*. (2010) studied that to achieve the best results for the "Dissolution" attribute of hard ribavirin capsules, higher amounts of the disintegrant (x_3) should be used while reducing the quantities of the binding agent (x_4) and the lubricant (x_7), ensuring no significant adverse effects on the "Hausner Ratio" (flowability), "Loss on Drying", or "Uniformity of Capsule Content Mass" attributes. Authors H. Pham-The *et al.* (2013) highlighted that the main difficulty in applying the random balance method lies in the fact that experiments must be planned so that the sum of all components does not exceed 100%.

Author O.I. Hordiienko & T.A. Hroshovyi (2021) demonstrated the best way to select the number of studied factors according to the formula N-1, where N is the number of experiments, in order to study the influence of a larger number of factors with the fewest possible number of experiments. Researchers selected critical quality indicators for tablets as the main feedback: loss on drying, flowability, angle of repose, bulk density, tapped density, stability, abrasion, disintegration, etc. In this work, in addition to the pharmacotechnological parameters adapted for hard gelatin capsules, there is a difference in the choice of indicator for evaluating flowability, namely, the "Hausner ratio" was preferred, as the authors believe it best illustrates the flowability of the capsule mass (good, satisfactory, etc.).

Scientific publications provide data on the use of DoE design by authors L.A. Fukleva *et al.* (2024) for studying the most commonly used types of mathematical planning of the experiment, and selecting the most appropriate model for developing the optimal composition of a vaginal ointment. Authors O.A. Ruban *et al.* (2018) identified key features and capabilities application of experimental design method in optimisation of composition and technology for matrix tablets containing *Vaccinium myrtillus* leaf dry extract. The random balance method has been applied by M. Demchuk *et al*. (2019) to study the effect of excipient quantities on the technological attributes of metformin orodispersible tablets. The random balance method has been used by S. Chernetska *et al.* (2021) to develop formulations and investigate the effect of excipient quantities on the technological attributes of dry extract-based mixtures and tablets derived from *Origanum vulgare* L. herb. The method was employed by O. Panysheva (2022) to study the effects of 27 excipients from five functional groups and to create of powder technology for oral solutions in sachets.

According to A.S. Deyneka & I.O. Zhuravel (2022), DoE enables a reduction in the number of scientific studies, streamlining, optimising, and intensifying research while minimising errors and delivering highly reliable and scientifically validated results at minimal cost. The authors B. Kovács *et al*. (2021) noted that DoE is a core component of the statistical toolkit for implementing the systematic "Quality by Design" (QbD) approach in both research and industrial settings, allowing for continuous improvement throughout the entire lifecycle of a drug. Researchers S. Beg *et al*. (2019) studied the trend since the late 20th century, with numerous DoE methods having been developed for application in pharmaceutical research. T. Waghule *et al*. (2021) noted that experimental designs can be classified as screening designs, while S. Beg (2021) highlighted optimisation designs.

In scientific articles authors M. Vasenda *et al.* (2023) highlighted that the direct compression method is used for tablet manufacturing, which allows for a better study of the impact of quantitative factors on the pharmacotechnological properties of powder masses. In this work, the wet granulation method was used, which differs from the sources mentioned above. This technology did not fully allow the analysis of the impact of quantitative factors on the indicators "Bulk density and tapped density" of capsule mass, as almost all excipients had a negligible effect, which was difficult to evaluate.

It should also be noted that in some scientific publications the desirability function (D) is used for the general evaluation of results for each experiment. This indicator is not mandatory when using the random balance method, but it facilitates the evaluation of results when the overall impact of factors in a given experiment on all the studied quality indicators needs to be assessed, rather than each separately. Scientific publications authors B.V. Pavliuk *et al.* (2022) provide data on the following compensators are used: sucrose, MCC 102, MCC 200, etc. Also, the number of experiments must be a multiple of 4, which is due to the peculiarity of constructing scatter diagrams. But the desirability function was not used in their scientific articles.

The obtained results indicate that the use of the random balance method allows for the effective optimisation of the composition of hard gelatin capsules with ribavirin. Comparison with the works of other authors confirmed the significance of selecting the quantitative characteristics of excipients to ensure pharmacotechnological parameters. Thus, the obtained results can serve as the basis for further research in the development of antiviral drugs with direct activity and other active pharmaceutical ingredients.

Conclusions

The use of the random balance method made it possible to determine the most significant quantitative factors and stabilise them at optimal levels in the composition of the developed ribavirin capsules. Based on statistical data and the magnitude of medians in the scatter diagrams, it was established that quantitative factors at "high" and "low" levels did not significantly affect the following attributes: "Bulk Density", "Tapped Density", "Disintegration". Thus, for selecting more significant excipients, the focus was placed on the following attributes: "Hausner Ratio", "Loss on Drying", "Uniformity of Capsule Content Mass", "Dissolution".

For the optimal formulation of the drug containing ribavirin as the active pharmaceutical ingredient (API), which ensures appropriate pharmacotherapeutic attributes, the following factors and their levels were selected, the following excipients were used: microcrystalline cellulose (Comprecel® M101D +) as a compensator; sodium croscarmellose (Solutab® A) at 6 mg per capsule; povidone (PlasdoneTM K29/32) at 7 mg; colloidal anhydrous silica (Aerosil® 200) at 2 mg; magnesium stearate (LIGAMED MF-2-V) at 1.5 mg.

The random balance method in experimental studies allowed for the scientific justification of the selection of quantitative ratios of excipients in the development of solid capsule formulations and achieving target parameters of the drug profile with ribavirin according to the "Disintegration" and "Dissolution" tests. Therefore, determining the most significant quantitative influencing factors at the pharmaceutical development stage enables the identification of the most critical functional excipients, which will affect the drug release profiles, especially in the case of poorly soluble substances.

The randomisation method has numerous advantages, as it prevents random bias in the experiment and ensures that comparable groups are created across all factors. Further research could be aimed at improving randomisation strategies to optimise the design of randomised clinical trials of medicines. Of particular interest is the application of this approach in small and medium-sized clinical trials ($n < 100$), where the use of randomisation helps to achieve a balance in treatment. This can provide more reliable and valid trial results, which, in turn, will increase the efficiency of the development and evaluation of new medicines.

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Conflict of Interest

None.

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Дослідження впливу допоміжних речовин на фармако-технологічні параметри капсул з рибавірином методом випадкового балансу

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Анотація. Одним із основних етапів створення твердих лікарських форм є фармацевтична розробка, коли закладаються якість, ефективність та безпека майбутнього препарату. Вибір біофармацевтичних факторів у плануванні технологічних досліджень є важливим завданням фармацевтичної розробки, що ускладнюється необхідністю комплексного врахування усіх факторів. Метою роботи було дослідження та аналіз впливу кількісних характеристик допоміжних речовин на показники якості порошкових мас та капсул твердих з рибавірином. Застосовано математичне планування експерименту, що дозволило створити оптимальнй склад шляхом встановлення взаємозв'язків впливу факторів на технологічні параметри, які мають забезпечувати фармакологічну дію рибавірину. У дослідженнях використано метод випадкового балансу для відбору оптимальних допоміжних речовин для включення у склад желатинових капсул. На основі отриманих статистичних даних побудувано діаграми розсіювання, де величина медіани показувала значущість впливу досліджуваних факторів на відповідну характеристику якості. Вивчено вплив кількісних факторів на властивості мас для капсулювання і твердих капсул з рибавірином, виготовлених методом вологої грануляції. Виявлено, що кількісні характеристики на вищих та нижніх рівнях не показують істотної сили дії на показники: «Насипна густина», «Насипна густина після усадки» для капсульних мас та «Розпадання» для капсул твердих. Найбільший вплив допоміжних речовин на коефіцієнт Гауснера для порошкових мас та однорідність маси вмісту капсул здійснювали зв'язуючі речовини, такі як гідроксипропілцелюлоза і повідон. З діаграми розсіювання виявлено, що найбільший вплив на поліпшення втрат у масі при висушуванні маси для капсулювання мали збільшена кількість мікрокристалічної целюлози та зменшений вміст кросповідону. Визначено фактори, що впливають на показник «Розчинення»: збільшення кількості натрію кроскармелози та зменшення вмісту магнію стеарату та повідону

Ключові слова: противірусні препарати прямої дії; математичне планування експерименту; насипна густина; коефіцієнт Гауснера; розпадання капсул; розчинення капсул