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DETERMINATION OF PROCESS PARAMETERS OF FLAVONOIDS EXTRACTION FROM BOGBEAN (MENYANTHES TRIFOLIATA L.) USING APPROACHES OF QUALITY BY DESIGN

Actuality. *Quality by Design (QbD) is a quality system for managing the product life cycle based on an enhanced systematic approach to its development. Identification of the design space parameters has great importance in pharmaceutical development as a key element of QbD implementation. The advantage of this approach is that conducting the process within the design space parameters allows to guarantee compliance with the product quality with the established requirements and is not considered by authorities as a change in process. Given the wide spectrum of pharmacological action of polyphenols, studying the conditions of extraction of this class of compounds from the bogbean raw material (Menyanthes trifoliata L.) is an actual direction. The implementation of QbD approaches will allow a systematic approach to the development of the process and to determine its optimal parameters.*

The aim of research. To determine the extraction process parameters of flavonoids from bogbean leaves and to investigate their impact on critical quality attributes. To establish the design space as a key element of QbD.

Material and methods. *The object of the study was powdered bogbean leaves (Menyanthes trifoliata L.). The raw material was extracted by filtration method using 40 and 70% ethanol as extractants. The dry residue, the yield of extractable matter, the quantitative content and the yield of total flavonoids were determined in the extract samples. The critical quality attributes were the content of the dry residue ωn in the liquid extract samples and the yield of total flavonoids Ln from the extracted raw material. The establishment of the design space was carried out by superimposing the spaces of the dry residue and the yield of flavonoids.*

Research results. *Based on experimental data the dependence of critical quality attributes on the variability of the extractant concentration and the drug extract ratio (DER) was established. According to experimental data and based on criteria for the acceptability of critical quality attributes the points were calculated for graphing the spaces of dry residue and flavonoid yield. The design space obtained by superimposing the spaces of dry residue and flavonoids yield allowed us to identify the optimal process parameters of bogbean leaves extraction under which the product meets the established quality criteria.*

Conclusion. *It has been determined that the critical quality attributes are the dry residue content in liquid extracts not less than 1% and the yield of total flavonoids not less than 0,74%. According to the design space, it has been established that the optimal process parameters for which the product meets the criteria of critical quality attributes are extraction with ethanol in the range of concentrations of 40–58% and DER of 1:4.7–7.4. Studies have proven that the usage of QbD approaches to determining extraction process parameters is an important tool within the API development phase.*

Key words: *extraction, extraction solvent, technology, technological process, preparation, polyphenols, flavonoids, extractable matters, herbal substance, design space.*

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ВИЗНАЧЕННЯ ПАРАМЕТРІВ ПРОЦЕСУ ЕКСТРАКЦІЇ ФЛАВОНОЇДІВ БОБІВНИКА ТРИЛИСТОГО (*MENYANTHES TRIFOLIATA* L.) ІЗ ЗАСТОСУВАННЯМ ПІДХОДІВ QUALITY BY DESIGN

Актуальність. *Quality by Design (QbD) – система якості з управління життєвим циклом продукту, в основі якої лежить поглиблений системний підхід до його розробки. Ідентифікація простору проєктних параметрів має велике значення у фармацевтичній розробці, адже є ключовим елементом реалізації QbD. Перевагою даного підходу є те, що ведення процесу в межах простору проєктних параметрів дозволяє гарантувати відповідність якості продукту встановленим вимогам та не розглядається регуляторними органами як зміна процесу. Зважаючи на широкий спектр фармакологічної дії поліфенолів, вивчення умов екстрагування даного класу сполук із сировини бобівника (Menyanthes trifoliata L.) є актуальним напрямом. Застосування підходів QbD дозволить системно підійти до розроблення процесу, визначити його оптимальні параметри.*

Мета дослідження. *Визначити параметри процесу екстракції флавоноїдів з листя бобівника трилистого, дослідити їхній вплив на критичні показники якості. Встановити простір проєктних параметрів як ключового елементу QbD.*

Матеріал і методи. *Об'єктом для дослідження було подрібнене листя бобівника трилистого (Menyanthes trifoliata L.). Сировину екстрагували фільтраційним методом з використанням 40 та 70% етанолу як екстрагентів. У зразках екстрактів визначали сухий залишок, вихід екстрактивних речовин, кількісний вміст та вихід суми флавоноїдів. Критичними показниками якості було визначено вміст сухого залишку ω_n у зразках рідких екстрактів, вихід суми флавоноїдів L_n із рослинної сировини. Побудову простору проєктних параметрів здійснювали шляхом накладання просторів сухого залишку та виходу флавоноїдів.*

Результати дослідження. *На основі даних експерименту було встановлено залежність критичних показників якості від варіабельності концентрації екстрагента та співвідношення сировина : екстракт. Виходячи з експериментальних даних і відповідно до критеріїв прийнятності критичних показників якості, було розраховано точки для побудови просторів сухого залишку та виходу флавоноїдів. Простір проєктних параметрів, отриманий унаслідок накладання просторів сухого залишку й виходу флавоноїдів, дозволив ідентифікувати оптимальні параметри процесу екстракції сировини листя бобівника, за яких продукт відповідає встановленим критеріям якості.*

Висновок. *Визначено, що критичними показниками якості є вміст сухого залишку в рідких екстрактах не менше ніж 1% і вихід суми флавоноїдів не менше ніж 0,74%. Згідно із простором проєктних параметрів встановлено, що оптимальними параметрами процесу екстракції листя бобівника, за яких продукт відповідає встановленим критичним показникам якості, є екстрагування етанолом у межах концентрацій 40–58% та співвідношення сировина : екстракт 1:4,7–7,4. Дослідження довели, що застосування підходів QbD до визначення параметрів процесу екстракції є важливим інструментом на етапі розроблення АФІ.*

Ключові слова: *екстракція, екстрагент, технологія, технологічний процес, препарат, поліфенольні сполуки, флавоноїди, екстрактивні речовини, рослинна сировина, простір проєктних параметрів.*

Introduction. Actuality. The development strategy of an active pharmaceutical ingredient (API) has great importance for the subsequent submission actions and evaluation by health authorities (HA). The developer can choose a "traditional" or "enhanced" approach to development or a combination of both. While the task of the traditional approach is to demonstrate the reproducibility of the process and test for compliance with established acceptance criteria, the enhanced approach requires in-depth scientific knowledge and its application to systematically evaluate and identify factors influencing critical quality attributes (CQAs) with the establishment of a design space (DS). Both approaches to API development are described in the ICHQ guideline 11 (EMA/CHMP/ICH/425213/2011).

Quality by Design (QbD) is a quality system for product life cycle management based on enhanced systematic approach to solid product development. QbD emphasizes product and process understanding, appropriate design of experiment and aims to ensure that the product meets quality requirements when the process is conducted within the DS. Generation of the DS is of great importance in pharmaceutical development as it is a key element of QbD implementation. The advantage of this approach is that conducting the process within the DS ensures that the product meets the established quality requirements and is not considered by HA as a change in process (Grangeia, 2020; EMA/CHMP/ICH/167068/2004).

In accordance with pharmacopoeia the analytical markers that characterize Bogbean (*Menyanthes trifoliata* L.) are iridoids. It is due to the pharmacological properties of this group of constituents that bogbean preparations are traditionally used for temporary loss of appetite and to relief of mild digestive disorders. However, it is promising to consider bogbean raw materials as a source of polyphenolic compounds. According to literature data, the polyphenolic component of bogbean leaves is represented by flavonols (kaempferol, quercetin, isorhamnetin) and their glycosides (hyperoside, rutoside (known as rutin), trifolin), as well as phenolic acids (chlorogenic, caffeic, ferulic, sinapic, vanilic, protocatechic). Given the wide spectrum of pharmacological action of polyphenols, studying the extraction conditions of this class of compounds for the purpose of developing APIs is an actual direction. Implementation of QbD approaches will allow a systematic approach to process development and determine its optimal parameters (EMA/HMPC/637830/2018; Derzhavna farmakopeia Ukrainy, 2024; Ph. Eur., 2024).

The aim of research. To determine the extraction process parameters of flavonoids from bogbean leaves and to investigate their impact on critical quality attributes. To establish the design space as a key element of QbD.

Materials and methods of research. The starting material for extraction was dried bogbean leaves (*Menyanthes trifoliata* L.) powdered to an average particle size of 0,6 mm and a bulk density of 0,255 g/cm^3 (manufacturer "Sumyphytopharmacia" Ltd, batch number 2977.U.2508).

Ethanol 70 and 40% (vol.) were used as extraction solvents. The choice of this concentration range was based on the study results of optimal conditions for the extraction of flavonoids from herbal raw materials. The range of polarity within the ethanol concentrations of 40–70% (vol.) shown the greatest efficiency in terms of the isolation of flavonoids coupled with the yield of extractable matters. In addition, one of the medicinal products of the bogbean leaves for traditional use is a tincture (1:5) obtained using 45% ethanol (vol.) (Dobrovolnyi, 2025; EMA/HMPC/637833/2018).

Extract samples were obtained by filtration extraction in a laboratory extractor under ambient conditions. The extractor was loaded with (150 g) starting raw material and extraction solvent. After setting the "mirror" level the raw material was infused for 1 hour. Subsequently, the raw material was extracted to a total drug extract ratio (DER) of 1:10. Extract samples were collected separately with a DER step of 1:1. In the samples of liquid extracts obtained with 70 and 40% (vol.) ethanolic solvents the dry residue, the yield of extractable matters and the quantitative content of total flavonoids were determined. The obtained data is given in table.

Determination of the dry residue content ω_n in samples of liquid extracts V_n was carried out according to the method of Derzhavna farmakopeia Ukrainy (DFU) 2.8.16 (Derzhavna farmakopeia Ukrainy, 2015).

Calculation of the yield of extractable matters D_n from extracted raw material was carried out using the following formula:

$$D_n = \sum_{n=1}^{n} \frac{\omega_n \times V_n}{m_c} \quad , \qquad (1)$$

where: ω_n – dry residue in separate portion of liquid extract, %;

V_n – volume of separate portion of liquid extract, ml;

m_c – mass raw material used for extraction, g.

Assay of flavonoids X_n was carried out by absorption spectrophotometry (DFU, 2.2.25.) on a PerkinElmer Lambda 35 spectrophotometer. Rutin was used as an analytical marker (Derzhavna farmakopeia Ukrainy, 2015).

Test solution (a). An aliquot of the extract sample V_n was placed in a 25 ml volumetric flask, 10.0 ml of *ethanol (70 per cent V/V) R* and 5,0 ml of the reagent solution were added, diluted to 25 ml with *ethanol (70 per cent V/V) R*, mixed and left for 40 min.

Test solution (b). An aliquot of extract sample V_n was placed in a 25 ml volumetric flask, diluted to 25 ml with *ethanol (70 per cent V/V) R* and mixed.

Reference solution (a). 50,0 mg of *rutin R*, previously dried in an oven to constant mass at 130 to 135 °C, was placed in a 100 ml volumetric flask, dissolved in 70 ml of *ethanol (70 per cent V/V) R* by heating in a water bath, cooled to room temperature, diluted to 100 ml with *ethanol (70 per cent V/V) R* and mixed.

Reference solution (b). 1,0 ml of *reference solution (a)* was placed in a 25 ml volumetric flask, 5,0 ml of reagent solution and 2,0 ml of buffer solution (pH = 4,0) were added, diluted to 25 ml with *ethanol (70 per cent V/V) R,* mixed and left for 40 min.

Reagent solution. 5,0 g of *aluminum chloride R* was placed in a 100 mL volumetric flask, dissolved in 60 ml of *ethanol (70 per cent V/V) R*, diluted to 100 ml with *ethanol (70 per cent V/V) R* and mixed.

Absorbance of test solutions and reference solution were detected at a wavelength of 407 nm using *test solution (b)* as a blank solution.

Calculation of the percentage content of total flavonoids X_n, expressed as rutin (dry substance) in separate portion of liquid extract V_n was carried out using the following formula:

$$X_n = \frac{A_{407n} \times m_0 \times 1 \times 25 \times 100 \times 100}{A_0 \times 25 \times 100 \times V_A \times \omega_n} = \frac{A_{407n} \times m_0 \times 100}{A_0 \times V_A \times \omega_n}, \quad (2)$$

where: A_{407n} – absorbance of test solution;

m_0 – absolute mass or rutin used to prepare reference solution, g;

A_0 – absorbance of reference solution;

ω_n – dry residue in separate portion of liquid extract, %.

V_a – volume of aliquot of separate portion of liquid extract V_n used to prepare reference solution, ml.

Calculation of the percentage content of total flavonoids G_n expressed as rutin (dry substance) in total extract V_{n+1} was carried out using the following formula:

$$G_n = \frac{\sum_{n=1}^{n} \frac{X_n \times \omega_n \times V_n}{10000}}{D_n \times m_c} \times 10\,000, \quad (3)$$

where: ω_n – dry residue in separate portion of liquid extract, %.

V_n – volume of separate portion of liquid extract, ml;

D_n – yield of extractable matters, %;

m_c – mass raw material used for extraction, g;

X_n – content of total flavonoids expressed as rutin (dry substance) in separate portion of liquid extract V_n, %.

The obtained data is given in table.

Determination of critical quality attributes (CQA). The dry residue content ω_n in liquid extract samples and the yield of total flavonoids L_n from extracted raw material were determined as critical quality attributes.

Research results and their discussion. According to the "traditional" approach to development which defines setpoints and operating ranges for process parameters, the set of dry residue threshold, yield of extractable matters and quantitative content of the analytical marker indicate the following optimal raw material extraction conditions:

– the process using 70% ethanol (vol.) reaches its efficiency at DER 1:7 and is characterized by a yield of extractable matters at the level of 25,73% and a content of total flavonoids in the obtained extract of 2,47%.

– the process using 40% ethanol (vol.) reaches its efficiency at DER 1:6 and is characterized by a yield of extractable matters at the level of 30,87% and a content of total flavonoids in the obtained extract of 2,76%.

Experimental data demonstrates the influence of ethanol concentration in the extraction solvent on the extraction of flavonoids and the yield of extractable matters which may indicate a positive effect of increasing the polarity of the solvent on the efficiency of the process. In addition, the dependence of the process efficiency on the DER has been established. The combination of both parameters forms the main factors influencing the achievement of optimal extraction conditions in the studied model.

Therefore, the extraction solvent concentration and DER can be considered as critical process parameters (CPP) as their variability affects the critical quality indicators (CQA). Accordingly, the analysis of experimental data allowed us to determine the CQA acceptance criteria.

The acceptance criterion for the dry residue content ω_n in samples of liquid extracts V_n was set to a value within 1% (ω_n). This threshold value for CQA was based on a preliminary analysis of the dynamics of extraction where it was determined that this indicator characterizes the greatest efficiency of the process. Conducting extraction outside this quality indicator was considered inexpedient.

The acceptance criterion for the yield of total flavonoids was selected as a range of 80–100% of the maximum yield of total flavonoids (L_{max}) obtained in the experiment. Considering that L_{max} is 0,93% (DER 1:10; extractant 40% ethanol) the value of the CQA was set as 0,74% (80% of L_{max}). The determined acceptance criterion indicates the efficiency of extraction of flavonoids from the extracted raw material. Calculation of the yield of total flavonoids L_n from extracted raw material was carried out using the following formula:

$$L_n = \frac{G_n \times D_n}{100}, \quad (4)$$

where: D_n – yield of extractable matters, %;

G_n – content of total flavonoids expressed as rutin (dry substance) in total extract V_{n+1}, %.

The obtained data is given in table.

The space within which the dry residue content ω_n in the extract was not less than 1% and the space within which the yield of total flavonoids L_n was not less than 80% of L_{max} were built in the form of diagrams. The coordinates of the points for graphing the spaces were calculated based on experimental data (table 1) and based on the assumption that the dry residue and the yield of flavonoids had a linear dependence on the process parameters. The abscissa axes plotted the DER ratio in the range from 1:1 to 1:10. The ordinate axes plotted the extraction solvent concentration in the range from 40 to 70%. The corresponding spaces are given in fig. 1 and fig. 2.

The establishment of the design space was carried out by superimposing the spaces of dry residue (fig. 1)

Table

Experimental data on the extraction of bogbean raw material with ethanolic extraction solvents

Sample, n	DER "Drug Extract Ratio"	V_n – volume of separate portion of liquid extract, ml	V_{n+1} – volume of total extract, ml	ω_n – dry residue in separate portion of liquid extract, %.	D_n, – yield of extractable matters, %	V_a – volume of aliquot of separate portion of liquid extract Vn, ml	A_{407n} – absorbance of test solution	X_n – content of total flavonoids in separate portion of liquid extract Vn, %	G_n – content of total flavonoids in total extract V_{n+1}, %	L_n – yield of total flavonoids from extracted raw material, %
Ethanol 70%										
1	1:1	150	150	5,20	5,20	0,25	0,377	3,545	3,55	0,18
2	1:2	150	300	5,66	10,86	0,20	0,214	2,310	2,90	0,31
3	1:3	150	450	4,72	15,58	0,25	0,096	0,993	2,32	0,36
4	1:4	150	600	3,93	19,51	0,30	0,085	0,880	2,03	0,40
5	1:5	150	750	2,75	22,26	0,45	0,309	3,052	2,16	0,48
6	1:6	150	900	2,11	24,37	0,60	0,561	5,406	2,44	0,59
7	1:7	150	1050	1,35	25,73	0,95	0,323	3,073	2,47	0,64
8	1:8	150	1200	0,91	26,64	1,40	0,251	2,395	2,47	0,66
9	1:9	150	1350	0,74	27,38	1,70	0,268	2,590	2,47	0,68
10	1:10	150	1500	0,47	27,85	2,70	0,079	0,767	2,44	0,68
Ethanol 40%										
1	1:1	150	150	10,72	10,72	0,15	0,311	2,356	2,36	0,25
2	1:2	150	300	7,70	18,42	0,20	0,280	2,216	2,30	0,42
3	1:3	150	450	5,41	23,83	0,25	0,332	2,994	2,46	0,59
4	1:4	150	600	3,38	27,21	0,45	0,509	4,080	2,66	0,72
5	1:5	150	750	2,12	29,32	0,60	0,343	3,294	2,70	0,79
6	1:6	150	900	1,55	30,87	0,90	0,430	3,768	2,76	0,85
7	1:7	150	1050	0,78	31,65	2,00	0,504	3,927	2,79	0,88
8	1:8	150	1200	0,44	32,09	2,00	0,465	6,499	2,84	0,91
9	1:9	150	1350	0,32	32,40	2,00	0,193	3,710	2,84	0,92
10	1:10	240	1590	0,27	32,83	2,00	0,132	3,024	2,85	0,93

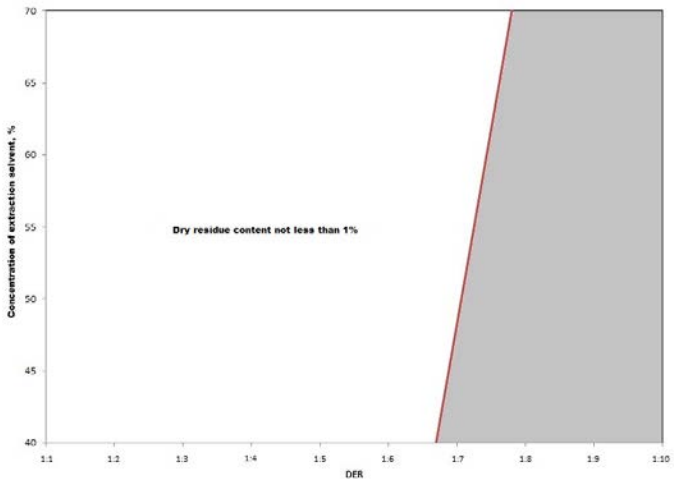

Fig. 1. Space within which the dry residue content ω_n in the extract is not less than 1%

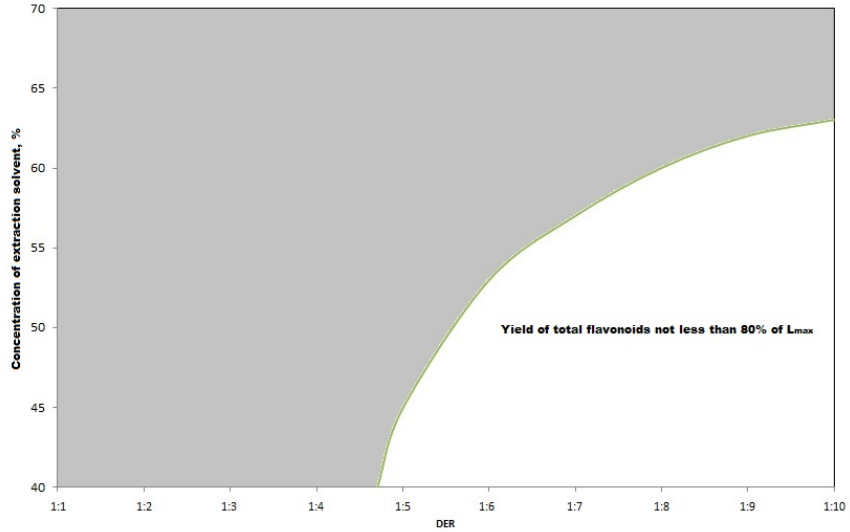

Fig. 2. Space within which the yield of total flavonoids L_n is not less than 80% of L_{max}

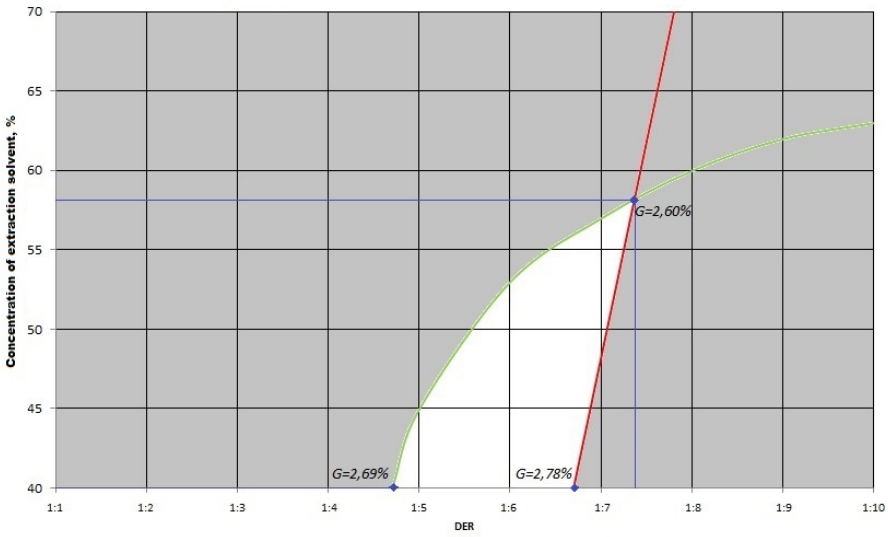

Fig. 3. Design space within which critical quality attributes comply with the acceptance criteria ($\omega_n \geq 1\%$; $L_n \geq 80\%$ L_{max})

and flavonoid yield (fig. 2) on each other. The resulting space (fig. 3) within which the extraction process allows us to obtain a product with the specified characteristics of critical quality attributes is given in fig. 3. The corresponding spaces within which the process ensures that the product meets the established quality criteria are shown in white on the diagrams.

As can be seen from the design space (Fig. 3) the optimal conditions for the extraction of bogbean leaves raw material under which the product meets the established CQA are extraction with ethanol within the concentration range of 40–58% and a DER of 1:4.7–7.4. It should be noted that the process parameters determined using QbD differ from the parameters determined using the "traditional approach", where the optimal quality indicators of extracts are achieved by extraction with 40–70% ethanol at DER of 1:6–7. Thus, the resulting space is technologically more flexible and provides a deeper understanding of the process, the work within which allows obtaining a product of the established quality with a wider range of critical parameters.

Conclusions. 1. A systematic analysis has been conducted and the nature of the extraction process of bogbean leaves with ethanol extraction solvents has been

studied. Within this study it has been determined that the critical quality attributes (CQA) are the dry residue content in liquid extracts not less than 1% and the yield of total flavonoids not less than 0,74%.

2. According to the design space (DS), it has been established that the optimal process parameters for which the product meets the criteria of critical quality attributes are extraction with ethanol in the range of concentrations of 40–58% and DER of 1:4.7–7.4.

3. Studies have proven that the usage of QbD approaches to determining extraction process parameters is an important tool within the API development phase. The results obtained will be used in the further development of herbal preparations.

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