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Development of the Composition and Technology for Obtaining Mini-Tablets of Propranolol Hydrochloride Using the Quality by Design Approach

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Infantile hemangioma (IH) is a benign vascular neoplasm, occurring in 4–10 % of newborns and requiring timely therapy in cases of complicated progression. Currently, propranolol is recognized as the “gold standard” for IH treatment due to its proven efficacy and safety. However, in the Russian Federation, there are no readily available dosage forms (DFs) of propranolol for children, which creates a significant problem for pediatric practice. In this regard, the development of a DFs that ensures accurate dosing and ease of use in children is relevant.

The aim. To develop the composition and technology for obtaining orodispersible mini-tablets (OMT) of propranolol hydrochloride for children using the Quality by Design (QbD) approach.

Materials and methods. The active pharmaceutical substance of propranolol hydrochloride and excipients were used: mannitol, microcrystalline cellulose 102 (MCC 102), crospovidone (CPV), sodium saccharin dihydrate, sodium stearyl fumarate (SSF), and colloidal silicon dioxide. The composition development was carried out using the QbD methodology, with experimental design planned using the Mixture Design (MD) method. The independent variables were the content of MCC 102, CPV, and SSF. OMT with a diameter of 3 mm were obtained by direct compression. The tablet blend and OMT were tested according to the methods presented in the State Pharmacopoeia of the Russian Federation, XV edition: flowability, bulk density and tapped density, crushing strength, friability, disintegration, and mass uniformity. The dose uniformity of the optimized composition was determined by HPLC.

Results. During the first stage, the target quality profile of the OMT was determined. In accordance with this, critical quality attributes (CQAs) were established: for the powder blend — flowability, bulk density, tapped density; for the OMT — crushing strength, disintegration, friability, and dose uniformity. A composition was developed and optimized, which allowed the required values for all CQAs to be achieved. Statistical analysis revealed significant inter-component interactions affecting the crushing strength and disintegration of the OMT.

Conclusion. The composition and technology for obtaining orodispersible mini-tablets of propranolol hydrochloride have been developed.

Keywords: propranolol hydrochloride; mini-tablets; orodispersible forms; Quality by Design; infantile hemangioma

Abbreviations: IH — infantile hemangioma; OMTs — orodispersible mini-tablets; DFs — dosage forms; QbD — Quality by Design; QTPP — Quality Target Product Profile; DoE — Design of Experiments; SSF — sodium stearyl fumarate; MCC — microcrystalline cellulose; CPV — crospovidone; CQA — critical quality attribute.

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Разработка состава и технологии получения мини-таблеток пропранолола гидрохлорида с применением подхода «качество через проектирование»

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Инфантильная гемангиома (ИГ) представляет собой доброкачественное сосудистое новообразование, встречающееся у 4–10% новорождённых и требующее своевременной терапии при осложнённом течении. На сегодняшний день пропранолол признан «золотым стандартом» лечения ИГ благодаря доказанной эффективности и безопасности. Однако в Российской Федерации отсутствуют доступные лекарственные формы (ЛФ) пропранолола для детей, что создает значительную проблему для педиатрической практики. В связи с этим актуальна разработка ЛФ, обеспечивающей точность дозирования и удобство применения у детей.

Цель. Разработка состава и технологии получения ородиспергируемых мини-таблеток (ОДМТ) пропранолола гидрохлорида для детей с использованием подхода «качество через дизайн» (Quality by Design, QbD).

Материалы и методы. Для достижения цели исследования использовали активную фармацевтическую субстанцию пропранолола гидрохлорида и вспомогательные вещества: маннитол, микрокристаллическая целлюлоза 102 (МКЦ 102), кросповидон (КПВ), натрия сахарината дигидрат, натрия стеарилфумарат (НСФ) и кремния диоксид коллоидный. Разработку состава проводили с использованием методологии QbD, планирование эксперимента методом Mixture Design (MD). Независимыми переменными выступали содержание МКЦ 102, КПВ и НСФ. ОДМТ диаметром 3 мм получали прямым прессованием. Таблеточную смесь и ОДМТ испытывали по методикам, представленным в Государственной фармакопее Российской Федерации XV издания: сыпучесть, насыпная плотность и плотность после уплотнения, прочность на раздавливание, истираемость, распадаемость, однородность массы. Однородность дозирования оптимизированного состава определяли методом ВЭЖХ.

Результаты. На первом этапе определили целевой профиль качества ОДМТ. В соответствии с ним установлены критические показатели качества (КПК): для порошковой смеси — сыпучесть, насыпная плотность, плотность после уплотнения; для ОДМТ — прочность на раздавливание, распадаемость, истираемость и однородность дозирования. Разработан и оптимизирован состав, позволивший достичь требуемых значений всех КПК. В ходе статистического анализа выявлены значимые межкомпонентные взаимодействия, влияющие на прочность и распадаемость ОДМТ.

Заключение. Разработан состав и технология получения ОДМТ пропранолола гидрохлорида.

Ключевые слова: пропранолола гидрохлорид; мини-таблетки; ородиспергируемые формы; качество через проектирование; инфантильная гемангиома

Список сокращений: ИГ — инфантильная гемангиома; ОДМТ — ородиспергируемые мини-таблетки; ЛФ — лекарственные формы; ЛП — лекарственный препарат; QbD — качество через проектирование; QTPP — целевой профиль качества; DoE — планирование эксперимента; НСФ — натрия стеарилфумарат; МКЦ — микрокристаллическая целлюлоза; КПВ — кросповидон; КПК — критические показатели качества.

INTRODUCTION

Infantile hemangioma (IH) is a benign vascular neoplasm, occurring, according to various data, in 4–10 % of newborns [1]. Currently, the pathogenesis of the disease is not absolutely studied [2], however, it is assumed that IH is a consequence of dysregulation of vasculogenesis and angiogenesis [3]. In most cases, IH does not pose a threat and resolves spontaneously, but in 10–15 % of cases, hemangiomas localized in the head and neck area, at the border with mucous membranes, pose a danger[1]. They can lead to complications such as bleeding, ulceration, deformation, and obstruction with functional impairments [1, 4].

Medication therapy is among the main methods

[1] Infantile hemangioma. Classificator of Clinical Guidelines. Available from: https:// cr.minzdrav.gov.ru/preview-cr/769_1. Russian

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for treating IH. Although corticosteroid therapy was considered the most effective approach for a long time, a number of serious side effects due to its prolonged use were subsequently identified [5]. Therapy of IH with the immunosuppressant sirolimus (rapamycin), an mTOR receptor inhibitor, is known. However, due to side effects such as immunosuppression, metabolic disorders, and nephrotoxicity, the drug is not a first-line treatment [4]. Beta-blockers, atenolol and timolol, are used for local and oral administration in the treatment of IH; however, propranolol remains the "gold standard" [3, 6, 7].

Propranolol belongs to non-selective beta-adrenoblockers and has antihypertensive, antianginal, and antiarrhythmic effects. Its use as a treatment for IH has been known since 2008 [8]. The dosage of propranolol according to clinical recommendations[2] depends on the form of IH and ranges from 0.5 to 3 mg per kg of body weight per day, with the dose divided into 2–3 administrations. Overdose can lead to the development of bradyarrhythmia and arterial hypotension. Currently, there are no available dosage forms (DFs) of propranolol for children in the Russian Federation [9]. In this regard, the development of propranolol in a DF that ensures accurate dosing and ease of use in young children is relevant.

Mini-tablets (MTs) are a promising DF for children. According to the definition by P. Lennartz and J.B. Mielck, MTs are tablets with a diameter of 2–3 mm or less [10]. They demonstrate high acceptability in young children, which allows them to be considered a preferred alternative to liquid DFs, particularly syrups [11]. Unlike the latter, MTs do not contain sugar and preservatives, have a stable dosage, do not require the use of a dosing device, and reduce the risk of dose discrepancy.

Interest in MTs has grown rapidly in recent years [11]. MTs have been developed for the treatment of gastrointestinal diseases [12, 13], cardiovascular [14–16], ophthalmological [17], and other pathologies [18–20]. The expediency and safety of using MTs in pediatric practice have been confirmed by regulatory decisions of the European Medicines Agency (EMA). For example, the drug Slenyto (melatonin) [21] is a prolonged-release MT approved for the treatment of insomnia in children from two years of age. The drug Aqumeldi (enalapril maleate) [22], produced in the form of orodispersible mini-tablets (ODMTs), is approved for use in children from the first days of life for the therapy of heart failure. The industrial production of these DFs confirms the technological feasibility and clinical acceptability of MTs even for the youngest age groups.

In accordance with the international standard ICH Q8 (R2), the Quality by Design (QbD) approach is recommended for the pharmaceutical development of medicines. QbD is based on a systematic approach to product design and development, which allows for increased development efficiency, reduced time costs, and optimization of the medicine composition [23]. The development includes the sequential determination of the Quality Target Product Profile (QTPP) of the medicine, identification of Critical Quality Attributes (CQAs), risk assessment, establishment of the design space, development of a control strategy, as well as Product Lifecycle Management and Continual Improvement. One of the key tools ensuring the effective implementation of QbD is Design of Experiments (DoE) [24]. The application of DoE can significantly reduce the time and resources spent on determining the optimal composition and technology for obtaining the developed drug [25]. Among various types of DoE, "mixture design" (MD) deserves special attention. This method allows for the simultaneous determination of the optimal ratio of components in a mixture and the influence of various technological parameters [26].

THE AIM was to develop the composition and technology for obtaining orodispersible mini-tablets of propranolol hydrochloride for children using the QbD approach.

MATERIALS AND METHODS

Materials

During the development of ODMTs, the pharmaceutical substance propranolol hydrochloride (Changzhou Yabang Pharmaceutical Co., Ltd., China) and the following excipients (Excipients) were used: mannitol—Pearlitol 200 SD (Roquette, France), microcrystalline cellulose (MCC) 102, crospovidone—PolyplasdoneTM XL-10 (Huangshan Bonsun Pharmaceuticals Co., Ltd., China), sodium saccharin dihydrate (China Pingmei Shenma Group Kaifeng Xinghua Fine Chemical Ltd., China), sodium stearyl fumarate—PRUV (JRS Pharma, Germany), colloidal silicon dioxide—Aerosil (Madhu Silica Pvt. Ltd., India).

For sample analysis by HPLC, acetonitrile for gradient HPLC (Greenway SPB LLC, Russia), ammonium formate (Thermo Fisher Scientific's, Germany), and formic acid (Scharlab S.L., Spain) were used. Type I ultrapure water was obtained from the Simplicity UV water purification system (Merck, Germany). A standard sample of propranolol hydrochloride (NCSO LLC, Russia) was used to prepare the standard solution. Sample filtration was carried out using a 25 mm polypropylene syringe filter with a pore diameter of 0.45 µm (Filter-Bio, China). Mobile phase filtration

[2] Ibid.

was carried out using 47 mm regenerated cellulose membrane filters with a pore diameter of 0.45 µm (Filter-Bio, China).

All weighings were performed on SHPBG-215i-ION semi-microbalances (Bel Engineering Srl, Italy).

Pharmaceutical development of mini-tablets

Defining the Target Quality Profile of Mini-Tablets

The first step is to define the characteristics of the ODMTs (oral drug delivery tablet) for next obtaining a safe and effective medicine, i.e., the target quality profile of the drug [27].

Defining critical quality attributes and risk assessment

At the initial stage of development, the CQAs of the ODMTs were identified: powder blend flowability, hardness, friability, disintegration time, and absence of adhesion to the tooling. During subsequent risk assessment, factors capable of influencing these CQAs were systematized: process parameters (mixing, compression force); API properties (particle shape and size); type and content of excipients (ratio of filler, disintegrant, and lubricant). Insufficient powder blend flowability and an imbalance in the content of superdisintegrant and lubricant have the greatest impact on achieving the target quality attributes, which was taken into account when planning the experiment. A detailed analysis and ranking of the identified risks are presented in a previously published work [28].

Experimental design and statistical analisys

The development and optimization of the propranolol hydrochloride ODMTs composition were carried out using DoE. The experimental design and statistical processing of the obtained data were performed using Minitab 21 software, USA. The critical significance level for hypothesis testing was taken as $\alpha = 0.05$.

The content of microcrystalline cellulose 102 (MCC 102, X_1, 31.0–36.5 %), crospovidone (CPV, X_2, 1.0–5.0 %) and sodium stearyl fumarate (SSF, X_3, 0.5–2.0 %) as a percentage of the total mass were considered as independent variables. The content of mannitol, sodium saccharin dihydrate, and aerosil was kept constant. The composition of the investigated ODMTs is presented in Table 1. The dependent variables (responses) evaluated were: tablet crushing strength (Y_1), friability (Y_2), disintegration (Y_3), powder blend flowability (Y_4), and Carr's index (Y_5).

An Extreme Vertex design (Table 2) was chosen as the experimental design MD.

Based on the obtained data, the ODMTs composition was optimized. The dependent variables were ranked by degree of significance and priority, with assigned weight and importance coefficients.

Technology for obtaining mini-tablets

The ODMTs were obtained by direct compression in several sequential stages. In the first stage, the active pharmaceutical ingredient and all excipients were sieved through a laboratory sieve with a mesh size of 315 µm. Sieved components, with the exception of SSF and colloidal silicon dioxide, were mixed in a Schatz M10 laboratory mixer (Powteq, China) at a rotation speed of 30 rpm for 30 min, after which the resulting mixture was sieved again. In the final stage, colloidal silicon dioxide and SSF were added and mixed at a speed of 20 rpm for 3 min.

The resulting mixture was loaded into an eccentric tablet press EP-1 (Erweka, Germany). Compression was carried out using a steel press tool, including 3 mm biconcave punches with a single tip and a die.

Powder mixture characteristics

Flowability

Flowability was assessed in accordance with the requirements of the State Pharmacopoeia of the Russian Federation, 15th edition (SPh RF XV ed.) GPhM.1.4.2.0016 "Powder Flowability"[3] using a GTB flowability tester (Erweka, Germany) by measuring the free flow time of 100.0 g of the mixture, placed in a 450 mL funnel with a 10.0 mm opening, in three replicates. The built-in mixing function of the tester was used.

Bulk density and tapped density

Bulk density and tapped density were assessed in accordance with the requirements of SPh RF XV ed. GPhM.1.4.2.0024 "Bulk Density and Tapped Density"[4] using an SVM-223 tester (Erweka, Germany). Bulk density before tapping was calculated by measuring the volume of 40.0 g of the mixture, freely poured into a 100 mL cylinder. Tapped density was calculated by determining the powder volume after 10, 500, and 1250 taps. The Hausner ratio and compressibility index were also calculated.

[3] GPhM.1.4.2.0016 "Powder Flowability". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/sypuchest-poroshkov/. Russian

[4] GPhM.1.4.2.0024 "Bulk Density and Tapped Density". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/nasypnaya-plotnost-i-plotnost-posle-uplotneniya/. Russian

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Characteristics of quality parameters of mini-tablets

Mass Uniformity

Mass uniformity was assessed in accordance with SPh RF XV ed. GPhM.1.4.2.0009 "Uniformity of Mass of Dosed Dosage Forms"[5] by individual and collective weighing of 20 ODMTs.

Hardness

The hardness of ODMTs (*n* = 10) was assessed in accordance with SPh RF XV ed. GPhM.1.1.1.0017 "Tablet Crushing Strength"[6] using a TBH-125 tester (Erweka, Germany).

Geometric parameters

The thickness and diameter of ODMTs (*n* = 10) were measured simultaneously with the crushing strength assessment using a TBH-125 tester (Erweka, Germany).

Friability

The friability of ODMTs (*n* = 10) was assessed in accordance with SPh RF XV ed. GPhM.1.1.1.0015 "Tablet Friability"[7], method 2, using a TAR-220 tester (Erweka, Germany). The tablets were pre-weighed, then placed in a drum at 20 revolutions per minute for 5 minutes. At the end, the tablets were dedusted and weighed again.

Disintegration

The disintegration time of ODMTs (*n* = 6) was assessed using a ZT-221 tester (Erweka, Germany) at 37 ± 0.5 °C. Due to the small size of the ODMTs, a modified assembly was used: a steel sieve with 0.25 × 0.25 mm cells was attached to the lower part of the basket (unlike the sieve specified in the GPhM).

Content Uniformity

The content uniformity of the optimized MT composition was assessed in accordance with SPh RF XV ed. GPhM.1.4.2.0008 "Content Uniformity"[8] by direct determination of the active substance content (method 1). The arithmetic mean (Xi), standard deviation (s), relative standard deviation (RSD), and acceptance value (AV) were calculated according to the method specified in the GPhM.

The determination of propranolol hydrochloride was carried out by high-performance liquid chromatography. The method was previously validated for linearity, accuracy, specificity, and repeatability (precision).

Mobile Phase A (MP A)

Approximately 630 mg of ammonium formate was placed in a 1000 mL volumetric flask and dissolved in 900 mL of water for chromatography R, and the pH of the solution was adjusted to 3.0 ± 0.1 with formic acid R. The resulting solution was transferred to a 1000 mL volumetric flask, and the volume was adjusted to the mark with water for chromatography R and mixed.

Mobile Phase B (MP B)

Acetonitrile for chromatography R.

Standard Solution

Approximately 11.4 mg (exact weight) of propranolol hydrochloride reference standard was placed in a 100 mL volumetric flask, 10 mL of water for chromatography R was added, dissolved, and the volume was adjusted to the mark with acetonitrile for chromatography R and mixed.

The concentration of propranolol base is approximately 0.1 mg/mL.

Sample Solution

1 ODMT of propranolol hydrochloride was placed in a 10 mL volumetric flask, 1 mL of water for chromatography R was added, sonicated for 15 min, cooled to room temperature, the volume was adjusted to the mark with acetonitrile for chromatography R, and mixed. The resulting solution was filtered through a syringe filter.

The concentration of propranolol base is approximately 0.1 mg/mL.

Chromatographic conditions

The analysis was performed on a LicArt 62 chromatographic system (Russia) with a gradient quaternary low-pressure pump QP-62d, an autosampler S-42dc, a column thermostat T-85C, and a DAD-62 spectrophotometric detector on an Atlantis HILIC Silica 150 × 4.6 mm column, particle size 5 µm, packed with L3 type sorbent (Waters, Ireland). Propranolol was determined at a wavelength of 290 nm. Elution was carried out in an isocratic mode using mobile phase (A : B) in a ratio of 20 : 80. Flow rate is 1 mL/min,

[5] GPhM.1.4.2.0009 "Uniformity of Mass of Dosage Forms". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/odnorodnost-massy-dozirovannykh-lekarstvennykh-form/. Russian

[6] GPhM.1.1.1.0017 "Tablet Crushing Strength". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-1/1-1-2/prochnost-tabletok-na-razdavlivanie/. Russian

[7] GPhM.1.1.1.0015 "Tablet Friability". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-1/1-1-2/istiraemost-tabletok/. Russian

[8] GPhM.1.4.2.0008 "Content Uniformity". State Pharmacopoeia of the Russian Federation, XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/odnorodnost-dozirovaniya/. Russian

column thermostat temperature—30 °C, autosampler temperature—6 °C. Chromatographic run time—6 min, propranolol hydrochloride retention time ~3.8 min.

The content of propranolol hydrochloride in ODMT relative to the nominal content was calculated using the formula:

$$G_{\%} = \frac{s_x \times a_{RS} \times W_x \times P \times 100}{S_{RS} \times W_{RS} \times L \times 100} = \frac{s_x \times a_{RS} \times W_x \times P}{S_{RS} \times W_{RS} \times L},$$

where S_x is the peak area of propranolol hydrochloride in the chromatogram of the sample solution, mAU×min; S_{RS} is the peak area of propranolol hydrochloride in the chromatogram of the reference standard, mAU×min; a_{RS} is the weighed amount of the reference standard, mg; L is the declared content of propranolol hydrochloride in ODMT, mg; W_x is the volume of the volumetric flask used for diluting the sample, W_{RS} is the volume of the volumetric flask used for diluting the reference standard, P is the content of propranolol hydrochloride in the reference standard, %.

RESULTS

The target quality profile of the designed ODMTs with justification of the selected characteristics and their target values is presented in Table 3.

Disintegration

As a result of the experimental evaluation of 10 ODMT compositions, the disintegration times varied from 7.00 to 23.00 s (Table 4). Most compositions showed stable and reproducible results (standard deviation within 1–2 s), with the exception of compositions 6 (15.33 ± 5.30 s) and 7 (10.33 ± 3.82 s), which were characterized by increased disintegration variability. Analysis of the regression model (Table 5) showed that all pairwise interactions between the mixture components had a statistically significant effect on disintegration time ($p < 0.05$). Negative coefficients for these interactions indicate that the actual disintegration time for binary mixtures is less than the calculated time predicted based on the additive contribution of each component. The strongest effect was observed for the pair PVPC and NSF (coefficient -9440).

Hardness

The experimentally determined hardness values for the studied compositions varied from 19.10 ± 1.22 to 33.00 ± 2.84 N (see Table 4). Analysis of the regression model for hardness (see Table 5) showed a heterogeneous pattern of interaction significance between components. Of the three possible pairwise interactions, two were statistically significant: the interaction of MCC 102 × SSF ($p = 0.028$) and CPV × SSF ($p = 0.015$). Negative coefficients for these interactions indicate that the actual hardness of tablets containing NSF with MCC 102 or SSF with CPV simultaneously was lower than the calculated hardness predicted based on the additive contribution of each component. The largest negative effect in magnitude was observed for the CPV × SSF interaction (coefficient -10362). The model showed that the key factor modifying hardness is the interaction of SSF with other mixture components.

Flowability

All studied compositions demonstrated satisfactory flowability: values ranged from 31.77 ± 0.65 s to 38.17 ± 0.94 s, which corresponds to a technologically acceptable range for direct compression (see Table 4). The reproducibility of the results was satisfactory for most compositions; a slight increase in variability was noted only for composition 7 (33.47 ± 3.78 s).

According to the results of the regression analysis (see Table 5), the linear effects of the components did not have a significant impact on flowability ($p > 0.05$). The interaction effects of MCC 102 × SSF ($p = 0.017$) and CPV × SSF ($p = 0.043$) were statistically significant; the interaction of MCC 102 × CPV did not reach the significance level ($p = 0.081$). Negative coefficients for significant interactions indicate improved flowability with the co-presence of the specified pairs. Thus, flowability is mainly determined by inter-component interactions, particularly those involving SSF.

Friability

The obtained data showed no statistically significant influence of interactions on friability ($p > 0.05$) (see Table 5). It should be noted that none of the compositions exhibited friability problems in the form of borderline values. The friability index for all studied compositions did not exceed 3 % (see Table 4).

Mass uniformity and geometric parameters

For all studied compositions, ODMTs were assessed for mass uniformity, thickness, and diameter (see Table 4). The average tablet weight varied from 19.50 ± 0.14 mg to 20.49 ± 0.13 mg, with low standard deviation values (0.07–0.14 mg) indicating high reproducibility of the compression process and uniform die filling. ODMT thickness ranged from 2.60±0.02 mm to 2.84±0.01 mm, and diameter ranged from 2.99±0.01 mm to 3.02±0.03 mm.

Optimization of composition

Based on the experimental data obtained, the composition of propranolol ODMT was optimized using a multifactorial approach. Strength, flowability, disintegration, and adhesion to the

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press tool were selected as responses. For each response, a weight and importance coefficient was assigned in the range of 0.1 to 10, where a higher weight amplified the response's influence on the optimization result. The objective functions included minimization, maximization, or achieving a target value within specified intervals (Table 6). The highest priority was assigned to the absence of adhesion: weight—10, importance—4, goal—minimization (target value 0, acceptable maximum—1). Disintegration, as a critical indicator of orally disintegrating dosage forms (ODDFs), was also subject to minimization: target value—10 s, upper limit—15 s, weight—1, importance—1. For strength, a maximization goal was set: lower limit—21 N, target value—23 N, weight—1, importance—2. Flowability, characterized by the least accurate predictive model, was optimized towards minimization: target value—34 s, upper limit—36 s, weight—1, importance—3. As a result of optimization, a composition satisfying the specified criteria was obtained.

As a result of the optimization performed, the following composition of mini-tablets (wt. %) was determined: MCC 102—31.55; CPV—5.00; SSF—1.45. The desirability function value for all responses was 1.00, indicating full compliance of the achieved indicators with the specified criteria (Table 7). Predicted values of critical quality parameters: strength—23.47 N; flowability—33.98 s; disintegration—7.1 s; adhesion—0.097 (practically complete absence of sticking).

The optimized composition was reproduced and subjected to experimental evaluation. Considering that the strength of the initial composition was insufficient, the authors increased the compression pressure to 1.0–1.1 kN, having confirmed the absence of sticking risk. The obtained mini-tablets were characterized by the following indicators: average mass 20.15 ± 0.11 mg, thickness 2.62 ± 0.01 mm, diameter 3.00 ± 0.01 mm, strength from 30 to 39 N (average 33.60 ± 2.05 N), disintegration 20.67 ± 2.12 s, friability 0.5 %. Thus, increasing the compression pressure allowed achieving strength fully compliant with pharmacopoeial requirements (> 30 N), while maintaining acceptable disintegration parameters and the absence of adhesion.

A test for dosage uniformity was also performed for the obtained mini-tablets (Fig. 1). The average content of propranolol hydrochloride was 99.05 % of nominal, standard deviation — 4.24, relative standard deviation — 4.28, calculated acceptability value — 10.18, which corresponds to established pharmacopoeial requirements (AV < 15).

Table 1 — Composition of propranolol hydrochloride mini-tablets

Ingredient Name	Function	Mass fraction in tablet, %	Quantity per mini-tablet, mg
Propranolol hydrochloride	Active pharmaceutical ingredient	5.70	1.14
Mannitol	Filler	27.15	5.43
Microcrystalline Cellulose 102	Filler	31.00–36.50	6.20–7.30
Crospovidone	Superdisintegrant	1.00–5.00	0.20–1.00
Sodium stearyl fumarate	Hydrophilic Lubricant	0.50–2.00	0.10–0.40
Silicon Dioxide	Glidant	1.00	0.20
Sodium Saccharin	Artificial Sweetener	1.00	0.20
Tablet Mass:		100.00	20

Table 2 — Mixture design experiment matrix

Experiment	Level values		
	MCC 102 content, %	CPV content, %	SSF content, %
1	31.00	5.00	2.00
2	33.00	3.00	2.00
3	31.75	5.00	1.25
4	32.50	5.00	0.50
5	33.75	3.00	1.25
6	35.75	1.00	1.25
7	33.75	3.00	1.25
8	35.00	1.00	2.00
9	36.50	1.00	0.50
10	34.50	3.00	0.50

Note: MCC, microcrystalline cellulose; CPV, crospovidone; SSF, sodium stearyl fumarate.

Table 3 — Target quality profile of mini-tablets

Characteristic	Target Value	Rationale
Dosage Form	Orodispersible mini-tablets	Ensures accurate dosing and ease of use in children under 1 year of age.
Dosage	1 mg of propranolol base in each mini-tablet	In accordance with clinical recommendations, the daily dose of propranolol is 0.5 to 3 mg/kg, divided into 2–3 administrations. The drug is prescribed for infants aged 35 days to 5 weeks, with a therapy duration of 6 to 24 months or more. The child's weight during this period varies from 2.5 to 12 kg; therefore, 1 to 4 mini-tablets will be administered per dose, ensuring ease of use.
Mini-tablets Mass	Not more than 20 mg	Ensures ease of use.
Mini-tablets Size	Mini-tablet diameter not more than 3 mm	Ensures ease of use.
Organoleptic Properties	Neutral taste, absence of bitterness	A neutral taste (not sweet) prevents the perception of the drug as confectionery, minimizing the risk of accidental overdose and the formation of a food-related behavioral habit. The absence of pronounced bitterness is necessary to prevent the gag reflex and refusal to swallow.
Description	White, round, biconvex tablets with a chamfer, without a score line	Splitting of mini-tablets is not permissible; the chamfer will ensure ease of use by smoothing sharp edges.
Authenticity	Compliance with regulatory document quality requirements	Identification of propranolol hydrochloride.
Disintegration	Not more than 30 s in water	A short disintegration time ensures that if a mini-tablet is accidentally chewed or held in the mouth, it will disintegrate instantly, eliminating the risk of aspiration of a solid foreign body, and also making it impossible to subsequently spit out the min-tablet, which ensures the completeness of the administered dose and safety of use.
Crush strength	Not less than 25 N	Ensures the integrity of the mini-tablet during transportation and storage.
Abrasion	Not more than 3 % (Method 1)	Ensures the integrity of the mini-tablet during transportation and storage.
Content uniformity	Acceptable value for 10 tablets not more than 15 %	Ensures the efficacy and safety of each mini-tablet.
Related Substances / Quantitative Determination	Compliance with regulatory document quality requirements	Ensures the efficacy and safety of the mini-tablet.
Microbiological Purity	Category 3A	Efficacy and safety of the medicines.

Table 4 — Parameters of tablet blend and mini-tablets

Parameter	Experiment									
	1	2	3	4	5	6	7	8	9	10
Blend Properties										
Flowability	38.17 ± 0.94	37.33 ± 0.28	33.77 ± 1.78	32.90 ± 1.15	35.13 ± 0.92	31.77 ± 0.65	33.47 ± 3.78	35.70 ± 0.97	34.77 ± 0.76	36.53 ± 1.67
Bulk density	0.49	0.50	0.50	0.50	0.49	0.50	0.49	0.49	0.49	0.49
Tapped density	0.66	0.66	0.67	0.66	0.65	0.65	0.65	0.65	0.64	0.64
Compressibility Index	25.31	24.38	25.46	23.99	24.53	23.15	24.39	23.46	22.84	23.55
Hausner Ratio	1.34	1.32	1.34	1.32	1.33	1.30	1.32	1.31	1.30	1.31
Mini-tablet Properties										
Average mass, mg	20.08 ± 0.10	20.17 ± 0.11	20.01 ± 0.09	20.49 ± 0.13	19.94 ± 0.14	19.91 ± 0.07	19.50 ± 0.14	20.06 ± 0.08	19.84 ± 0.07	19.57 ± 0.11
Average thickness, mm	2.84 ± 0.01	2.79 ± 0.01	2.80 ± 0.09	2.74 ± 0.02	2.75 ± 0.01	2.75 ± 0.00	2.69 ± 0.01	2.76 ± 0.00	2.70 ± 0.01	2.60 ± 0.02
Average diameter, mm	3.02 ± 0.02	2.99 ± 0.01	2.99 ± 0.08	3.01 ± 0.01	3.02 ± 0.03	3.01 ± 0.02	3.02 ± 0.02	3.00 ± 0.01	3.01 ± 0.03	3.02 ± 0.03
Disintegration, s	7.00 ± 1.84	10.33 ± 1.06	9.33 ± 1.06	14.33 ± 1.06	11.00 ± 0.00	15.33 ± 5.30	10.33 ± 3.82	20.00 ± 1.84	23.00 ± 1.84	17.00 ± 1.84
Strength, N	21.80 ± 1.51	21.90 ± 1.26	25.50 ± 2.90	33.00 ± 2.84	20.30 ± 1.94	21.10 ± 1.80	19.10 ± 1.22	20.30 ± 1.52	25.80 ± 2.22	27.50 ± 0.89
Abrasion, %	0.75	0.60	0.50	0.25	0.46	0.45	0.57	0.50	0.41	0.77

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Table 5 — Regression coefficients and significance levels

Independent Variable	Disintegration		Strength		Flowability		Carr's Index	
	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value
MCC 102	33.62	> 0.05	33.09	> 0.05	38.23	> 0.05	21.31	> 0.05
CPV	615	> 0.05	680	> 0.05	-455	> 0.05	1.1	> 0.05
SSF	8219	> 0.05	7730	> 0.05	6271	> 0.05	-1032	> 0.05
MCC 102×CPV	-754	0.103	-665	0.128	555	0.081	37.4	0.553
MCC 102×SSF	-8827	0.026	-8325	0.028	-6696	0.017	1139	0.05
CPV×SSF	-10623	0.015	-10362	0.015	-5097	0.043	1345	0.033

Note: MCC, microcrystalline cellulose; CPV, crospovidone; SSF, sodium stearyl fumarate.

Table 6 — Composition optimization parameters

Response	Aim	Lower	Target	Upper	Weight	Importance
Strength, N	Maximize	21	23	–	1	2
Flowability, s	Minimize	–	34	36	1	3
Disintegration, s	Minimize	–	10	15	1	1
Sticking	Minimize	–	0	1	10	4

Table 7 — Predicted responses

Response	Value	Individual probability of achieving desired results
Strength, N	23.47	1.00
Flowability, s	33.98	1.00
Disintegration, s	7.13	1.00
Sticking	-0.097	1.00
Composite Probability of Achieving Desired Results		1.00

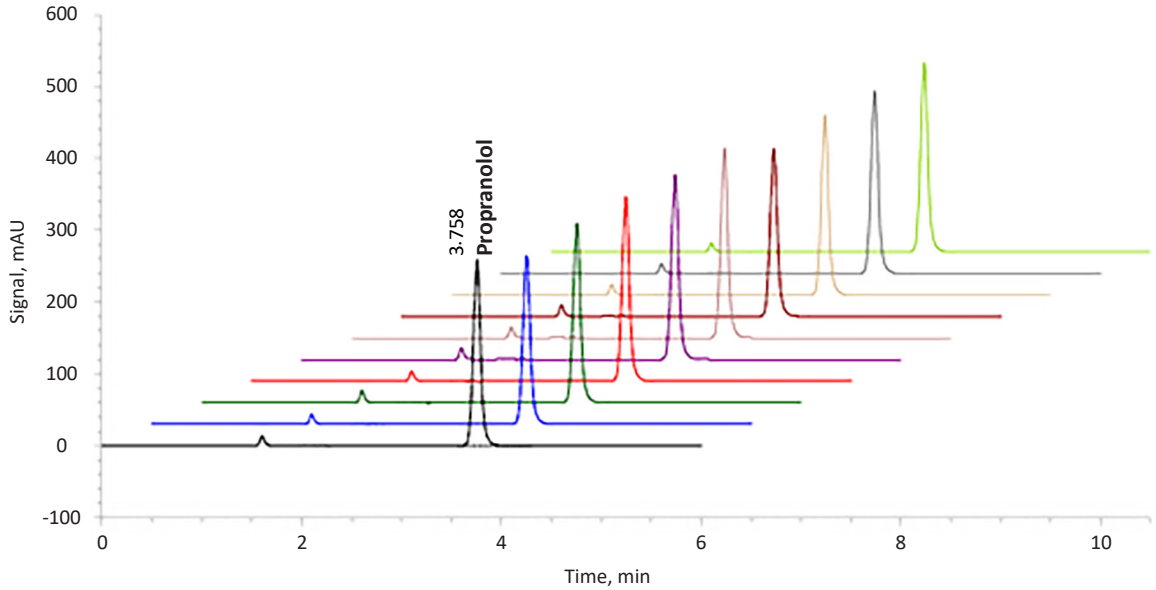

Figure 1 — Chromatograms of test solutions for determining the content uniformity of propranolol mini-tablets.

DISCUSSION

A number of the obtained results, in the opinion of the authors, require more detailed discussion and interpretation in the context of existing literature data.

Justification for the choice of experimental design

The MD method was chosen as the experimental design by the authors. Unlike the Response Surface Methodology, where factors are independent, MD considers components as part of a mixture: the response here is determined not by absolute values, but by the ratio of proportions, the sum of which always equals 100%. There are three types of MD: simplex lattice, simplex centroid, and optimal mixture (Extreme vertex), where "simplex" denotes equal ranges of all components, "lattice"—a grid method of selecting experimental points, and "centroid"—includes only central points. The latter type, extreme vertex, is used when two-sided constraints (lower and upper bounds) are imposed on the components or linear constraints are added for several components[9]. Extreme vertex was chosen as one of the most suitable for the development of a multi-component pharmaceutical composition. The chosen design allowed reducing the number of experimental points from 27 (full three-factor experiment) to 10, including 2 degrees of freedom and one central point, performed in duplicate. In accordance with the specifics of MD, the influence of individual linear variables is not included in the calculation due to the constraint of constant sum of proportions. Their contribution to the response is fully accounted for through a system of significant interactions. The presence of significant negative interactions between all pairs of components allows for targeted optimization of the MT composition to achieve minimal disintegration time.

Justification of the composition and technology for obtaining orally disintegrating mini-tablets

The direct compression method is most commonly used in the production of mini-tablets [11], as its advantages are due to the reduced number of technological stages and, consequently, economic efficiency. The authors of the present study followed this example and also used the direct compression method.

The risk analysis performed showed that the effectiveness of the direct compression method is due to the flowability of the powder mixture. Considering the low content of the active ingredient (propranolol hydrochloride content—5.7 %), flowability is mainly determined by the composition of excipients [14]. To select the optimal composition, the authors analyzed existing ODMT formulations [16, 29–31] obtained by direct compression, as well as reference data on excipients[10].

The main group of excipients in mini-tablets are fillers. The choice of mannitol was necessary—it is one of the few excipients that fully meets the objectives of developing orally disintegrating forms due to its favorable organoleptic properties and low hygroscopicity[11]. However, the use of mannitol in high concentrations led to adhesion of the powder mixture to the punches, due to which its content was limited to 55.3%. At the same time, varying the proportion of mannitol near this value did not significantly affect flowability. To compensate for the filler, MCC 102 was additionally introduced into the composition. Its choice is due to optimal flowability, as well as its ability to perform the function of a binder, ensuring the formation of strong tablets during direct compression. The proportion of MCC 102 was set in the range of 31 % to 36.5 %, which was dictated by the need to comply with the main MD constraint—achieving a total mixture mass equal to 100 %.

However, even with an optimal ratio of fillers, the flowability of the mixture remained insufficient for stable filling of small-sized dies. The die filling process is critical for ensuring the quality of mini-tablets, as their uneven filling leads to variability in mass and, consequently, active ingredient content [32]. The use of a 3 mm diameter die in the present study necessitated a significant increase in the flowability of the tablet mixture. For this purpose, colloidal silicon dioxide was introduced into the composition at a fixed concentration of 1.0%—the upper limit of the recommended range[12]. This measure allowed achieving satisfactory flowability and stabilizing the tableting process.

The second critical quality parameter was disintegration time, which is determined by the content of both disintegrants and superdisintegrants and lubricants. Since the target disintegration time for mini-tablets was less than 30 s, the content of CPV and SSF was chosen as independent variables.

[9] Design of Experiments for Pharmaceutical Product Development: Volume I: Basics and Fundamental Principles; Beg S, editor; Singapore: Springer Singapore; 2021. DOI: 10.1007/978-981-33-4717-5

[10] Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients, 6th ed. London: Pharmaceutical Press; 2009

[11] Ibid.

[12] Ibid.

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At the same time, an increase in the proportion of superdisintegrant, on the one hand, can contribute to accelerated disintegration, and on the other hand, reduce the mechanical strength of mini-tablets and worsen the flowability of the mixture. The choice of CPV as a superdisintegrant is due to its ability to ensure rapid disintegration of tablets [33, 34]. The content of the superdisintegrant varied in the range of 1 % to 5 %, which corresponds to the recommended limits for this group of excipients.

The content of the lubricant was also of decisive importance: its deficiency leads to adhesion of the mixture to the punch surfaces, while an excess causes an increase in disintegration time and a decrease in the strength of mini-tablets [30]. The choice of SSF as a lubricant is due to its advantages compared to traditional stearates [35]. It is characterized by lower hydrophobicity and no pronounced retardation of disintegration rate compared to magnesium stearate, while maintaining comparable lubricating ability and not inferior in its effect on tablet strength. It is important to note that its lubricating effectiveness increases with increasing mixing time, and tablet disintegration is not impaired [36].

During the experiment, it was found that compositions containing 0.5 % SSF caused adhesion of the tablet mass to the punch surfaces after pressing only a few units. Despite satisfactory mechanical strength indicators, these compositions could not be considered acceptable. In this regard, an additional response was introduced into the optimization scheme—adhesion of the mixture to the press tool, which was expressed on a binary scale: 0—no sticking, 1—sticking. This indicator had priority in the selection of the composition.

Quality assessment of obtained mini-tablets

When developing mini-tablets, special attention should be paid to the validity of pharmacopoeial testing methods, as standard procedures do not always take into account the geometric features of this dosage form.

The first example is the standardization of the strength indicator. The State Pharmacopoeia of the Russian Federation, XV edition, establishes requirements for the minimum strength of tablets with a diameter of 6 mm and above, equal to 30 N; however, the regulated standards are not applicable to mini-tablets with a diameter of 3 mm. Guided by practical expediency, the authors established a target strength of at least 25 N, which ensures the integrity of mini-tablets during packaging, transportation, and subsequent use.

A similar problem arises when assessing the disintegration of mini-tablets [11]. The main part of the disintegration apparatus is a collecting basket. According to GPhM.1.4.2.0013 “Disintegration of Solid Dosage Forms”, a mesh with holes of 2.0 ± 0.2 mm should be attached to the lower surface of the bottom plate of the basket. At the same time, the size of mini-tablets is 3 mm or less. Often, ODMTs pass through the sieve holes during disintegration testing, leading to unreliable results. One solution has been proposed by Kleinebudde [11]. The ODMT is placed in a cylinder 15 mm high and 10 mm in internal diameter, closed at the top and bottom with a mesh of 710 μm pore diameter. This cylinder was placed in a disintegration testing apparatus. The authors proposed another method: using a sieve with a pore size of 0.25 × 0.25 mm instead of the pharmacopoeial sieve fixed to the lower surface of the basket. This modification proved successful, as it reliably retained the ODMTs in the basket throughout the test and yielded reproducible, objective disintegration time results.

Regarding the results of the abrasion assessment, it should be noted that the reliability of the obtained values may be limited due to the mismatch between the geometric parameters of the ODMTs and the dimensions of the apparatus drum, as stipulated by the SPh RF XV ed. In the authors’ opinion, the pharmacopoeial method requires adaptation for an objective assessment of ODMT abrasion.

Study Limitations

The study is limited to the laboratory stage; further investigation into storage stability, biopharmaceutical studies, and subsequent clinical trials are required.

CONCLUSION

During the study ODMTs of propranolol hydrochloride intended for personalized therapy of IH in children were developed and obtained. The application of the QbD methodology and the Design of Experiments (DoE) method allowed for a scientifically grounded formulation, quantitative assessment of the influence of excipients on CQA, and identification of significant inter-component interactions. The optimized formulation ensures the required technological characteristics of the ODMTs—strength, disintegration, abrasion, and content uniformity—and fully complies with established requirements.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Yaroslav S. Novikov — conceptualization, methodology, investigation, writing—original draft, visualization; Maria D. Uryasova — methodology, investigation; Svetlana N. Egorova — conceptualization, methodology, guidance, writing—original draft, writing—review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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