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Assessment of potential risks at the pharmaceutical development stage of minitablets

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The production of mini tablets (MTs) differs significantly from the production of regular-sized tablets and involves certain risks. The article analyzes scientific publications on the topic of MTs development and production, and based on the data obtained, assesses the risks associated with it.

The aim: To conduct a risk assessment during the pharmaceutical development of MTs.

Materials and methods. The research materials were based on the ICHQ8 guidelines for pharmaceutical development and ICHQ9 guidelines for quality risk management, State Pharmacopoeia of the Russian Federation XV edition, scientific publications on the pharmaceutical development and production of MTs. The study was conducted using the PHA (preliminary hazard analysis) method. The following were considered as critical quality attributes (CQAs) of MTs: disintegration, dissolution, uniformity of dosage units, uniformity of mass, crushing strength, and friability. Hazards were identified using the Ishikawa diagram method. Risk analysis was performed based on data from scientific publications on the development and production of MTs. Articles were searched for between 1990 and 2024 in the ScienceDirect, PubMed, Google Scholar, and elibrary.ru databases. Based on the information presented in these articles and using a logical method, the probability of occurrence and severity (consequences) of the risks were determined. Risk assessment was carried out using a risk matrix.

Results. Among the parameters of the MTs production process, the compression and mixing stages pose a danger. The compression is associated with a high risk for the following CQAs: dissolution, uniformity of dosage units, uniformity of mass, and crushing strength. Mixing is critical to ensuring dosage uniformity. Parameters of the active pharmaceutical ingredient (API), such as particle size and shape, significantly affect dissolution. In addition, the compressibility and flowability of the API are risk factors for ensuring the uniformity of dosage and MTs mass. The choice of excipients (EPs) is of great importance in the development of MTs. The type and content of the filler are of the greatest risk to the studied MTs. An irrational choice of disintegrant and anti-friction EPs can lead to impaired disintegration and dissolution of MTs.

Conclusion. As a result of the risk assessment, hazards were identified, and key risks associated with the pharmaceutical development of MTs were analyzed and evaluated. Particular attention was paid to the main groups of hazards — the influence of the properties of API, EPs, and production process parameters on MTs CQAs. It was found that during the development of MTs, the shape and size of the API particles, the compressibility and flowability of the powder mixture, the type and content of the filler and disintegrant, as well as such technological process parameters as pressing and mixing, pose a particular risk.

Keywords: mini-tablets, risk assessment, quality by design, dosage forms for children.

Abbreviations: DF — dosage form; EP — excipient; SPh XV — State Pharmacopoeia of the Russian Federation XV edition; MT — mini-tablet; PHA — Preliminary Hazard Analysis; CQA — critical quality atribute; API — active pharmaceutical ingredient.

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Оценка возможных рисков на этапе фармацевтической разработки мини-таблеток

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Производство мини-таблеток (МТ) значительно отличается от выпуска таблеток обычного размера и сопряжено с определёнными рисками. В статье проведён анализ научных публикаций на тему разработки и производства МТ, и на основе полученных данных оценены связанные с этим риски.

Цель. Провести оценку рисков при фармацевтической разработке МТ.

Материалы и методы. В качестве материалов исследования за основу были взяты руководства по фармацевтической разработке ICHQ8 и управлению рисками для качества ICHQ9, рекомендации Государственной фармакопеи РФ XV издания, научные публикации по фармацевтической разработке и производству МТ. Исследование проводили методом PHA (предварительного анализа опасностей). В качестве критических показателей качества (КПК) МТ были рассмотрены: распадаемость, растворение, однородность дозирования, однородность массы, прочность на раздавливание, истираемость. Идентификация опасностей проводилась методом построения диаграммы Исикавы. Анализ рисков проводился на основании данных научных публикаций на тему разработки и производства МТ. Поиск статей осуществлялся за период с 1990 по 2024 год в базах данных ScienceDirect, PubMed, Академия Google и elibrary.ru. На основании сведений, представленных в этих статьях, и логическим методом были определены вероятность возникновения и тяжесть (последствия) рисков. Оценивание рисков проводилось с использованием матрицы рисков.

Результаты. Среди параметров технологического процесса производства МТ представляют опасность стадии прессования и смешивания. Прессование связано с высоким риском для следующих КПК: растворение, однородность дозирования, однородность массы и прочность МТ на раздавливание. Смешивание критически важно для обеспечения однородности дозирования. Параметры активной фармацевтической субстанции (АФС), такие как размер и форма частиц, существенно влияют на растворение. Кроме того, прессуемость и сыпучесть АФС являются рискообразующими факторами для обеспечения однородности дозирования и массы МТ. Огромное значение при разработке МТ имеет выбор вспомогательных веществ (ВВ). Наибольший риск воздействия на изучаемые КПК представляет тип и содержание наполнителя. Нерациональный выбор дезинтегранта и антифрикционного ВВ может привести к нарушению распадаемости и растворения МТ.

Заключение. В результате оценки рисков были идентифицированы опасности, проанализированы и оценены ключевые риски, связанные с фармацевтической разработкой МТ. Особое внимание было уделено основным группам опасностей — влиянию свойств АФС, ВВ и параметрам производственного процесса на КПК МТ. Выявлено, что при разработке МТ особый риск представляет форма и размер частиц АФС, прессуемость и сыпучесть порошковой смеси, тип и содержание наполнителя и дезинтегранта, а также такие параметры технологического процесса, как прессование и смешивание.

Ключевые слова: мини-таблетки; оценивание рисков; качество через дизайн; лекарственные формы для детей

Список сокращений: ЛФ — лекарственная форма; ЛП — лекарственный препарат; ВВ — вспомогательное вещество; МТ — мини-таблетка; PHA — предварительный анализ рисков (Preliminary Hazard Analysis); КПК — критический показатель качества; АФС — активная фармацевтическая субстанция.

INTRODUCTION

The lack of special dosage forms (DFs) with reduced dosage for children is an important problem in modern pediatric pharmacotherapy. To a large extent, medicines developed only for adults are used in pediatrics outside the approved indications (off-label) [1]. For example, angiotensin-converting enzyme inhibitors (captopril, enalapril), angiotensin II receptor blockers (losartan, valsartan), β-blockers (carvedilol), diuretics (spironolactone, hydrochlorothiazide, furosemide), cardiac glycosides (digoxin), etc. are used to treat heart failure in children [2]. Often, there are no

specially developed DFs for children of these medicines on the pharmaceutical market, which forces their usage intended for adults. This approach entails increased risks associated with the lack of reliable data on the safety and efficacy of medicines for the children's body [3].

In the context of current problems in pediatric pharmacotherapy, the task of developing new DFs for children is relevant. However, the process of creating specialized drugs for children is associated with certain difficulties. Solid DFs, including tablets and capsules, can cause swallowing problems in children, which negatively affects adherence to the prescribed course of treatment. Liquid DFs, such as solutions and suspensions, are more preferable, but they also have disadvantages: short shelf life, risk of microbial contamination, the presence of non-indifferent excipients (EPs), as well as inaccurate dosing [4, 5].

A promising DF for children is mini-tablets (MTs). The number of publications on the topic of MT development has increased significantly recently [6]. At the same time, orodispersible MTs, which combine the advantages of liquid DFs and conventional tablets, are of great interest [7]. According to Lennartz and Mielck, MTs are tablets with a diameter of 2–3 mm or less [8]. MTs have a number of advantages: easy swallowing, flexible dosing, ensuring accurate dosing, high stability compared to liquid DFs [9]. Unlike pellets, MTs have a constant shape and size, a smooth surface, a low degree of porosity and high mechanical strength, which together facilitates the application of a coating on MTs [10].

MTs are a suitable DF for children of different ages. Klingmann et al. studied the acceptability of uncoated MTs in newborns. The study involved 151 children, with an average age of 4.07 days. The study participants received 2 mm diameter and 7 mg MT-placebo. As a result, 82.2% of children completely swallowed the MT, and none of the newborns experienced severe complications in the form of aspiration [11]. In another study, also conducted by Klingmann et al., the effect of coated and uncoated MT-placebo on children aged 6 months to 5 years was studied. The MT was placed on the child's tongue, after which he was offered to swallow them, drinking with a selected drink (no more than 3 sips). 306 children took part in the study. No child experienced aspiration problems as a result of taking uncoated MTs. Only two cases of coughing were recorded after taking coated MTs among children aged 0.5 to 1 year, but these cases were not clinically significant [12].

In accordance with the ICH Q8 guideline[1], one of the stages of pharmaceutical development is risk assessment. Risk assessment is a valuable scientific process used in quality risk management to identify material indicators and process parameters that potentially affect the critical quality attributes (CQA) of a drug. Risk assessment is usually carried out at an early stage of the pharmaceutical development process and is repeated as more information becomes available and more knowledge is gained[2]. At the same time, in accordance with the ICH Q9 guideline[3] on quality risk management, risk assessment consists of identifying hazards, analyzing and evaluating risks [14]. In the process of pharmaceutical development of MTs, conducting a risk assessment is a critical step to ensure the high quality of the final product. Risk assessment is necessary to identify all potential elements with an increased level of risk and their subsequent detailed study as part of the planning of experimental studies.

THE AIM. Assessment of potential risks at the pharmaceutical development stage of MTs for children.

MATERIALS AND METHODS

The research materials were based on the ICH Q8[4] guidelines for pharmaceutical development and ICH Q9[5] guidelines for quality risk management, recommendations of the State Pharmacopoeia of the Russian Federation XV edition (SPh XV)[6], scientific publications on pharmaceutical development and production of MTs.

The following were considered as CQA MTs: disintegration, dissolution, uniformity of dosage, uniformity of mass, crushing strength, abrasion.

Hazard identification

At the first stage of risk assessment, the PHA (Preliminary Hazard Analysis)[7] method was used to identify hazards — the systematic use of information to identify hazards related to the issue regarding risk or problem description [13, 14]. The Ishikawa diagram ("fishbone") was used to assess cause-and-effect relationships. It is a graphical tool for organizing and presenting knowledge and ideas generated as a result of the collective analytical process of the

[1] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[2] Ibid.

[3] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

[4] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[5] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

[6] State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/. Russian

[7] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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research team. Causes are classified according to their significance or level of detail, resulting in a hierarchical structure similar to a fish skeleton, where the main categories of causes are represented as "bones" connected to the "spine" [15, 16]. Using this method, the main groups of hazards were logically identified. The most significant groups were located closer to the top of the fish.

Risk analysis and measurement

At the second stage, the analysis and measurement of risks associated with the identified hazards[8] was carried out. For this purpose, data from scientific publications on the development and production of MTs were used. The search for articles was carried out for the period from 1990 to 2024 in the ScienceDirect, PubMed and Google Scholar databases using the keywords: "minitablets", "minitablets", "minitablets development", "minitablets manufacturing", and in elibrary.ru using the keywords "mini-tablets". The initial search identified 82 publications; after removing duplicates, 52 unique articles remained, which were evaluated by titles and abstracts for relevance. For a detailed analysis of risks according to established criteria (publications 1990–2024, focus on MTs development / production, availability of full text), 15 of the most relevant articles containing experimental data on the composition and technology of MTs production were selected. Based on the information presented in these articles, and by logical method, the probability of occurrence and severity (consequences) of risks were determined.

The probability of a risk occurring was assessed on a scale: A — almost certainly (1:2), B — likely (1:10), C — possible (1:100), D — unlikely (1:1000), E — rare (1:10000). The severity of the risk was assessed on a 5-point scale: 1 — insignificant, 2 — stopping the technological process, 3 — rejection of the batch, 4 — non-compliance with the specification, 5 — detected only by the patient [17].

Risk assessment

At the last stage, risk assessment was carried out — comparing the identified and analyzed risk with the specified risk criteria [14]. For this, a risk matrix described by N. Baker was used (Table 1). Risks were divided into low, medium and high [17].

RESULTS AND DISCUSSION

Hazard identification

At the first stage, the main groups of hazards affecting CQA were identified: properties of the active pharmaceutical substance (API), type and content of EP, equipment used, parameters of the technological process, packaging, quality control, staff, environment[9] (Fig. 1).

As shown in Figure 1, the main hazards associated with API are the shape and size of particles, flowability and compressibility properties, hygroscopicity. The choice of the main groups of EPs, such as fillers, disintegrants, anti-friction and binding substances, is important in the development of MTs. The main parameters of the technological process, such as speed, time and degree of grinding and mixing, pressing pressure affect the quality indicators of MTs. The choice of equipment, namely a mixer, grinder, type of tablet press and a set of press tools, also poses a hazard.

The choice of packaging type, material of primary and secondary packaging and quality control of MTs is also important[10]. Hazards associated with personnel and the environment are general in nature and are also important in the development of MTs.

At the second stage, the influence of the most significant hazards in pharmaceutical development[11] (API, EP, parameters of the production process) on CQA was analyzed. Other risks (equipment, packaging, personnel and environment) were excluded from the analysis, since their role is manifested at later stages of MT production.

Mass and dosage uniformity

Mass uniformity and dosage uniformity are important CQA for low-dose DFs. Alalaiwe et al. report that the risk of dosage and mass non-uniformity increases as the tablet size decreases. One way to reduce the risk is to reduce the particle size. However, reducing the size can lead to a deterioration in the flowability of the powder due to particle adhesion and segregation, which can ultimately reduce the uniformity of dosage and mass of MTs obtained by direct compression [18].

As part of a study conducted by I. Stoltenberg et al., the development of 2 mm diameter orodispersible MTs containing hydrochlorothiazide at a dosage of 1 mg was carried out. The manufacturing process was carried out by direct compression using various EP, including Ludiflash, Parteck ODT, Pearlitol Flash, Pharmaburst 500 and Prosolv ODT. The final MTs were characterized by an average weight in the range from 6.41 to 6.61 mg. The authors of the study emphasize the critical role of the pressing process in ensuring the uniformity of dosage and mass of tablets. It was found

[8] Ibid.

[9] Ibid.

[10] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[11] Ibid.

that parameters such as the flowability of the mixture, the size and shape of particles do not have a noticeable effect on the uniformity of dosage [19].

Khan et al. note that to ensure a constant tablet weight and dosage uniformity, it is necessary to ensure good powder flowability. This ensures that the required amount of powder enters the matrix. The authors studied the effect of mixing parameters of a powder mixture of carvedilol with various EPs on the dosage uniformity of MTs. In addition to carvedilol (0.5 and 2 mg), the MTs included EP such as mannitol, microcrystalline cellulose and magnesium stearate. It was assumed that increasing the mixing time contributes to improving the uniformity of dosage, however, extending the mixing to 15 min led to segregation of carvedilol particles, as a result of which heavier particles sank to the bottom of the mixture. As a result, the authors determined the optimal mixing mode: 5 minutes at a speed of 250 rpm, followed by the addition of microcrystalline cellulose [20].

In their study, Lura and Breitkreutz investigated the effect of various press tools used to form tablets on the mass uniformity of MTs. The authors obtained 2 and 3 mm MTs using punches with 1, 7 and 19 tips on the Styl'OneEvo tablet compactor. As a result, the greatest differences in mass are observed in the zones in which the matrix holes were constantly under the shoe (feeder) and in the holes located closer to the edges of the matrix. The researchers note that the process of filling the matrix is a critical process in the production of MTs, and the mass uniformity of MTs depends on the system of press tools and mechanisms for filling the matrix [21].

The data presented indicate that in the pharmaceutical development of MTs, the flowability of the powder mixture, pressing pressure, type and content of the filler have a significant impact on the uniformity of dosage and mass of MTs. Pressing pressure probably (B) affects the listed CQA and can lead to rejection of the batch (3) (Table 2). Particular attention should be paid to the mixing process. Insufficient or excessive mixing time probably (B) can lead to settling of large API particles or uneven distribution of the lubricant, which will lead to non-uniformity of MT dosage and rejection of the batch (3) (Table 2). Almost certainly (A) poor flowability of the API and filler mixture will lead to problems filling the matrix and ultimately — to stopping the technological process (2) or rejection of the batch (3) (Tables 3 and 4).

Abrasion

Abrasion is the damage to tablets under the influence of mechanical shock or abrasion during processing (shaking, vibration, etc.)[12]. In a study conducted by Alalaiwe et al., 3 mm diameter sildenafil MTs were obtained on a rotary tablet press at a pressing pressure of 8 kN. The authors of the study determined the effect of EP, namely pregelatinized starch (Starch 1500) and microcrystalline cellulose (Avicel PH 105), on the abrasion of tablets. During 9 tests, the abrasion of MTs ranged from 0.65% to 1.22%. It was found that with an increase in the concentration of microcrystalline cellulose (from 10 to 40%) and pregelatinized starch (from 2% to 10%), the abrasion of tablets decreased, with pregelatinized starch having the greatest impact on this indicator [18].

Mitra et al. in their study examined the effect of particle size and ibuprofen content in MTs with a diameter of 1.2, 1.5, 2 and 2.5 mm on the abrasion index. The researchers did not find a statistically significant effect of variables such as particle size and ibuprofen content on the abrasion of MTs. Nevertheless, it was found that smaller MTs (1.2 mm) showed higher abrasion rates, ranging from 0.8% to 1.1%, compared to larger diameter tablets (2.5 mm), in which this indicator was from 0.1% to 0.2% [22].

In the study Stoltenberg et al. applied a modified method for studying the abrasion of orodispersible MTs of hydrochlorothiazide. 1 g of MTs in a closable vial were shaken using a Universalshaker SM 25 mechanical shaker (EdmundBühler, Hechingen, Germany) for 1 hour at a frequency of 200 rpm. Then the samples were dedusted using an air jet sieve with a mesh size of 125 µm and a pressure of 600 Pa for 1 min. Samples were weighed before and after processing. All samples obtained at a pressing pressure of 5 kN to 10 kN had an abrasion of less than 1%. In addition, the authors noted that the abrasion of MTs does not always correlate with their crushing strength. The Prosolv® ODT composition, pressed at 3 kN, showed higher crushing strength compared to the Pearlitol® Flash composition, pressed at 5.5 kN, which in turn had satisfactory abrasion. Based on these results, the authors concluded that it is necessary to apply a pressing pressure of at least 5.5 kN to achieve optimal tablet strength [19].

Taking into account the above, it was concluded that the presence of EP, the size of MTs and the pressing pressure affect the abrasion index in MTs. Often, with an increase in pressing pressure, the abrasion of tablets decreases. Almost certainly (A) insufficient pressure can lead to non-compliance of MTs with the specification (4) (Table 2). The type and

[12] GPhM.1.1.1.0015 Abrasion. 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/

ОРИГИНАЛЬНАЯ СТАТЬЯ
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content of the filler probably (B) can also lead to non-compliance with the specification (4) (Table 3). The effect of API should be considered only with its high content in MTs. It is worth noting that the method for determining abrasion, intended for conventional tablets, is not sensitive enough, therefore, for MTs, it is advisable to consider other methods, for example, the method for determining abrasion for granules and spheroids [23].

Crushing strength

The crushing strength of tablets (tablet resistance to pressure) shows the force required to destroy tablets[13]. In a study conducted by Stolnberg et al., the dependence of the strength of orodispersible MTs of hydrochlorothiazide on the pressing pressure and incoming EP was evaluated. It was found that a crushing strength of more than 7 N is achieved in compositions with Parteck ODT at a pressing pressure of 5.5 kN (7.4 N) and 8 kN (11.8 N), Ludiflash at a pressure of 8 kN (8.1 N), and Pharmaburst at a pressure of 8 kN (8 N). At the same time, compositions with Proslov ODT at a pressure of 5.5 kN and 8 kN, as well as Pearlitol Flash at a pressure of 8 kN and 10 kN, showed a crushing strength of less than 7 N [19].

Alalaiwe et al. studied the crushing strength of sildenafil MTs. The strength of the obtained MTs varied from 2.86 kiloponds (28 N) to 5.31 kiloponds (52 N). In addition, the crushing strength increased with increasing content of MCC and pregelatinized starch [18].

In a study by Cho et al., the effect of fillers and lubricants on the strength and ejection force of MTs was studied. The authors obtained acyclovir MTs on a STYL'OneEvo compactor using a set of punches with 29 tips. MCC 101 (from 24.25% to 97%) and pregelatinized starch (from 24.25% to 97%) were selected as fillers for comparison, and magnesium stearate (0.5% and 2%) was used as lubricants. Granules were pre-obtained by wet granulation. The authors claim that pregelatinized starch was more effective in reducing the ejection force of MTs. Increasing the amount of magnesium stearate also led to a decrease in the ejection force. However, the researchers draw attention to the fact that the use of lubricants in high quantities is undesirable due to the decrease in the mechanical strength of MTs [24].

Thus, one of the main factors to pay attention to when developing MTs is the pressing pressure (Table 2). Almost certainly (A) non-optimal pressing pressure will lead to non-compliance with the specification in terms of MT crushing strength (4). The choice of the appropriate filler will probably (B) ensure good adhesion of the particles of the powder mixture and, therefore, sufficient strength of the MT, which prevents serious consequences in the production of MTs (4) (Table 4). Also, special equipment may be needed to measure the crushing strength of MTs [18].

Dissolution

Dissolution is used to determine the amount of active substance that is released into the dissolution medium from the medicine in a solid dosage over a certain period of time[14]. In a study conducted by Mitra et al., the effect of particle size and ibuprofen content, as well as the diameter of MTs on release was studied. A USP I type dissolution apparatus was used for the tests. The researchers indicate that MTs with 3% ibuprofen content show a higher release rate compared to MTs containing 25% ibuprofen: 80% and 45% in 30 min, 90% and 65% — 60 min, respectively, while complete dissolution is achieved after 90 min. The authors also note that with an increase in the diameter of MTs (from 1.2 mm to 2.5 mm) with 25% ibuprofen content and a particle size of 60 µm, a decrease in the release rate is observed. In addition to this, it was found that the particle size affects the release efficiency: MTs with 25% ibuprofen content and a particle size of 60 µm showed a faster release compared to those with a particle size of 100 µm, with results of 74% and 61% in 30 min, and 91% and 83% — 60 min, respectively [22].

[13] GPhM.1.1.1.0017 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/

[14] Ibid.

Table 1 — Risk matrix

		Severity				
		1	2	3	4	5
Probability	A					
	B					
	C					
	D					
	E					

Note: risks: — low, — medium, — high.

Table 2 — Risks of critical quality attributes due to technological process parameters

Critical quality attributes	Technological process parameters			
	Sieving	Mixing	Lubrication	Pressing
Disintegration	Low	Low	Low	Medium
Dissolution	Low	Low	Low	High
Dosage uniformity	Low	High	Low	High
MT mass uniformity	Low	Low	Low	High
Crushing strength	Low	Low	Medium	High
Abrasion	Low	Low	Low	Low

Table 3 — Risks of critical quality attributes due to pharmaceutical-technological properties of active pharmaceutical ingredient

Critical quality attributes	Pharmaceutical-Technological Properties of active pharmaceutical ingredient			
	Flowability	Particle Size and Shape	Compressibility	Solubility
Disintegration	Low	Low	Medium	Medium
Dissolution	Low	High	Medium	High
Dosage uniformity	High	Medium	High	Low
Mass uniformity	High	Medium	High	Low
Crushing Strength	Low	Low	Low	Low
Abrasion	Low	Low	Low	Low

Table 4 — Risks of critical quality attributes due to the type and content of excipients

Critical quality attributes	Groups of excipients (type and content)			
	Fillers	Disintegrants	Binders	Antifriction
Disintegration	Medium	High	Medium	Medium
Dissolution	Medium	High	Medium	High
Dosage uniformity	High	Low	Low	Medium
Mass uniformity	High	Low	Low	Low
Crushing strength	High	Medium	Medium	Medium
Abrasion	High	Medium	Medium	Medium

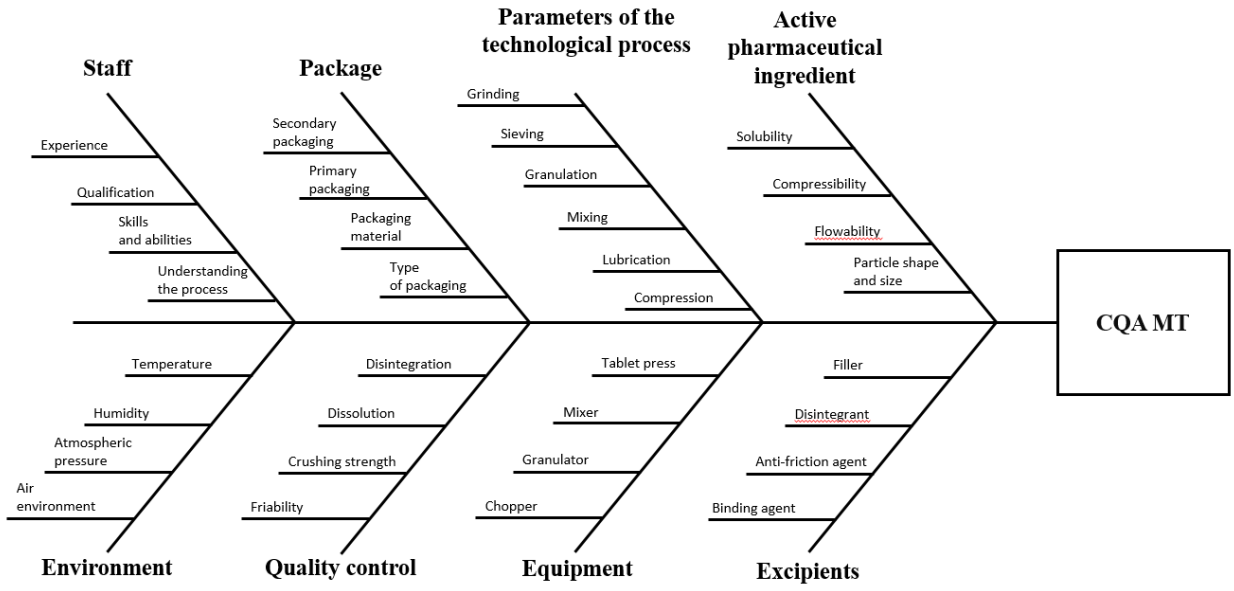

Figure 1 – Factors affecting the critical quality indicators of mini-tablets.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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In a study by Alalaiwe et al. it was shown that the release of sildenafil from MTs was more influenced by the content of pregelatinized starch. With an increase in the content of pregelatinized starch (from 2% to 10%), the percentage of sildenafil released increased from 76.49% to 89.31% during the 30-minute test [18].

At the same time, it should be borne in mind that standard methods for determining dissolution may not be suitable for MTs, and in some cases modified methods are required. One such method is described by Hellberg et al. The study used a modified method for determining the dissolution of ODT MTs of sodium salicylate using a mini-vessel of 250 mL, mini-blades 1/3 the size of standard blades and different rotation speeds of the mini-blades. The authors conclude that this method proved useful for testing MTs, however, similar results can be obtained using standard equipment [25].

Thus, API and EP have a significant impact on the dissolution of MTs. Almost certainly (A) the wrong choice of disintegrant or lubricant will lead to a deviation of the specified CQA and a decrease in the effectiveness of the drug, which can only be detected by the patient (5).

Disintegration

According to PhM.1.4.1.0015 “Tablets”, if the pharmacopoeial article provides for a test for the “Dissolution” indicator, then it is allowed not to conduct a test for the “Disintegration” indicator [15]. Nevertheless, this indicator (the ability of solid dosage DFs to disintegrate in a liquid medium over a certain period of time)[15], in our opinion, is very important and necessary in the pharmaceutical development of MTs.

In a study conducted by Subh et al., it was demonstrated that the disintegration of tablets largely depends on the type and content of EP. The authors obtained 5 mm paracetamol MTs with a dosage of 40 mg by direct compression. During the experiment, the effect of the content of various EP on the disintegration time of MTs was evaluated: Pharmaburst (from 10 MG to 70 mg), sodium starch glycolate (from 1 MG to 10 mg) and magnesium stearate (from 1 MG to 6 mg). It was found that the content of magnesium stearate has the greatest impact on the rate of disintegration, which is confirmed by its influence coefficient, equal to 11.10, while for Pharmaburst and sodium starch glycolate the coefficients were –0.4 and –0.6, respectively [9].

As part of a study conducted by Warnken et al., 2 mm diameter MTs containing 50% clofazimine were obtained by direct compression. Clofazimine is poorly soluble in water and has a small particle size. The paper emphasizes that the process of pressing clofazimine is associated with difficulties due to the formation of intermolecular bonds between small particles, which prevents the disintegration of tablets. The authors added various EP, including 1% sodium stearyl fumarate and 5% croscarmellose sodium. The greatest decrease in disintegration time was recorded when using croscarmellose sodium, which, without dissolving in water, is able to swell, thereby ensuring rapid disintegration of tablets. To reduce the interfacial interaction between the tablet matrix and the powdered substance, it was proposed to use 1% sodium stearyl fumarate and 1% sodium lauryl sulfate. The use of the widely used glidant magnesium stearate was recognized as impractical, since it can create a hydrophobic layer that prevents the disintegration and dissolution of tablets [26].

In the study Stolnderg et al. characterized the negative effects associated with the use of lubricants, which lead to a decrease in wetting and an increase in the disintegration time of ODT MTs of hydrochlorothiazide. The authors compared the effectiveness of magnesium stearate and sodium stearyl fumarate, used as lubricating additives in concentrations from 2% to 5%. The results showed that sodium stearyl fumarate provides faster disintegration of MTs, even at higher content, which indicates its advantages as a lubricant compared to magnesium stearate [19].

However, in a study by Sabbatini et al. it is argued that the presence of a lubricant does not affect the kinetics of water absorption in the presence of a disintegrant. The authors studied the disintegration of tablets depending on the amount of croscarmellose sodium (from 0% to 5%) with a constant amount (3%) of different lubricants, such as magnesium stearate, sodium stearyl fumarate and sodium lauryl sulfate. The disintegration time depended only on the concentration of the disintegrant, and the type of lubricant had no effect. Tablets without disintegrant remained intact for more than 15 min, but with the addition of croscarmellose sodium, the time decreased to less than 20 s [27].

Based on this, when developing MTs, special attention should be paid to the choice of lubricants, since they significantly affect the disintegration index (Table 4). If possible, the addition of magnesium stearate should be avoided, since it probably (B) forms a hydrophobic layer and thereby reduces disintegration,

[15] GPhM.1.4.2.0013 Disintegration. State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/raspadaemost-tvyerdykh-lekarstvennykh-form-/

leading to non-compliance with the specification (4). Almost certainly (A) disintegration depends on the type and content of the disintegrant (Table 4). Its choice is one of the key factors in the development of orodispersible MTs (A). Pressing pressure also has a noticeable effect (C), reducing the disintegration of MTs (3) (Table 2). In addition, for orodispersible MTs, it is necessary to consider conducting a wettability test [23].

At the final stage, a risk assessment of the parameters of the technological process (Table 2), API (Table 3) and EP (Table 4) on the CQA MTs was carried out using a risk matrix.

As a result of the risk assessment, it was found that among the parameters of the technological process (Table 2), the processes of pressing and mixing pose a hazard. Pressing is associated with a high risk for the following CQA: dissolution, uniformity of dosage and uniformity of mass of MTs and crushing strength of MTs. Mixing is critical to ensure dosage uniformity. API parameters (Table 3), such as particle size and shape, significantly affect dissolution. In addition, the compressibility and flowability of API poses a hazard in ensuring the uniformity of dosage and mass of MTs. The choice of EP is of great importance in the development of MTs (Table 4). The greatest risk to the studied CQA is the type and content of the filler. An irrational choice of disintegrant and antifriction EP can lead to a violation of the disintegration and dissolution of MTs.

Study limitations

The limitations of the study include the lack of experimental data on the pharmaceutical development and industrial production of MTs. Further experimental studies on the pharmaceutical development of MTs for pediatric practice are recommended, taking into account the identified risk factors.

CONCLUSION

Thus, hazards were identified, key risks associated with the pharmaceutical development of MTs were analyzed and assessed. Special attention was paid to the main groups of hazards — the influence of API properties, EP and parameters of the production process on the CQA MTs. It was revealed that in the development of MTs, the shape and size of API particles, the compressibility and flowability of the powder mixture, the type and content of the filler and disintegrant, as well as such parameters of the technological process as pressing and mixing, pose a particular risk. These pharmaceutical factors must be taken into account in pharmaceutical development

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Yaroslav S. Novikov — the concept and methodology, study conducting, draft writing a of the manuscript, writing the manuscript (reviewing and editing), visualization; Svetlana N. Egorova — the concept, scientific guidance, writing the manuscript (reviewing and editing). All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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