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DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF COATED TABLETS WITH RHEUM CORDATUM LOSINSK. EXTRACT

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Objective: Development of a rational composition, optimal technology, standardization criteria for tablets with Rheum cordatum extract, establishing the stability of the composition and storage conditions.

Methods: As an active pharmaceutical substance, a standardized extract of Rheum cordatum was used. Pharmacopoeial excipients for the production of tablet mass are magnesium hydroxycarbonate, croscarmellose sodium, microcrystalline cellulose, Plasdone S-630, magnesium aluminum metasilicate, calcium stearate, purified water and film coating Opadry 85F18422 White. To obtain tablets qualified equipment was used in the technological process: a tablet mass mixer, a rotary tablet press, highly efficient film coating equipment, a packaging machine / blister machine. When developing the tablets, we were guided by the «Quality by design» concept of medicines, based on ICH guidelines: ICH Q11 «Development and manufacture of medicinal substances», ICH Q8 «Pharmaceutical Development» and ICH Q10 «Pharmaceutical Quality System». Standard pharmacopoeial research methods were used.

Results: 50 experimental mass models for tableting have been developed in the variants of combining excipients and active substance in an effective single dose of 300 mg. Only 4 models of the core tablets obtained met the selection criteria (abrasion, crush resistance, disintegration, and dissolution). The optimal tableting method using wet granulation is substantiated, which makes it possible to obtain tablets of the proper pharmacopoeial quality and the following composition: soft rhubarb root extract, magnesium hydroxycarbonate, croscarmellose sodium, microcrystalline cellulose 102, Plasdone S-630, magnesium aluminum metasilicate, calcium stearate. To coat the obtained tablet cores, the following film coating composition was selected: Opadry 85F18422 White, consisting of polyvinyl alcohol, titanium dioxide E 171, macrogol 4000 and talc.

Conclusions: The pharmaceutical development of coated tablets with an extract of Rheum cordatum has been done. The rational composition and optimal technology for producing tablet cores coated with a film coating of Opadry 85F18422 White were established. The quality of the obtained tablets was evaluated, the stability of the composition for 9 months was studied, the results of quality indicators are within acceptable standards, and research in this direction is going on.

Keywords: *Extract, coated tablets, pharmaceutical development, composition, technology, stability.*

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РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ ТАБЛЕТОК, ПОКРЫТЫХ ОБОЛОЧКОЙ, С ЭКСТРАКТОМ RHEUM CORDATUM LOSINSK

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Цель: разработка рационального состава, оптимальной технологии, критериев стандартизации таблеток с экстрактом ревеня сердцевидного, установление стабильности состава и условий хранения.

Материал и методы: в качестве активной фармацевтической субстанции использовали стандартизированный экстракт ревеня сердцевидного густой. Для получения таблеточной массы использовались вспомогательные вещества фармакопейного качества – магния гидроксикарбонат, натрия кроскармеллоза, микрокристаллическая целлюлоза, Plasdone S-630, магния алюмометасиликат, кальция стеарат, вода очищенная и покрытие плёночное Opadry 85F18422 White. Для получения таблеток в технологическом процессе использовано квалифицированное **Оборудование**: смеситель таблеточной массы, роторный таблеточный пресс, высокоэффективное оборудование для нанесения плёночной оболочки, упаковочная машина / блистировочная машина. При разработке таблеток руководствовались концепцией обеспечения качества лекарственных средств «Качество путём разработки», основанной на руководствах ICH: ICH Q11 «Разработка и производство лекарственных субстанций», ICH Q8 «Фармацевтическая разработка» и ICH Q10 «Фармацевтическая система качества». Использованы стандартные фармакопейные методы исследования.

Результаты: разработаны 50 экспериментальных моделей масс для таблетирования в вариантах сочетания вспомогательных веществ и активной субстанции в эффективной разовой дозе 300 мг. Из полученных таблеток-ядер только 4 модели соответствовали предъявляемым критериям отбора (истираемость, стойкость при раздавливании, распадаемость и растворение). Обоснован оптимальный метод таблетирования с помощью влажной грануляции, позволяющий получить таблетки надлежащего фармакопейного качества и следующего состава: экстракт корня ревеня густой, магния гидроксикарбонат, натрия кроскармеллоза, микрокристаллическая целлюлоза 102, Plasdone S-630, магния алюмометасиликат, кальция стеарат. Выбран следующий состав плёночного покрытия полученных таблеток-ядер: Opadry 85F18422 White, состоящий из поливинилового спирта, титана диоксида Е 171, макрогола 4000 и талька.

Заключение: произведена фармацевтическая разработка таблеток, покрытых оболочкой с экстрактом ревеня сердцевидного. Установлены рациональный состав и оптимальная технология получения таблеток-ядер, покрытых плёночной оболочкой Opadry 85F18422 White. Проведена оценка качества полученных таблеток, изучена стабильность состава в течение 9 месяцев, результаты показателей качества находятся в пределах допустимых норм, исследования в этом направлении продолжаются.

Ключевые слова: *экстракт, таблетки, покрытые оболочкой, фармацевтическая разработка, состав, технология, стабильность.*

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Introduction

The creation of new import-substituting drugs of domestic production is one of the most important tasks of the pharmaceutical industry of Kazakhstan. In this regard, the study of domestic types of medicinal plant materials and their processing, the creation of medicines based on them and their introduction into medical practice is relevant.

Of particular interest are plants of the genus Rhubarb (*Rheum* L.) of the Polygonaceae family, which are a valuable source of biologically active substances and widely used in official and traditional medicine. The pharmacological action of plants of the genus Rhubarb (*Rheum* L.) is due to the sum of biologically active substances, such as anthracene derivatives, flavonoids in the form of glycosides and aglycones, tannins, etc. [1-4]. It is known that plants of the genus *Rheum* L. possess a laxative, antioxidant, anti-inflammatory, antitumor, antimicrobial, antifungal, antiulcer, analgesic and hepatoprotective effect [5-9].

Rheum cordatum Losinsk. is a herbaceous plant of the genus Rhubarb (*Rheum* L.), growing in the Western Tien Shan, Karatau and the Chu-Ili mountains [10].

Scientists of S.D. Asfendiyarov Kazakh National Medical University, together with scientists from the Department of Pharmacognosy with a course of medicinal plants at the Lublin Medical University (Poland) and the Department of Industrial Pharmacy and Chemistry of Natural Compounds of the National University of Pharmacy (Kharkiv, Ukraine), conducted a full-scale study of the raw materials of *Rheum cordatum* collected in the Chu-Ili mountains. A complete pharmacognostic analysis of *Rheum cordatum* raw materials was performed. A high content of anthracene derivatives in the roots of *Rheum cordatum* was revealed and high antioxidant activity of the extract from the roots was established, which, according to the results of toxicological studies, is assigned to the class of low toxic substances (V toxicity class) [11].

The standardization of medicinal plant materials "*Rheum cordatum* roots" and "*Rheum cordatum* soft extract" was carried out in accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan (SPh RK), its stability during storage was studied. The conducted studies formed the basis for the development of herbal medicine based on an extract from the roots of *Rheum cordatum*.

Purpose of research

Development of a rational composition, optimal technology, standardization criteria for tablets with *Rheum cordatum* extract, the establishment of composition stability and storage conditions.

Materials and methods

Soft extract of *Rheum cordatum* was used as an active pharmaceutical substance. The technological characteristics of this substance (fluidity, bulk density and compressibility) showed the need to use excipients for the technology of tablets.

Tablets are justified as a dosage form due to the accuracy and uniformity of dosage, high bioavailability, stability during storage and transportation, the possibility of masking unpleasant taste and smell, the application of protective film coatings, high performance, and etc. [12].

In accordance with the functional characteristics and technological purpose, pharmacopoeial-quality magnesium-hydroxycarbonate (DMV Fonterra, Germany), croscarmellose sodium (Roquette, France), microcrystalline cellulose (JRS Pharma, Germany), Plasdone S-630 (Ashland, USA), magnesium aluminometasilicate (Fuji Chemical Industries, Japan), calcium stearate (Peter Greven, Germany), film coating Opadry 85F18422 White (Colorcon) and purified water were used as excipients for the preparation of the tablet mass.

To obtain tablets in the technological process, qualified equipment was used: a tablet mass mixer (Dott BonapacePM-10, Italy), a rotary tablet press (Dott Bonapace, CPR-18, Italy), highly efficient film-coating equipment (Colter BGB-10F, China), a packaging machine / blistering machine (Calculating machine IMA TV4, Italy).

When developing the tablets, we were guided by the Quality by Design concept of medicines, based on ICH guidelines: ICH Q11 "Development and manufacture of medicinal substances", ICH Q8 "Pharmaceutical Development" and ICH Q10 "Pharmaceutical Quality System".

Pharmacopoeial methods of analysis were used in the research [13].

Results and their discussion

Analysis of the pharmaceutical market of laxative medicines of the Republic of Kazakhstan (RK) showed the feasibility of expanding the range of herbal preparations containing anthracene derivatives [14].

In the experiment we studied tablet models using auxiliary substances in various combinations, with the active substance content in an effective dose of 300 mg in one tablet.

Most plant-based medicinal substances, including rhubarb root extract, are unsuitable for direct compression technology when tableting. In this regard, the method of wet granulation is substantiated, which allows achieving positive technological characteristics of the tableted mass: uniformity of fractional composition, flowability, an optimal value of bulk density, angle of repose, etc.

The qualitative and quantitative composition of excipients was experimentally established within the framework of their functional characteristics and technological purpose (Table 1).

The composition of the obtained granules with varying filler and humidifier was studied.

In the experiment the following fillers were used: microcrystalline cellulose (MCC) 101, lactose monohydrate, MCC 102, dibasic calcium phosphate anhydrous, and pregelatinized starch. The best results in bulk density and fluidity were obtained when MCC 102 was introduced into the composition of the tablet cores. A filler, magnesium hydroxycarbonate, was used as an alkalizing agent, which promotes the breakdown of anthracene derivatives contained in rhubarb extract.

To form a granulated mass the following humidifier compositions were studied: 10% Plasdone S-630 solution, 5% starch paste, 1% and 2% aqueous hydroxypropyl methylcellulose solution, and 2%, 5%, 10%, 20% aqueous solution of polyvinylpyrrolidone. Observations showed that the use of a 10% Plasdone S-630 solution made it possible to obtain a moist, homogeneous mass without the formation of conglomerates.

The use of potato starch as a part of the granulate did not ensure the disintegration of the tablets; moreover, starch reduced the strength of the tablets; therefore, the possibility of using more effective disintegrants such as croscarmellose sodium, Polyplasdone XL and sodium starch glycolate was investigated.

As a result of studies, it was found that the use of sodium croscarmellose at a concentration of 10% as a disintegrant allows achieving regulated disintegration. Table 2 shows the technological properties of the optimal composition.

Table 1 *Characteristic features of excipients*

Name of the excipient	Normative regulatory document for quality	Content in the dosage form	Functional – purpose
Magnesium hydroxycarbonate	SPh RK [13], EPh [15]	Not regulated Up to 45%	Alkalizing agent
Croscarmellose sodium	SPh RK [13], EPh [15]	Not regulated	Disintegrant
Microcrystalline cellulose	SPh RK [13], EPh [15]	Up to 90%	Filler
Plasdone S-630	SPh RK [13], EPh [15]	Not regulated Recommended 1-5%	Binder
Magnesium aluminometasilicate	SPh RK [13], EPh [15]	10-50%	Adsorbent
Calcium stearate	SPh RK [13], EPh [15]	Up to 1%	Anti-friction
Water purified	SPh RK [13], EPh [15]	Not regulated	Solvent
Ethyl alcohol	SPh RK [13], EPh [15]	Not regulated	Solvent
Opadry 85F18422 White	SPh RK [13], EPh [15]	Up to 4%	Film coating

EPh – European pharmacopoeia; SPh RK – State Pharmacopoeia of the Republic of Kazakhstan

Table 2 *Optimum composition*

Fractional composition, %						Bulk density, g/cm³	Flow ability g/s	Angle of repose,˚
>1,0 mm	1,0-0,7 mm	0,7-0,5 mm	0,5-0,25 mm	0,25-0,18 mm	<0,18 mm			
58,41±0,1	21,80±0,1	9,35±0,1	6,27±0,1	2,85±0,1	1,32±0,1	0,55±0,02	7,24±0,03	29±1,00

When developing the composition of tablets with rhubarb root extract, one of the pressing problems was the sticking of the tablet mass onto the press tool.

As non-sticking and lubricating substances in a comparative aspect, calcium stearate and magnesium stearate were used in an amount of 1% by weight of the tablet. When a series of tablets was pressed, which included calcium stearate, no sticking of the tablet mass to the punches was observed.

Thus, 50 experimental mass models for tableting have been developed in the combination of excipients and the active substance in an effective single dose of 300 mg. Of the obtained core tablets, only 4 models met the selection criteria (abrasion, crush resistance, disintegration, and dissolution).

To coat the obtained tablet cores the following film coating compositions were selected:

Aquarius Preferred HSP BPP 218011 White (Colorcon), composition: hydroxypropyl methylcellulose (hypromellose), copolyvidone, polyethylene glycol 6000 (macrogol 6000), glyceryl caprylocaprate, polydextrose, titanium dioxide (E171).

Opadry 85F18422 White, composition: polyvinyl alcohol, titanium dioxide E171, macrogol 4000, talc.

The great uniformity of the aqueous film coating, the smooth surface of the tablet and the improved gloss allowed the Opadry 85F18422 White to be selected.

A 20% suspension was prepared for the Opadry 85F18422 White film coating. A weighted amount of film coating was suspended with a mixer in a sufficient amount of purified water. Obtained at the stage of tableting the core tablets with dark inclusions were covered with a film membrane in a coater with a perforated drum for the given technological parameters presented in Table 3.

Coating in an amount of 3.85 % by weight of the tablet is sufficient to obtain tablets of good quality.

So table 4 presents the composition of the coated tablets with the extract of heart-shaped rhubarb, satisfying all the requirements.

The finished product is a round, biconvex tablet coated with a film coating of white or almost white color, with a diameter of 13±0.2 mm, a height of 4.2±0.2 mm.

The technological flowchart for producing coated tablets is shown in Fig. It consists of the following technological stages: preparation of raw materials and materials, mixing of excipients, preparation of a humidifier with an extract, moistening, wet granulation, drying, dry granulation, dusting, tableting, dust removal, coating and glossing, packaging of finished tablets.

The technology for producing coated tablets with extract of *Rheum cordatum* has been tested in pilot batches in the pharmaceutical development department (R&D) at Viva pharm LLP.

Table 3 *Coating Mode*

Preset technological parameters	Film coating Opadry 85F18422 White
Download (g)	2400.0
Inlet temperature, ˚C	50-55
Outlet temperature, ˚C	40-45
Air pressure (bar)	2.0
Coating rate ml/min	15.0
The amount of film dispersion (g)	500.0
Incoming air speed RPM	1250
Outgoing air speed RPM	1250

Table 4 *Composition of the coated tablets with the extract of Rheum cordatum*

Core composition	**Contents**	
	mg	**wt. %**
Rheum cordatum roots extract	300.0	48.08
Magnesium hydroxycarbonate	128.40	20.58
Croscarmellose sodium	60.0	9.62
Microcrystalline cellulose 102	48.0	7.69
Plasdone S-630	3.60	0.58
Magnesium aluminometasilicate	54.0	8.65
Calcium stearate	6.0	0.96
Total: tablet core	600.0	
Coating mass	24.0	3.85
Weight of a coated tablet	624.0	100.0

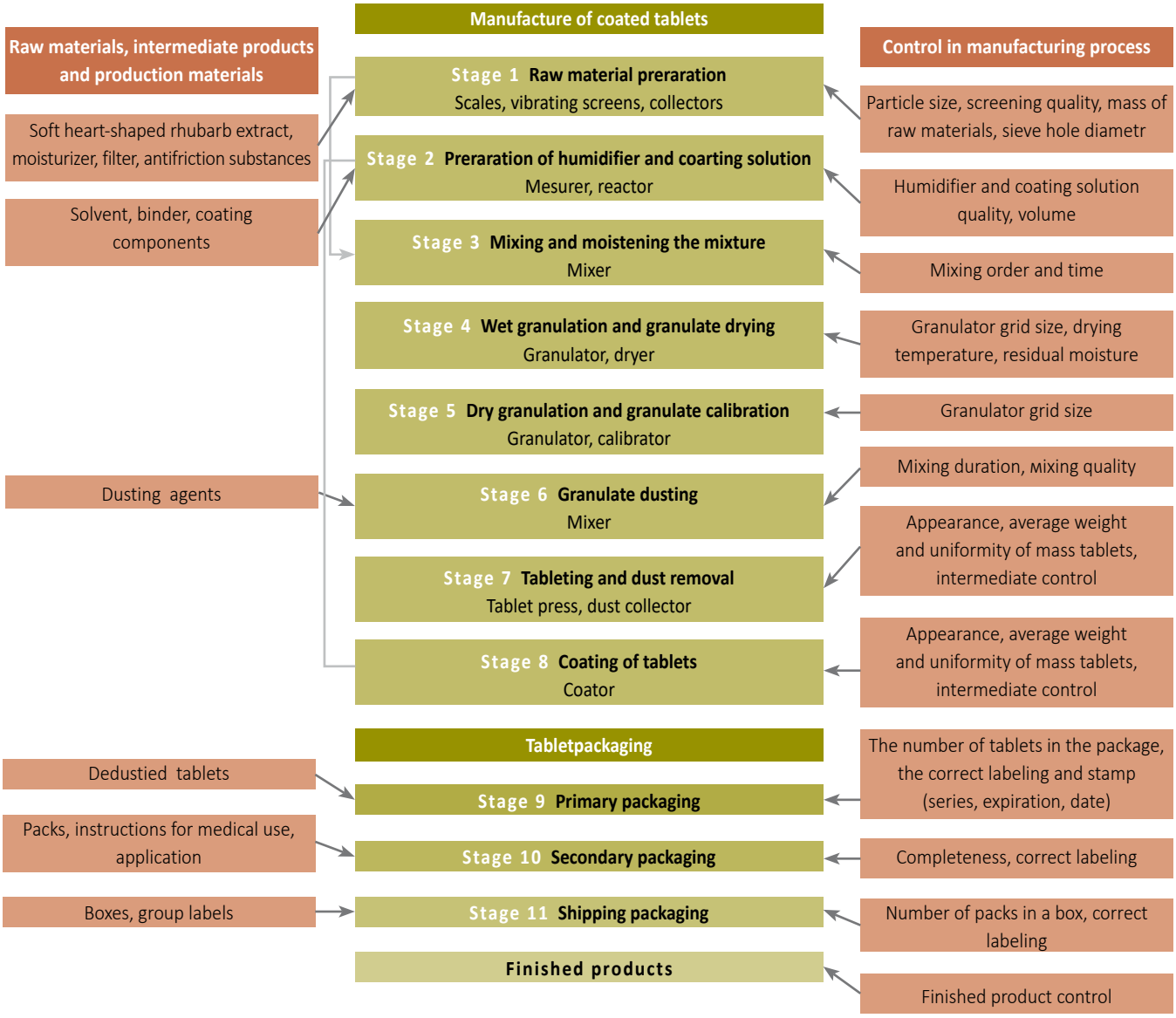

Fig. *The technological flowchart of obtaining coated tablets*

The quality of the finished tablets was evaluated in accordance with the requirements of the SPh RK by the following quality indicators: description, identification, average weight and deviation from the average weight, disintegration, dissolution, abrasion, weight loss upon drying, microbiological purity, quantitative determination.

Conclusions

A rational composition of coated tablets with an extract of *Rheum cordatum* in an effective dose of 300 mg has been developed; experimentally justified as fillers are MCC 102, a humidifier – 10% aqueous solution of Plasdone S-630, a disintegrant – sodium croscarmellose, an alkalizing agent – magnesium hydroxycarbonate, antifriction agents – magnesium aluminometasilicate and calcium stearate. An optimal technology has been developed for producing tablet cores with an extract of *Rheum cordatum* and film coating with a suspension of Opadry 85F18422 White. The quality of the obtained tablets was evaluated, the stability of the composition for 9 months was studied, the results of quality indicators are within acceptable standards, and research in this direction is going on.

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Информация об источнике поддержки в виде грантов, оборудования, лекарственных препаратов

Финансовой поддержки со стороны компаний-производителей лекарственных препаратов и медицинского оборудования авторы не получали

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