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Determination of the composition of a combination of active pharmaceutical ingredients of the herbal medicinal product with the hepatoprotective action

Aim. To study the recommended doses and calculate the component composition of a combination of the amorphous solid dispersion of silymarin, the dry artichoke leaf extract and the dry peppermint leaf extract for its further use as part of medicinal products for the treatment of diseases of the hepatobiliary system.

Materials and methods. The study object was the combination of the amorphous solid dispersion of silymarin, the artichoke leaf dry extract and the peppermint leaf dry extract. To determine the recommended doses of individual components of the combination, the bibliosemantic method was used. To calculate the component composition of the combination, data from monographs of the European Medicines Agency and the Commission E were used.

Results. Based on the pharmacological properties and recommended doses of the individual components, the composition of the combination of active pharmaceutical ingredients of plant origin was developed. The content of the solid dispersion of silymarin in one dosage of the combined product was set at the equivalent of 35 mg of silymarin calculated with reference to silibinin corresponding to 162.2-191.7 mg of the substance. The content of the artichoke leaf dry extract in one dosage of the combined product was 100 mg. The content of the dry peppermint leaf extract in one dosage of the combined product was set at 125 mg. The total content of active pharmaceutical ingredients in one dosage unit of the medicinal product was within 387.2-416.7 mg. The daily dose was set within 6 single doses. Considering the pharmaco-technological properties of the components of the combination, as well as taking into account the properties of Syloid® XDP 3150 as a carrier of the solid dispersion of silymarin, the optimal dosage form for the combination developed is hard gelatin capsules. The composition of the combination of active pharmaceutical ingredients determined in this study will provide a wide range of the pharmacological activity of the herbal medicinal product, namely: hepatoprotective, hepatoregenerative, anticholestatic, lipid-lowering and antispasmodic effects.

Conclusions. It has been determined that the active ingredients of the API combination of the hepatoprotective herbal medicinal product are the amorphous solid dispersion of silymarin, the artichoke leaf dry extract and the peppermint leaf dry extract. It has been calculated that the component composition of the individual ingredients of the combination in one dosage unit of the medicinal product should be: the equivalent of 35 mg of silymarin in the form of an amorphous solid dispersion, 100 mg of the artichoke leaf dry extract and 125 mg of the peppermint leaf dry extract. It has been found that, considering the pharmaco-technological properties of the components of the combination, the optimal dosage form for the combination developed is hard gelatin capsules.

Keywords: *technology; technological process; combination; medicinal product; polyphenols; active pharmaceutical ingredient; herbal substance, extract.*

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Визначення складу комбінації активних фармацевтичних інгредієнтів рослинного лікарського засобу гепатопротекторної дії

Мета – дослідити рекомендовані дози та розрахувати компонентний склад комбінації аморфної твердої дисперсії силімарину, сухого екстракту листя артишоку та сухого екстракту листя м'яти перцевої з метою її подальшого застосування у складі лікарських засобів для лікування захворювань гепатобіліарної системи.

Матеріали та методи. Об'єктом дослідження була комбінація аморфної твердої дисперсії силімарину, сухого екстракту листя артишоку та сухого екстракту листя м'яти перцевої. Для визначення рекомендованих доз індивідуальних компонентів комбінації було використано бібліосемантичний метод. Для розрахунку компонентного складу комбінації було використано дані монографій Європейського агентства лікарських засобів та Комісії Е.

Результати та їхнє обговорення. На основі фармакологічних властивостей і рекомендованих доз індивідуальних компонентів було розроблено склад комбінації активних фармацевтичних інгредієнтів рослинного походження. Вміст твердої дисперсії силімарину в одному дозуванні комбінованого засобу було встановлено в еквіваленті 35 мг силімарину в перерахунку на силібінін, що відповідає 162,2-191,7 мг субстанції. Вміст сухого екстракту листя артишоку в одному дозуванні комбінованого засобу було встановлено як 100 мг. Вміст сухого екстракту м'яти в одному дозуванні комбінованого засобу було встановлено як 125 мг. Загальний вміст активних фармацевтичних інгредієнтів в одній дозованій формі лікарського засобу лежить у межах 387,2-416,7 мг. Добова доза була встановлена в межах 6 прийомів разових доз. З огляду фармакотехнологічних властивостей складових комбінації, а також беручи до уваги властивості Syloid® XDP 3150, як носія твердої дисперсії силімарину, оптимальною лікарською формою для розробленої комбінації є тверді желатинові капсули. Установлений у дослідженні склад комбінації активних фармацевтичних інгредієнтів дозволить забезпечити широкий спектр фармакологічної активності рослинного лікарського засобу, а саме: гепатопротекторну, гепаторегенерувальну, антихолестатичну, ліпідознижувальну та спазмолітичну дію.

Висновки. Визначено, що компонентами комбінації АФІ лікарського засобу гепатопртекторної діє є аморфна тверда дисперсія силімарину, сухий екстракт листя артишоку та сухий екстракт листя м'яти перцевої. Розраховано, що компонентний склад індивідуальних складових комбінації в одній дозованій одиниці лікарського засобу має становити: еквівалент 35 мг силімарину у вигляді аморфної твердої дисперсії, 100 мг сухого екстракту листя артишоку та 125 мг сухого екстракту листя м'яти перцевої. Установлено, що з погляду фармакотехнологічних властивостей складових комбінації оптимальною лікарською формою для розробленої комбінації є тверді желатинові капсули.

Ключові слова: *технологія; технологічний процес; комбінація; препарат; поліфенольні сполуки; активний фармацевтичний інгредієнт; рослинна сировина; екстракт.*

Introduction. The growing dynamics of liver and hepatobiliary system diseases in Ukraine requires the development of effective and safe medicinal products (MP). A feature of this type of therapy is the long-term use of drugs by the patient, mostly without the doctor`s supervision. Given the above, combined herbal medicinal products (HMPs) can be an effective tool in solving this problem. Their advantage is a relative safety with the long-term use, no need for doctor's supervision during the therapy and a wide spectrum of action, depending on the active pharmaceutical ingredients (APIs) in the combination [1-3].

Silymarin, a mixture of flavolignans from Milk thistle (*Silybum marianum* (L.) Gaerth.), is one of the most studied active ingredients of herbal origin with the hepatoprotective activity. Due to its anti-inflammatory, antioxidant and antifibrotic effects, silibinin as the main flavolignan of silymarin is used to treat a wide range of liver diseases, including such chronic diseases as cirrhosis and hepatocellular carcinoma. The effective use of silymarin and silibinin is limited by their low oral bioavailability. However, studies of amorphous solid dispersions on porous carriers demonstrated a significant improvement in the release rate of silymarin. Compared with crystalline silymarin, solid dispersions based on Syloid® XDP 3150 and Avicel® PH-102 showed an approximately 16- and 7-fold increase in the amount of APIs released in 1 hour, respectively. The addition of Tween® 80 increased the release rate of the active substance from solid dispersions based on Avicel® PH-102 and had a minor effect on the release of silymarin from dispersions based on Syloid® XDP 3150. However, the ability of Tween® 80 to inhibit the gut wall efflux opens up the possibility of modulating the bioavailability of silymarin without changing the drug release profile [4, 5].

The hepatoprotective, hepatoregenerative and anticholestatic effects of the Artichoke leaf extracts (*Cynara Scolymus* L.), which are associated with phenolic compounds, allow to consider extracts of this herbal substance as promising components in combination with silymarin. In addition to hepatoprotective effects of silymarin, this API is able to supplement the spectrum of pharmacological properties of the combination with a choleretic effect and expand the therapeutic range of the combined MP use [6-8].

In case of spastic disorders of the gallbladder and bile ducts, there is a need to remove secreted bile. Therefore, it is advisable to introduce antispasmodic APIs into the composition of the combination. Such a component can be the Peppermint leaf extract (*Mentha piperita* L.) since the extracts of this plant are known for their antispasmodic and choleretic properties [9].

Thus, to develop a combination based on bioavailable silymarin, the artichoke leaf extract and the peppermint leaf extract is a promising task when creating a combined HMP for the comprehensive treatment and prevention of hepatobiliary system diseases.

The **aim of the work** was to study the recommended doses and calculate the component composition of the combination of the amorphous solid dispersion of silymarin, the artichoke leaf dry extract and the peppermint leaf dry extract for its further use as part of MP for the treatment of diseases of the hepatobiliary system.

Materials and methods. Silymarin in the form of the amorphous solid dispersion, the dry artichoke leaf extract and the dry peppermint leaf extract were components of the combination of HMP.

The amorphous solid dispersion of silymarin was obtained using the organic solvent evaporation method, which consisted in dissolving a standardized milk thistle dry extract (*Silybum marianum fructus*, the drug extract ratio – 20-50:1, the extraction solvent – acetone) in acetone, followed by the sequential addition of Tween® 80 and the mesoporous carrier Syloid XDP® 3150 and subsequent removal of the solvent by evaporation. The acceptance criteria of the silymarin content in the solid dispersion calculated with reference to silibinin (a dry substance) was set within 18.26-21.58 %. The component composition of the amorphous solid dispersion of silymarin is shown in Table 1 [5].

The values of the artichoke leaf dry extract (*Cynarae folium*) were the drug extract ratio – 10:1, the extraction solvent – water. The acceptance criteria of the quantitative characteristics of the dry extract were determined: the content of polyphenols calculated with reference to cynarin was not less than 5.0 %, and the

Table 1

The composition of the amorphous solid dispersion of silymarin

Component	Component content, %
A standardized milk thistle fruit dry extract (*Silybum marianum fructus,* DER 20-50:1, the extraction solvent – acetone), the silymarin content calculated with reference to silibinin (a dry substance) 55-65 %	33.2
Mesoporous silica Syloid® XDP 3150	66.5
Tween® 80	0.3
Total, %	100

content of chlorogenic acid was not less than 0.6 % (a dry substance).

The values of the peppermint leaf dry extract (*Menthae piperritae folium*) were the drug extract ratio – 4-8:1, the extraction solvent – ethanol 26-66 % vol. The acceptance criteria of the quantitative characteristics of the dry extract were determined: the content of rosmarinic acid was not less than 0.5 %, and the content of flavonoids calculated with reference to hesperidin was 7.0 % (a dry substance).

The calculation of the daily dose of APIs without constituents with the known therapeutic activity or active markers was carried out using the formula:

$$D.D_{extract} = \frac{D.D_{herbal\ substance}}{DER}$$

where: D.D – is the daily dose of the extract as an API in the composition of HMP, mg; $D.D_{herbal\ substance}$ – is the recommended daily dose of the herbal substance, mg; DER – is the drug extract ratio.

Results and discussion. *Amorphous solid dispersion of silymarin*. According to the monograph of the European Medicines Agency (EMA), the traditional use of the milk thistle dry extract (*Silybum marianum fructus*, DER 20-70:1, the extraction solvent – acetone) in the HMP in a single dose of 82-239 mg 2-3 times daily with a maximum daily dose up to 478 mg contributes to support of the liver function, symptomatic relief of digestive disorders, sensation of fullness and indigestion [10, 11].

The above-mentioned EMA recommendations characterize the extract only by DER and do not link the dosage of the product with its quantitative characteristics, particularly silymarin. From the perspective of using the milk thistle extract standardized by silymarin it is justified to refer to the recommendations of the Commission E. According to the relevant monograph, the average daily dose of silymarin calculated as silibinin is 200-400 mg. Such preparation is recommended for use in the toxic liver damage, supportive treatment in chronic inflammatory liver diseases and hepatic cirrhosis [12].

Considering the composition of the solid dispersion of silymarin (18.26-21.58 mg silibinin/100 mg) and taking into account the recommendations of the Committee on Herbal Medicinal Products (HMPC) of the EMA and the Commission E on single and daily doses of milk thistle preparations, the content of the solid dispersion of silymarin in one dosage unit of the combined HMP was set at the equivalent of 35 mg of silymarin calculated with reference to silibinin. This content, according to the quantitative characteristics, corresponds to 162.2-191.7 mg of the substance (Tab. 2), which is an expedient amount in terms of the total mass of one dosage unit of the finished product and the dosage of silibinin in competitors. Accordingly, the daily dose was set within 6 single doses per day, corresponding to 210 mg of silymarin calculated with reference to silibinin.

Artichoke leaf dry extract. According to the EMA monograph, the traditional use of extracts obtained with the aqueous extraction solvent is recommended in the composition of HMPs in a single dose of 200-640 mg and a daily dose of 400-1320 mg for the extract of dried leaves (DER 2-7.5:1, the extraction solvent – water) and in a single dose of 200-900 mg and a daily dose of 600-2700 mg for the extract of fresh leaves (DER 15-35:1, the extraction solvent – water). According to the monograph, these herbal products are indicated for traditional use in HMP for the symptomatic relief of digestive disorders, such as dyspepsia with a feeling of fullness, bloating and flatulence [13, 14].

The artichoke leaf dry extract is not a standardized or quantified extract, therefore, its content in a single dose of the combined MP and, accordingly, its daily dose was calculated based on the DER. The calculation of the daily dose of this API was carried out according to the formula.

Considering the recommendations of the Commission E and HMPC EMA on a single and daily dose of artichoke preparations, namely 6.0 g of fresh or dried leaves of *Cynara Scolymus* L., the daily dose of the API planned to use in the combined composition was calculated. According to the calculation, the daily dose of such artichoke leaf dry extract (*Cynarae folium*, DER 10:1, the extraction solvent – water) is 600 mg.

Considering that the planned frequency of taking a single dose was 6 units per day, the content of the dry extract in one dosage of the combined HMP was set as 100 mg (Tab. 2).

Table 2

Characteristics of the API combination in a single dose of the herbal medicinal product

API	The content in a dosage unit of the medicinal product, mg
The amorphous solid dispersion of silymarin (standardized milk thistle fruit dry extract *Silybum marianum fructus*, DER 20-50:1, the extraction solvent – acetone; Syloid® XDP 3150; Tween® 80) that corresponds to 35 mg silymarin calculated with reference to silibinin	162.2-191.7
The artichoke leaf dry extract (*Cynarae folium*, DER 10:1, the extraction solvent – water)	100.0
The peppermint leaf dry extract (*Menthae piperritae folium*, DER 4-8:1, the extraction solvent – ethanol 26-66 % vol.)	125.0
Total, mg	**387.2-416.7**

Peppermint leaf dry extract. According to the EMA monograph, the traditional use of peppermint preparations is described for comminuted herbal substances for the tea preparation, tincture (1:5; ethanol 45 % vol.) and tincture (1:5; ethanol 70 % vol.). The recommended daily doses of such peppermint preparations in tea should be equivalent to 4.5-9 g of leaves and 6-9 ml of tincture [15].

The above-mentioned EMA recommendations are difficult to implement for the peppermint dry extract (DER 4-8:1, ethanol 26-66 % vol.), which is intended to be used as part of the API combination. Along with this, the recommendations of the Commission E are more convenient for calculating the content of the dry extract in a dosage unit and the corresponding daily dose of the MP. According to this monograph, the daily dose of the peppermint preparation for use in spastic complaints of the gastrointestinal tract, as well as a gallbladder and bile ducts should be equivalent to 3-6 g of dried leaves of *Mentha piperita* L [12].

The peppermint leaf dry extract is not a standardized or quantified extract, therefore, the calculation of its content in a single dose of the combined MP and, accordingly, its daily dose was calculated similarly to the artichoke extract, namely based on the DER. The calculation of the daily dose of the peppermint extract was carried out according to the formula.

Considering the recommendations of the Commission E and HMPC EMA on a single and daily dose of peppermint preparations, namely 3-6 g of dried leaves of *Mentha piperita* L., the daily dose of the API was calculated. The average values of DER and the amount of the herbal substance were used for the calculation. According to the calculation, the daily dose of the peppermint leaf dry extract (*Menthae piperritae folium*, DER 4-8:1, the extraction solvent – ethanol 26-66 % vol.) is 750 mg.

Considering that the planned frequency of taking a single dose was 6 units per day, the content of the dry extract in one dosage of the combined HMP was set as 125 mg. The composition of the combination of HMPs as API in one dosage unit of the HMP is shown in Table 2.

Thus, based on the pharmacological properties and recommended doses of the individual components, the composition of the combination of APIs of plant origin was developed. The total content of APIs in one dosage unit of the HMP is within 387.2-416.7 mg. Considering the pharmaco-technological properties of the components of the combination, as well as taking into account the properties of Syloid® XDP 3150 as a carrier of the solid dispersion of silymarin, the optimal dosage form for the combination developed is hard gelatin capsules. The composition of the API combination determined in this study will provide a wide range of the pharmacological activity of the HMP, namely: hepatoprotective, hepatoregenerative, anticholestatic, lipid-lowering and antispasmodic effects.

Conclusions and prospects for further research. It has been determined that the active ingredients of the API combination of the hepatoprotective HMP are the amorphous solid dispersion of silymarin, the artichoke leaf dry extract and the peppermint leaf dry extract.

It has been calculated that the component composition of the individual ingredients of the combination in one dosage unit of the medicinal product should be: the equivalent of 35 mg of silymarin in the form of an amorphous solid dispersion, 100 mg of the artichoke leaf dry extract and 125 mg of the peppermint leaf dry extract.

It has been found that, considering the pharmaco-technological properties of the components of the combination, the optimal dosage form for the combination developed is hard gelatin capsules.

The further stage of research will be development of the finished medicinal product in the form of hard gelatin capsules based on the combination of APIs determined.

Conflicts of interest: authors have no conflict of interest to declare.

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