# ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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## DEVELOPMENT OF THE COMPOSITION OF ENTERIC COATED TABLETS BASED ON ADEMETIONINE 1.4-BUTANEDISULPHONATE

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*Key words: excipients; compatibility; ademetionine 1.4-butanedisulphonate; film coating*

*Excipients are integral components of almost all medicines. They allow giving the necessary technological properties, which provide accurate dosing, proper strength and disintegration of tablets, to the tabletting mass. However, when developing a medicine not only the selection of the rational composition should be considered, but also the fact that excipients should not affect the properties of the active pharmaceutical ingredient and do not lead to its degradation. During the work the optimal composition of a tablet based on the substance of ademetionine 1.4-butanedisulphonate has been chosen and substantiated; compatibility of all components in the medicine has been proven.*

Excipients are integral components of almost all medicines. Their rational use greatly increases the importance of pharmacotherapy and allows creating highly innovative dosage forms suitable for use and with a long shelf life. Typically, requirements for excipients are only to their granulometric composition, physical and chemical properties etc. since they can localize the action and significantly affect release (resorption) of the active substance and the pharmacological activity of the substance: enhance the effect of medicines or otherwise reduce their activity.

A proper selection of excipients is a topical issue of modern technology of medicinal forms. However, it is long known that when they are applied, pharmacokinetics and pharmacodynamics of the active substance can be adjusted [2].

One of the stages of drug development is to select and study physical, chemical and technological properties of excipients [9, 10]. Thus, the aim of our work was to analyse and determine the optimal concentration and compatibility of components of the medicine based on ademetionine.

In the course of the study we faced the following tasks:

1. to determine the proportion of the components in the tablet core;
2. to select the optimal film coating that would not only provide the enteric effect, but also protect the tablet from moisture since ademetionine 1.4-butanedisulphonate is a hygroscopic substance [1].

**Materials and Methods**

When developing the tablet composition the medicine Heptral (Abbott SpA, Italy) was a reference drug consisting of ademetionine 1.4-butanedisulphonate in the amount of 760 mg (corresponding to 400 mg of ademetionine cation). Excipients included in the tablet core were taken according to the Heptral composition, but their concentrations were chosen experimentally taking into account the optimal bulk density, fluidity and compressibility.

The resulting medicines were investigated by means of infrared spectroscopy (IR Fourier spectrometer, Nicolet IS50 Thermo) from the polymeric material obtained by the module of distributed total internal reflection (SPhU 2.2.24): before studying the samples of tablets the background signal of spectrometer was recorded in the range of 4000 to 400 $cm^{-1}$ with resolution of 4 $cm^{-1}$. The part of the tablet with the size of about 3×3 mm was placed on the window of the block of distributed total internal reflection and pressed by the clamp. The spectrum ranging from 4000 to 400 $cm^{-1}$ with resolution of 4 $cm^{-1}$ was recorded. Compatibility of the components was analysed using liquid chromatography (Agilent 1200 liquid chromatograph). The results were compared with the data obtained while studying the reference drug.

To study stability in acid Disintegration (SPhU 2.9.3) and Dissolution (SPhU 2.9.1) tests were conducted. Disintegration test was conducted on an ERWEKA ZT 72 device under the following conditions: the ambient temperature was (37±1)°C, the tablet should be stable in 0.1 M solution of hydrochloric acid for 2 h and disintegrate in the phosphate buffer solution *R* with pH 6.8 for not longer than 30 min.

Dissolution test was conducted using an ERWEKA DT1614 device with a blade, the ambient temperature was (37±0.5)°C; the blade rotation speed was 100 rpm. The requirements to the medicine were as follows: not more than 10% of the active substance should be released

in the medium of 0.1 M solution of hydrochloric acid in 2 h and at least 75% should be released in the phosphate buffer solution pH 6.8 for 90 min [3].

**Results and Discussion**

As a result of the laboratory studies the optimal composition of the tablet core based on the substance of ademetionine 1.4-butanedisulphonate was found (Tab. 1).

It is confirmed by the results obtained in the study of the tablet cores using infrared spectroscopy (Fig. 1).

Fig. 1 shows that the infrared absorption spectra of the sample based on ademetionine 1.4-butanedisulphonate s. 20714 and the reference drug Heptral coincide by the frequency of characteristic bands and their intensity.

After determining the optimal composition our task was to prove that these components were compatible, i.e. excipients in the tablet composition did not interact with the active substance and did not lead to its degradation. For this purpose the model mixtures of each excipients with ademetionine 1.4-butanedisulphonate were prepared, the samples obtained were stored under conditions of accelerated stability (t = 40°C, humidity was 75%) for four weeks. The substance of ademetionine 1.4-butanedisulphonate was as a reference model. The study of the samples was conducted using an Agilent1200 liquid chromatograph (Fig. 2).

Table 1

The optimal composition of the tablet core

| Components | Ratio |
|---|---|
| Ademetionine : sodium starch glycolate | 43:1 |
| Ademetionine : microcrystalline cellulose 200 | 8:1 |
| Ademetionine : aerosil | 172:1 |
| Ademetionine : magnesium stearate | 172:1 |

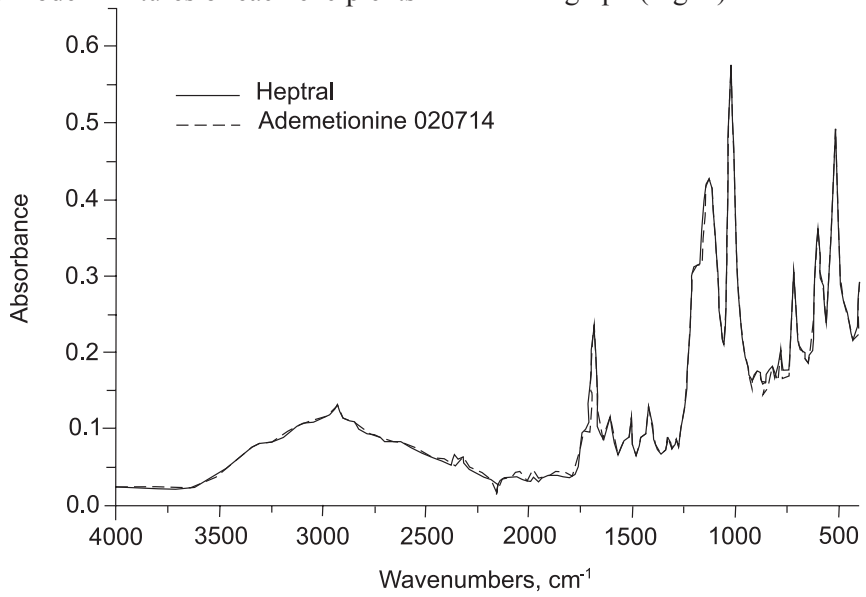


Fig. 1. IR-spectra of the sample s. 020714 and the reference drug Heptral.

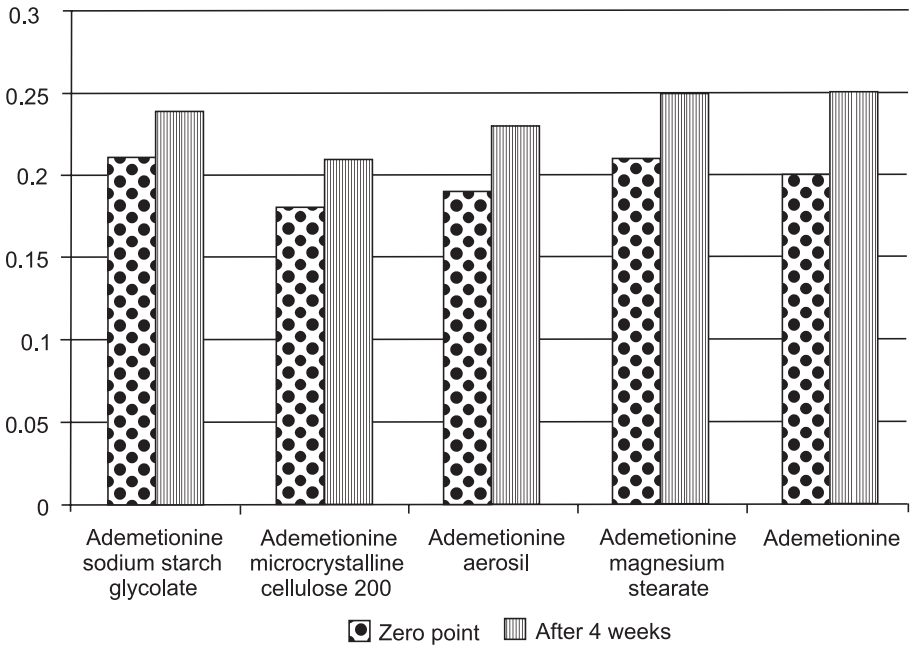


Fig. 2. Determination of compatibility of the drug components.

Table 2

Determination of the coating concentration

| The content of Acryl EZE 93A coating in the tablet | Disintegration. Not more than 15 min | Dissolution, % of the active substance transition | |
|---|---|---|---|
| | | Not more than 30 min in the phosphate buffer with pH 6.8 | The absence of the action for 2h in 0.1 M hydrochloric acid solution |
| 12% | 11′20″ | 150 min | Satisfied |
| 10% | 11′21″ | 54 min | Satisfied |
| 8% | 11′23″ | 27 min | Satisfied |

As it is seen from the results obtained, in the process of model mixtures aging the amount of unidentified impurities meets the specifications, and it is less than the values obtained in the study of the substance ademetionine 1.4-butanedisulphonate under the same conditions. Therefore, the qualitative and quantitative composition chosen does not affect the active ingredient, does not lead to its degradation, and does not affect the shelf life of the medicine.

The next step of our research was to develop the composition and concentration of a suitable film coating in order to protect the active pharmaceutical ingredient from the effects of adverse external factors, reduce the irritating effects while taking this medicine, mask the unpleasant taste and odour, and create the effect of prolongation and localize the medicine in the intestine [5, 8].

Currently, one of the most common enteric coatings that have all the properties listed above is the composition ACRYL-EZE. It consists of the following components: copolymer of methacrylic acid (a film former), triethyl citrate (plasticizer), sodium lauryl sulphate, sodium bicarbonate, titanium dioxide and talc. From the literature data it is known that of the concentration of coating in the amount of 8-12% of the total weight of the tablet provides the enteric effect [6]. Taking this into account three samples with the tablet core containing 8, 10 and 12% of coating of the total weight of the tablet were prepared (Tab. 2).

According to the manufacturer's recommendations the concentration of the coating solution was 20%; simethicone solution was used as a defoaming agent, and polyethylene glycol 6000 was a plasticizer.

The results obtained show that the sample with 8% film coating of the tablet weight meets the requirements. In addition, it should be noted that all concentrations of the coating studied provide protection from moisture.

CONCLUSIONS

The optimal composition of the tablet core has been chosen and substantiated.

It has been proven that all the components of the medicine are compatible and do not cause degradation of the substance.

The optimal concentration of the film coating for enteric tablets based on ademetionine 1.4-butanedisulphonate has been found.

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**РОЗРОБКА СКЛАДУ ТАБЛЕТОК НА ОСНОВІ АДЕМЕТІОНІН 1,4-БУТАНДИСУЛЬФОНАТУ, ВКРИТИХ КИШКОВОРОЗЧИННОЮ ОБОЛОНКОЮ**

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***Ключові слова**: допоміжні речовини; сумісність; адеметіонін 1,4-бутандисульфонат; плівкове покриття*

*Допоміжні речовини є невід'ємними складовими майже всіх лікарських препаратів, які дозволяють надавати масі для таблетування необхідних технологічних властивостей, що забезпечують точність дозування, належну міцність і розпадання таблеток. Проте при розробці препарату слід зважати не лише на підбір раціонального складу, а й враховувати те, щоб допоміжні компоненти не впливали на властивості активного фармацевтичного інгредієнта та не призводили до його деградації. У ході роботи було підібрано і обґрунтовано оптимальний склад таблеток на основі субстанції адеметіоніну 1,4-бутандисульфонату, доведено сумісність всіх компонентів, що входять до даного лікарського засобу.*

**РАЗРАБОТКА СОСТАВА ТАБЛЕТОК НА ОСНОВЕ АДЕМЕТИОНИН 1,4-БУТАНДИСУЛЬФОНАТА, ПОКРЫТЫХ КИШЕЧНОРАСТВОРИМОЙ ОБОЛОЧКОЙ**

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***Ключевые слова:** вспомогательные вещества; совместимость; адеметионин 1,4-бутандисульфонат; пленочное покрытие*

*Вспомогательные вещества являются неотъемлемыми составляющими почти всех лекарственных препаратов, которые позволяют придавать массе для таблетирования необходимые технологические свойства, обеспечивающие точность дозирования, надлежащую прочность и распадаемость таблеток. Однако при разработке препарата следует учитывать не только подбор рационального состава, но и учитывать то, чтобы вспомогательные компоненты не влияли на свойства активного фармацевтического ингредиента и не приводили к его деградации. В ходе работы был подобран и обоснован оптимальный состав таблеток на основе субстанции адеметионина 1,4-бутандисульфоната, доказана совместимость всех компонентов, которые входят в состав лекарственного средства.*