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Sv. M. Kovalenko

National University of Pharmacy, Kharkiv

SUBSTANTIATION OF THE EXCIPIENTS CHOICE USING THE ANALYSIS OF VARIANCE WHEN DEVELOPING TABLETS WITH THIOCTIC ACID AND TAURIN

Mathematical methods were used to optimize the process of development of the composition and technology of combined tablets based on taurin and thioctic acid and influenced by many different factors. These methods allowed reducing the number of experiments significantly and accumulate information about the process under study.

Using the analysis of variance the choice of excipients has been substantiated when developing the combined drug for prevention and treatment of diabetic complications. It has been found that the composition of tablets based on taurin and thioctic acid includes the following excipients: microcrystalline cellulose and corn starch as fillers, cross-carmellose sodium as a disintegrant; polyvinylpyrrolidone and hydroxypropyl methylcellulose as wetting agents.

Key words: diabetic complications, analysis of variance, excipients.

STATEMENT OF THE PROBLEM

In the world more than 284 million people suffer from diabetes mellitus (DM) [10, 12, 13, 14]. In Ukraine about a million patients are registered; in addition, there are 120 thousand children at the age from 15 to 5 years among them. Development of DM leads to terrible consequences: blindness, gangrene and amputation of lower limbs. The first complications of the disease become apparent already at the time of diagnosis, and in 10-20 years the patient can be fully disabled. More than 4 million people die each year from complications of diabetes [10, 12, 13]. Because of the early disability and high mortality DM has become a priority in the national healthcare systems of all countries of the world.

Today, the urgent issue is development of new highly effective drugs combining different pharmacological effects, which against the background of normalization of the carbohydrate metabolism will affect the various complications of diabetes.

The above facts were substantiation for the absolute prospects of creating a new combined drug based on sulphur organic acids (taurin and thioctic acid) in the form of tablets for prevention and treatment of diabetic complications.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

The crystallographic, physical, chemical and technological indicators of active substances – taurin and thioctic acid have been studied. It has been found that the mixture of the substances of thioctic acid and taurin under research has a low fluidity and relatively low compressibility.

Experimental studies have proven the impossibility of obtaining tablets with a combination of such substances as taurin and thioctic acid by direct compression. It is conditioned by a different size and shape of the particles of the substances studied, a great difference of indicators of compressibility and fluidity, as well as different solubility of active substances: the substance taurin is soluble in water, and the substance thioctic acid is soluble in organic solvents.

It has been proven that for obtaining the original combined drug with thioctic acid and taurin for pharmacotherapy of diabetic complications the use of the method of preliminary wet granulation is the most appropriate.

It is commonly known that the choice of excipients is one of the main factors in drug development that affects the pharmacological action of the dosage form and its pharmacotechnological characteristics.

Excipients in the manufacture of tablets are designed to provide the tablet mass the necessary technological properties that provide accuracy of a dose, the mechanical strength, the ability to disintegrate and the stability of tablets during storage [4, 8, 9].

IDENTIFICATION OF ASPECTS OF THE PROBLEM UNSOLVED PREVIOUSLY

The composition of excipients was selected taking into account the technological characteristics of the mixture of taurin and thioctic acid, as well as providing compliance with key indicators of quality of tablets (disintegration, friability, resistance to crushing, etc.).

As the result of the previously conducted research the list of excipients for manufacture of the tablet mass of the combined drug was selected. The excipients under study are included in the list of substances approved for use in the pharmaceutical industry, described in the European Pharmacopoeia, SPhU, United States Pharmacopeia. They are included in the List of names of excipients, which are part of medicinal products, approved by the order of the Ministry of Public Health of Ukraine dated 19.06.2007 No. 339 [6].

The pharmacotechnological characteristics of the active substances and excipients selected were identified experimentally [6].

At next step it was necessary to substantiate the composition and the ratio of excipients and to determine optimal conditions of tableting.

OBJECTIVE STATEMENT OF THE ARTICLE

The aim of our work is to substantiate the choice of excipients using analysis of variance when developing a tableted dosage form based on taurin and thioctic acid for prevention and treatment of diabetic complications.

PRESENTATION OF THE MAIN MATERIAL OF THE RESEARCH

Excipients traditionally included in the composition of tablets and ensured their quality were used as objects of research when developing solid dosage forms.

The ability to compression was determined by resistance to crushing using the device of a PTB 311 E model of PHARMA TEST company (Germany). Disintegration was checked on the device of a «PTZ-S» model of PHARMA TEST company (Germany) [9 – 11].

It is necessary to conduct 24 experiments ($N = 4 \cdot 3 \cdot 2 = 24$) for the study of three factors (A, B, C): factor A is taken at four levels, factor B – at three levels, and factor C – at two levels in a complete factorial experiment. The calculation procedure was described in the work [7]. Processing of the results was performed using the MS Excel 2013 programme.

RESULTS AND DISCUSSION

To find the optimal composition of the excipients selected the mathematical theory of planning the experiment for mixtures was used [1, 11].

To construct a mathematical model on the basis of plans for mixtures the Statistica 8.0 programme was used. This programme provides ready-made matrixes of experimental designs and automatically calculates all parameters of the mathematical model.

Since the list of possible excipients, which may be included in the drug composition is quite diverse, and it, in turn, can lead to unreasonably large number of experiments on searching the optimal composition, we decided to neglect such fillers as sucrose, glucose, icing sugar because they are glucogenic substances and not indifferent for diabetics, but to study MCC, starch 1 (corn), starch 2 (potato), lactose.

Moreover, no monosubstances were used, but their combinations with starches in the ratio of 1:1. Of disintegrants the most frequently used substances in the technology of tablets – cross-carmellose sodium and sodium starch glycolate – were selected. Of binders we chose solutions of polyvinylpyrrolidone (PVP), copovidone (plasdone S-630) and hydroxypropyl methylcellulose (HPMC) possessing the best moisturizing characteristics (Table 1).

Table 1

EXCIPIENTS STUDIED WHEN DEVELOPING THE COMPOSITION AND TECHNOLOGY OF TABLETS

Factors	Levels of factors
A – fillers and structure-forming agents	a1 – MCC : starch 1 (6:6 pts. wt.) a2 – MCC : starch 2 (6:6 pts. wt.) a3 – lactose : starch 1 (6:6 pts. wt.) a4 – lactose : starch 2 (6:6 pts. wt.)
B – binders	b1 – PVP solution b2 – copovidone solution b3 – HPMC solution
C – disintegrants	c1 – cross-carmellose sodium (6 pts. wt.) c2 – sodium starch glycolate (6 pts. wt.)

To select excipients with the greatest influence on the properties of tablets such as disintegration time, friability and resistance to crushing the method of the analysis of variance was used. This method allows to identify the most significant factors, and together with the method of multiple comparison according to Duncan criterion will allow to have a number of advantages among levels of the factors studied and select the most promising

substances for further optimization of the methods of mathematical planning of the experiment.

Table 2 presents the results of the analysis of variance: experimental Fisher's variance ratios (Fe) among factors A, B, C by their impact on the disintegration time Y1, friability Y2 and resistance of tablets to crushing Y3 (the impact is considered reliable if the experimental Fisher's variance ratio is higher than the table one Fisher's variance ratio, i.e. if Fe > Ft).

As can be seen from Table 3, all factors significantly affect the disintegration time, friability and resistance of tablets to crushing (for all factors the condition Fe > Ft is satisfied), moreover, a range of significance of factors is as follows: A > C > B> AB/AC/BC. The residue of dispersion indicates the presence between factors interaction, for example, AB, AC, BC.

Using the method of Duncan multiple comparison a number of advantages of factor levels among themselves was identified.

Table 3 gives the ranges of levels of factors by their influence on the main control parameters of tablets according to the SPhU: disintegration time, friability and resistance to crushing.

Therefore, the optimal factor is: among fillers A a1 – MCC : starch 1 (6 : 6 pts. wt.); among binders B b3 – HPMC solution or b1 – PVP solution, or their mixture; among disintegrants C c1 – cross-carmellose sodium (6 pts. wt.).

CONCLUSIONS AND PROSPECTS FOR FURTHER RESEARCH

1. Using the analysis of variance the optimal composition of excipients has been determined when developing a tableted dosage form for prevention and treatment of diabetic complications.

2. It has been found that the composition of tablets based on taurin and thioctic acid includes the following excipients: microcrystalline cellulose and corn starch as fillers, cross-carmellose sodium as a disintegrant; polyvinylpyrrolidone and hydroxypropyl methylcellulose as wetting agents.

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Table 2

ANALYSIS OF VARIANCE OF THE EXPERIMENTAL DATA IN DETERMINING DISINTEGRATION TIME - Y1, FRIABILITY - Y2 AND RESISTANCE TO CRUSHING – Y3

Sources of dispersion	Degree of freedom	Fe1 for Y1	Fe2 for Y2	Fe3 for Y3	Ft (0.05)
Factor A	3	301.1	33.7	150.5	3.0
Factor B	2	117.4	23.3	27.0	3.4
Factor C	1	177.8	36.0	5.1	4.3
The residue (interaction)	17	31.2	8.2	23.5	2.1
Error inside the cell	24	–	–	–	–
The total amount	47	–	–	–	–

Table 3

SUMMARY DATA CONCERNING THE EFFECT OF LEVELS OF FACTORS ON DISINTEGRATION TIME, FRIABILITY, RESISTANCE OF TABLETS TO CRUSHING

The control parameter	Factor A	Factor B	Factor C
Disintegration time	a1 > a2 > a3 > a4	b3 > b1 > b2	c1 > c2
Friability	a1 > a2 > a3 = a4	b3 = b1 > b2	c1 > c2
Resistance to crushing	a1 > a2 > a3 > a4	b1 = b3 > b2	c1 > c2
Optimal factor	a1	b1 ≡ b3	c1

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Св. Н. Коваленко

ОБОСНОВАНИЕ ВЫБОРА ВСПОМОГАТЕЛЬНЫХ ВЕЩЕСТВ С ИСПОЛЬЗОВАНИЕМ ДИСПЕРСИОННОГО АНАЛИЗА ПРИ РАЗРАБОТКЕ ТАБЛЕТОК С ТИОКТОВОЙ КИСЛОТЫ И ТАУРИН

С целью проведения оптимизации процесса разработки состава и технологии комбинированных таблеток на основе таурина и тиоктовой кислоты, на протекание которого влияет множество различных факторов были применены матетематических методы, которые позволили значительно сократить количество експериментов и увеличить информацию о процессе, который изучался.

С помощью дисперсионного анализа было обосновано выбор вспомо-ных веществ при разработке комбинированного лекарственного препарата для профилак политики и лечения диабетических осложнений. Установлено, что в состав таблеток на основе таурина и тиоктовой кислоты входят следующие вспомогательные вещества: как наполнители — целлюлоза микрокристаллическая и крахмал кукурузный; как разрыхлитель — натрия кроскармеллоза; как увлажнители — поливинилпирролидон и гидроксипропилметилцеллюлоза.

Ключевые слова: диабетические осложнения, дисперсионный анализ, вспомогательные вещества, распадаемость, таблетки, тиоктовая кислота, таурин, сахарный диабет.

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Св. М. Коваленко

ОБГРУНТУВАННЯ ВИБОРУ ДОПОМІЖНИХ РЕЧОВИН З ВИКОРИСТАННЯМ ДИСПЕРСІЙНОГО АНАЛІЗУ ПРИ РОЗРОБЦІ ТАБЛЕТОК З ТІОКТОВОЮ КИСЛОТОЮ І ТАУРИНОМ

З метою проведення оптимізації процесу розробки складу і технології комбінованих таблеток на основі таурину та тіоктової кислоти, на протікання якого впливає велика кількість різноманітних факторів, були застосовані математичні методи, що дозволили значно скоротити кількість експериментів і збільшити інформацію про процес, що вивчався.

За допомогою дисперсійного аналізу було обгрунтовано вибір допоміжних речовин при розробці комбінованого лікарського препарату для профілактики та лікування діабетичних ускладнень. Встановлено, що до складу таблеток на основі таурину та тіоктової кислоти входять наступні допоміжні речовини: як наповнювачі – целюлоза мікрокристалічна та крохмаль кукурудзяний; як розпушувач – натрію кроскармелоза; як зволожувачі – полівінілпіролідон і гідроксипропілметилцелюлоза.

Ключові слова: діабетичні ускладнення, дисперсійний аналіз, допоміжні речовини, розпадання, таблетки, тіоктова кислота, таурин, цукровий діабет.

Адреса для листування:
61118 , м. Харків, вул. Блюхера, 4,
Кафедра товарознавства НФаУ
E-mail: aromafarm@mail.ru
lana_koval@mail.ru

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