Ukrainian Scientific Medical Youth Journal
Issue 2 (139), 2023
Creative Commons «Attribution» 4.0

ISSN 2786-6661
eISSN 2786-667X

UDC: 615.453.6.014.2:[615.212+615.224
https://doi.org/10.32345/USMYJ.2(139).2023.121-127

Received: April 17, 2023
Accepted: June 05, 2023

Justification of the choice of excipients for obtaining tablets based on thiotriazoline and paracetamol

Khomin Nataliya[1], Hroshovyi Taras[2], Vasenda Marjana[2], Plaskonis Yuliya[3]

[1]5th year Master student of the Faculty of Pharmacy, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

[2]DSc, PhD, Professor, Department of Management and Economics of Pharmacy with Drug Technology, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

[3]PhD, Associate Professor, Department of Management and Economics of Pharmacy with Drug Technology, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

Address for correspondence:

Vasenda Marjana

E-mail: vasenda@tdmu.edu.ua

Abstract: *one of the most frequently used analgesics and antipyretics in the world is paracetamol, despite its hepatotoxicity. The analysis of scientific works showed that common application paracetamol with thiotriazoline decrease in its hepatotoxicity. Pharmacologists offer a combined medicine containing the analgesic-antipyretic paracetamol and thiotriazoline with hepatoprotective action. For the specified combination of paracetamol and thiotriazoline, it is necessary to create a rational dosage form – tablets. To this purpose, it is necessary to select excipients, to investigate their influence on the technological parameters of tablets based on thiotriazoline and paracetamol, to substantiate the choice of the best excipients in the development of a tablet medicinal product. In order to develop the optimal composition of paracetamol tablets with thiotriazoline by wet granulation, the following technological operations were used: sieving, weighing, mixing, moistening, granulation, drying, repeated granulation, powdering and pressing. We used excipients that meet the requirements of the SPhU and ensure the fulfillment of all technological indicators of the quality of tableted drugs. For the implementation of the experiment, mathematical planning was used, namely a five-factor plan based on the Hyper-Greaco-Latin square. In the course of research, the dependence of all studied parameters (mass homogeneity, friability, resistance of tablets to crushing and disintegration time) was determined on auxiliary substances that were included in the composition of tablets based on thiotriazoline and paracetamol according to the selected experimental plan. Technological quality indicators of the obtained tablets, namely Microcrystalline cellulose (MCC) 101, Arbocel P 290, sodium croscarmellose, Aerosil 200, stearic acid, as a binding solution – 5% starch paste.*

Keywords: tablets, paracetamol, azol, dispersion analysis, excipients.

Introduction

One of the most frequently used analgesics and antipyretics in the world is paracetamol, despite its hepatotoxicity (Rollstin, A. D., & Seifert, S. A. 2013, Koppen, A. et. al. 2014, Kang, A. M. et. al. 2020, Chiew, A. L. et. al. 2020). To reduce the toxic effect on the liver, it is necessary to follow the recommendations on the maximum daily dose of paracetamol and not to use it together with other medicines. Therefore, research in this direc-

ISSN 2786-6661
eISSN 2786-667X

tion, namely the causes and mechanisms of the toxic effect on the liver by paracetamol in order to develop more effective treatment and prevention strategies in case of overdose, is relevant for medicine (Wong, A. et. al. 2017, Wong, A., & Graudins, A. 2017). It has been proven that the hepatotoxicity of paracetamol is significantly reduced when it is used together with thiotriazoline (Посохова, К. А., та ін. 2013, Посохова, К. А., & Вольська, А. С. 2012, Посохова, К. А., та ін. 2014). Pharmacologists offer a combined medicine containing the analgesic-antipyretic paracetamol and thiotriazoline with hepatoprotective action. The combination of these substances in one dosage form is an opportunity to achieve the minimum hepatotoxic effect of paracetamol and, at the same time, to ensure the optimal pharmacological effect on the body. For the specified combination of paracetamol and thiotriazoline, it is necessary to create a rational dosage form – tablets.

Aim

The study the influence of excipients on the pharmaco-technological parameters of tablets based on thiotriazoline and paracetamol obtained by the method of wet granulation and to substantiate the choice of the best of them in the development of a tablet medicine using the method of mathematical planning of the experiment is the purpose of this article.

Materials and methods

When creating combined tablets containing paracetamol and thiotriazoline, their physical properties and quantity in the composition of the tablets were previously taken into account. The obtained mixtures of paracetamol powders with thiotriazoline have pharmaco-technological properties that indicate that the method of wet granulation should be used to obtain tablets.

At receiving tablets, much attention is paid to the choice of excipients used in wet granulation: fillers, disintegrants, sorbents, lubricants, binding solutions. Excipients must ensure the fulfillment of certain pharmaco-technological requirements by the SPhU for tablets (фармакопея України, Д. (2015)). During the work, 25 different excipients were studied, which grouped in five groups of five substances each: fillers (factor A – a_1 – MCC 101, a_2 – arbocel R 290, a_3 – Emcompress, a_4 – lactose, a_5 – powdered sugar); disintegrants (factor B – b_1 – potato starch, b_2 – sodium croscarmellose, b_3 – sodium carboxymethyl starch, b_4 – sodium starch glycolate, b_5 – pregelatinized starch); binding solutions (factor C – c_1 – 3% starch paste, c_2 – 5% PVP, c_3 – 5% MC 15, c_4 – 5% PVA, c_5 – 5% HPMC 2910); samples of microcrystalline cellulose (factor D – d_1 – Aerosil 380, d_2 – Aerosil 200, d_3 – fluoride calcium silicate, d_4 – neusilin US2, d_5 – siloid 244 FP) and lubricants (factor E – e_1 – magnesium stearate, e_2 – calcium stearate, e_3 – stearic acid, e_4 – sodium stearyl fumarate, e_5 – sodium lauryl sulfate).

For the study of five qualitative factors, a Greaco-Latin 5x5 (Грошовий, Т. А. та ін. 2008) was chosen. The matrix of the planning of the experiment and the results of the study of technological indicators of the quality of tablets based on thiotriazoline and paracetamol are given in the table 1.

Results

For the purpose of develop the optimal composition of paracetamol tablets with thiotriazoline by wet granulation, the following technological operations were used: sieving, weighing, mixing, moistening, granulation, drying, repeated granulation, powdering and pressing. Model mixtures were prepared as follows: the mixture of paracetamol and thiotriazoline was carefully mixed, filler and disintegrant were added and mixed again. The powder mass was moistened with a solution of a binder until the formation of a plastic mass. The wet mass was rubbed through a sieve with a hole diameter 3 mm and dried at a temperature 60 °C. The dried granules were rubbed through a sieve with a diameter 1.5 mm and powdered with slippery, lubricating substances.

25 series of tablets were obtained, mass uniformity, friability, resistance to crushing and disintegration time were investigated. The research results were subjected to variance analysis, and graphic dependencies were built for the most significant factors.

When studying the uniformity of the tablets mass based on thiotriazoline and paracetamol, it was established that only factor E – the nature of the lubricants – has an effect on this indicator (Fig. 1).

Fig. 1. Influence of the lubricants nature on the uniformity of the tablets mass based on thiotriazoline and paracetamol.

ISSN 2786-6661
eISSN 2786-667X

Table 1. Experiment design matrix and test results of tableting mass and tablets based on paracetamol with thiotriazoline

No	Factor					Response							
	A	B	C	D	E	y_1	y'_1	y_2	y'_2	y_3	y'_3	y_4	y'_4
1.	a_1	b_1	c_1	d_1	e_1	4,06	3,43	101,3	109,8	0,79	0,71	4,0	5,0
2.	a_1	b_2	c_2	d_2	e_2	3,78	2,56	149,9	134,5	0,60	0,65	8,0	10,0
3.	a_1	b_3	c_3	d_3	e_3	4,67	3,43	135,9	141,8	0,57	0,51	9,0	11,0
4.	a_1	b_4	c_4	d_4	e_4	3,23	3,08	95,2	98,9	0,96	0,92	36,0	39,0
5.	a_1	b_5	c_5	d_5	e_5	2,45	1,90	138,6	125,5	0,85	0,89	37,0	39,0
6.	a_2	b_1	c_2	d_3	e_4	3,87	3,25	66,1	69,0	0,93	0,90	8,0	11,0
7.	a_2	b_2	c_3	d_4	e_5	2,96	2,60	92,4	102,9	0,47	0,42	6,0	7,0
8.	a_2	b_3	c_4	d_5	e_1	4,94	3,46	84,8	67,1	0,85	0,96	3,0	3,0
9.	a_2	b_4	c_5	d_1	e_2	2,88	2,12	131,2	124,8	0,76	0,84	50,0	58,0
10.	a_2	b_5	c_1	d_2	e_3	3,54	2,59	105,2	103,0	0,76	0,84	5,5	7,0
11.	a_3	b_1	c_3	d_5	e_2	3,12	2,86	115,0	114,6	0,47	0,49	56,0	65,0
12.	a_3	b_2	c_4	d_1	e_3	4,07	3,56	112,0	103,4	0,44	0,49	6,0	9,0
13.	a_3	b_3	c_5	d_2	e_4	2,11	2,60	112,4	97,70	0,66	0,73	10,5	13,0
14.	a_3	b_4	c_1	d_3	e_5	2,94	2,23	107,0	102,5	0,79	0,83	65,0	65,0
15.	a_3	b_5	c_2	d_4	e_1	4,50	3,62	118,6	121,9	0,59	0,51	65,0	65,0
16.	a_4	b_1	c_4	d_2	e_5	3,53	3,14	95,40	104,7	0,43	0,39	65,0	65,0
17.	a_4	b_2	c_5	d_3	e_1	4,11	3,43	128,9	109,4	0,78	0,91	7,0	8,0
18.	a_4	b_3	c_1	d_4	e_2	3,62	3,02	145,5	149,6	0,68	0,71	12,0	13,0
19.	a_4	b_4	c_2	d_5	e_3	4,55	3,23	195,2	165,7	0,56	0,63	28,0	25,5
20.	a_4	b_5	c_3	d_1	e_4	2,87	2,13	161,5	190,2	0,54	0,52	65,0	65,0
21.	a_5	b_1	c_5	d_4	e_3	4,29	3,11	87,95	86,9	0,47	0,49	36,0	39,0
22.	a_5	b_2	c_1	d_5	e_4	4,27	3,56	93,5	87,5	0,63	0,68	4,0	5,5
23.	a_5	b_3	c_2	d_1	e_5	4,48	3,44	156,3	132,5	0,48	0,52	7,5	8,0
24.	a_5	b_4	c_3	d_2	e_1	4,23	3,22	169,1	161,2	0,43	0,49	65,0	65,0
25.	a_5	b_5	c_4	d_3	e_2	2,57	2,14	145,2	149,8	0,41	0,48	65,0	65,0

Note:
y_1 and y'_1 – homogeneity of the tablets mass, ±% of the first and second series, respectively;
y_2 and y'_2 – resistance of tablets to crushing, N of the first and second series, respectively;
y_3 and y'_3 tablet friability,% of the first and second series, respectively;
y_4 and y'_4 – tablet disintegration time, min. first and second series, respectively.

The smallest deviation from the average weight of tablets based on thiotriazoline and paracetamol is observed when using calcium stearate (±2,87%), sodium lauryl sulfate (±2,98%) and sodium stearyl fumarate (±3,09%). These substances have an advantage over stearic acid (±3,70%) and magnesium stearate (±3,90%).

Dispersion analysis of experimental data on determining the resistance of tablets based on thiotriazoline and paracetamol to crushing showed the statistical significance of all 5 factors: A > B > C > E > D > res.

In fig. 2. the influence of fillers (factor A) on the resistance to crushing of tablets is given.

According to the given fig. 2, the greatest resistance to crushing is provided by the introduction of lactose (144,63 N) into the tablet mass. We also get a good result when using powdered sugar (126,98 N), MCC 101 (123,15 N) and Emcompress (110,52 N). The worst result is obtained

ISSN 2786-6661
eISSN 2786-667X

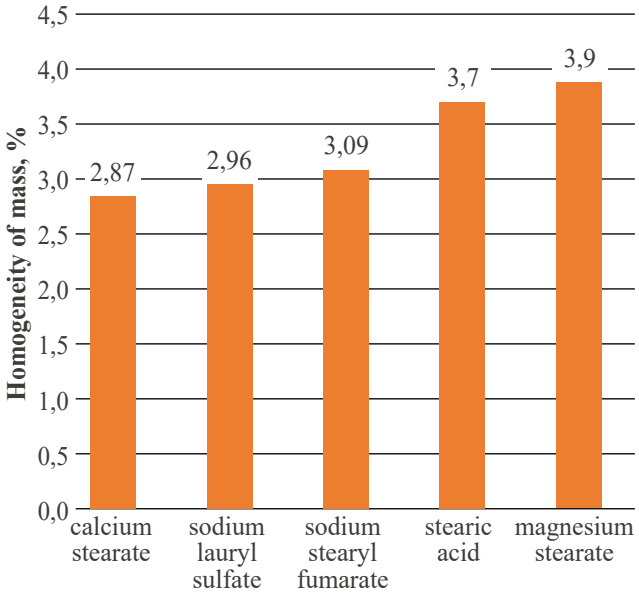

Fig. 1. Influence of the lubricants nature on the uniformity of the tablets mass based on thiotriazoline and paracetamol

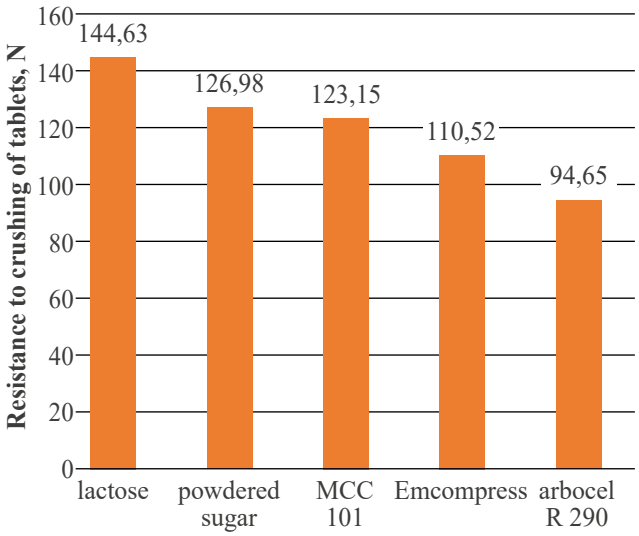

Fig. 2. The influence of fillers on the resistance to crushing of tablets based on thiotriazoline and paracetamol

when using arbocel R 290. Analyzing factor B, the strongest tablets are obtained when using pregelatinized starch (136,96 N) and starch glycolate (135,09 N). The worst result is obtained when potato starch (95,08 N) is added to the tablet. Among binders, 5% MC 15 and 5% PVP provide the best resistance to crushing. The value of resistance to crushing in both cases was higher than 130 N. The ranked number of advantages of the lubricants effect on the resistance to crushing of the studied tablets is as follows: calcium stearate (136,01 N), stearic acid (123,01 N), magnesium stearate (117,22 N), sodium lauryl sulfate (115,7 N), sodium stearyl fumarate (107,2 N). The tablets containing samples of microcrystalline cellulose (factor D) – Aerosil 380 (132,28 N) were the most resistant to crushing, which had advantages over Aerosil 200 (123,33 N), syloid 244 FP (118,46 N), fluoride calcium silicate (115,57 N) and neusilin US2 (109,98 N).

When studying tablets based on thiotriazoline and paracetamol for friability based on dispersion analysis, the experimental data can be placed in the following sequence: A > D > E > C, factor B does not affect this indicator.

Having analyzed the results according to the studied indicator, can be concluded that the obtained model tablets meet the requirements of the SPhU, because loss in mass does not exceed 1%.

In fig. 3 shows the effect of factor A on the friability of paracetamol tablets with thiotriazoline.

The influence of the most significant factor A on the friability of tablets based on thiotriazoline and paracetamol shows that the most resistant to abrasion were the series in which powdered sugar (0,46%) was used as a filler, lactose (0,54%) and Emcompress (0,55%). These substances had an advantage over MCC 101 (0,74%) and Arbocel R 290 (0,77%).

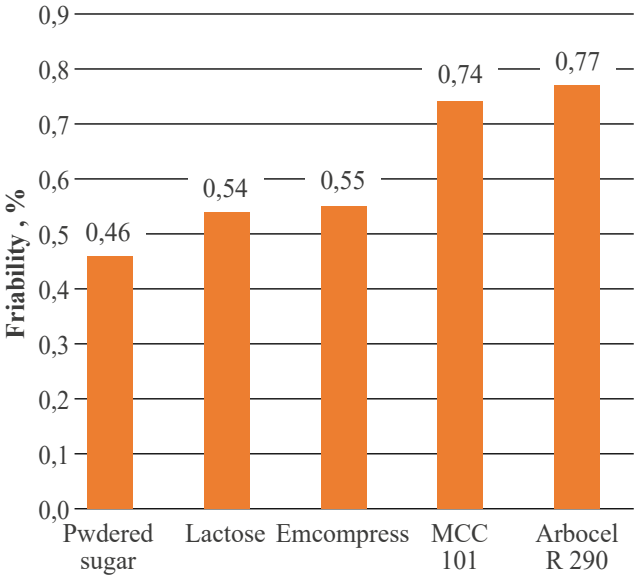

Fig. 3. The influence of fillers on the friability of tablets based on thiotriazoline and paracetamol

ISSN 2786-6661
eISSN 2786-667X

The least abrasion of tablets based on thiotriazoline and paracetamol was obtained when using neusilin (0,45%) and Aerosil 200 (0,55%) as samples of MCC. When using Aerosil 380, siloid 244 FP, fluoride calcium silicate, the value of the research indicator did not significantly deteriorate.

The effect of lubricants on the friability of the studied tablets is possible present as follows number of advantages: stearic acid (0,53%) >calcium stearate (0,54%) >sodium lauryl sulfate (0,61%) >magnesium stearate (0,64%) >sodium stearyl fumarate (0,75%).

Among the binders studied, it provided the lowest tablet abrasion value 5% MC 15 (0,49%), followed by –5% of PVP (0,58%), these binding solutions had an advantage over 5% PVA (0,63%), 3% starch paste (0,67%) and 5% of HPMC 2910 (0,69%).

Disintegration time is an important indicator of the quality of a tablet product. According to the SPhU, the disintegration time of tablets that are not coating should not exceed 15 minutes. Among the received model tablets in some series, namely 4, 5, 9, 11, 15, 16, 19, 24, 25, the disintegration time was more than 15 min.

Based on dispersion analysis, the studied quality factors for the specified indicator can be placed in the following sequence: B > A > C > E > D. The influence of the most significant factor B on the time of tablet disintegration is shown in Fig. 4.

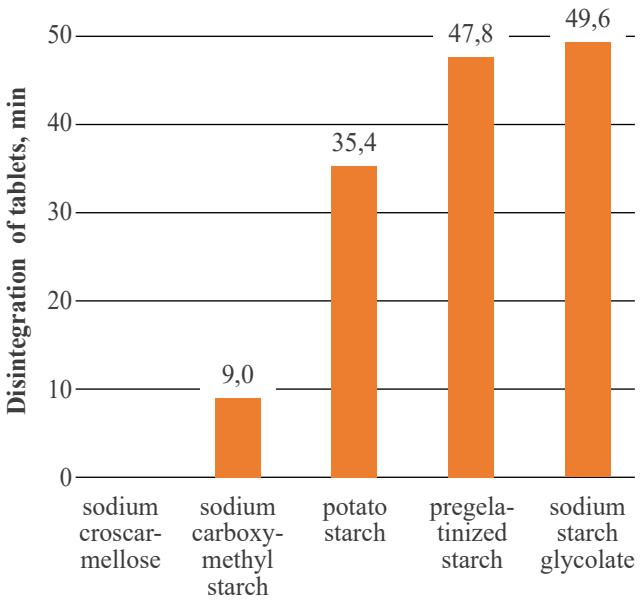

Fig. 4. The disintegrants effect on the disintegration time of tablets based on thiotriazoline and paracetamol

From the data of fig. 4, it can be seen that the shortest disintegration time that meets the requirements of SPhU was in tablets that contained sodium croscarmellose (7 min) and sodium carboxymethyl starch (9 min). When using potato starch, pregelatinized starch, and sodium starch glycolate, the disintegration time increases to 50 minutes.

When examining tablets, the disintegration time is ranked as follows: arbocel R 290 (15,8 min) > MCC 101 (19,8 min) > lactose (35,3 min) > powdered sugar (36,0 min) > Emcompress (41,9 min).

Among binding solutions, the best disintegration time of tablets is provided by the use of 3% starch paste (18,6 min). The worst disintegration time is obtained with moistened tableting mass by 3% MC 15 (41,4 min)

The effect of lubricants on the disintegration of the obtained tablets can be illustrated by the following number of advantages: stearic acid (17,6 min), sodium stearyl fumarate (25,7 min), magnesium stearate (29,0 min), sodium lauryl sulfate (36,4) and calcium stearate (40,2 min).

Analyzing the effect of microcrystalline cellulose samples on the dissolution time of tablets based on thiotriazoline and paracetamol, they can be placed as follows: siloid 244 FP (26,6 min) > Aerosil 380 (27,7 min) > Aerosil 200 (31,4 min) = fluoride calcium silicate (31, 4 min) > neusilin US2 (31,8 min).

Conclusions

1. By using a five-factor experiment – the Greako-Latin square, the influence of 5 quality factors on the main quality indicators of tablets based on thiotriazoline and paracetamol was established.
2. Ranked series of advantages of the effect of excipients on 4 reviews (indicators), namely uniformity of mass, abrasion resistance, resistance to disintegration and disintegration, were constructed.
3. On the basis of the obtained results, the best excipients were selected for the development of the composition and technology of a tableted medicinal product based on thiotriazoline and paracetamol by wet granulation, namely: MCC 101, Arbocel R 290, sodium croscarmellose, Aerosil 200, stearic acid, as a binder solution – 5% starch paste.

ISSN 2786-6661
eISSN 2786-667X

Funding
This study hadn't obtained external funding.

Conflicts of interest
Authors have no conflict of interest to declare.

Consent to publication
No patient data or identifying information was used in the preparation of this manuscript. Therefore, no consent to publication was required from patients. Therefore, no consent to publication was required from patients.

ORCID ID and authors contribution
0009-0003-2698-3949 (B, D) Khomyn Nataliia
0000-0002-6427-2158 (A, C, E) Hroshovyi Taras
0000-0002-1548-0145 (A, B, D, F) Vasenda Marjana
0000-0001-5299-1879 (D, E, F) Plaskonis Yuliya

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis
and interpretation, D – Writing the article, E – Critical revision of the article, F – Finalapproval of article

REFERENCES

Грошовий, Т. А., Марценюк, В. П., Кучеренко, Л. І., Вронська, Л. В., & Гуреєва, С. М. (2008). Математичне планування експерименту при проведенні наукових досліджень в фармації. Тернопіль: Укрмедкнига, 368.

Посохова, К. А., & Вольська, А. С. (2012). Профілактика гепатотоксичної дії парацетамолу за допомогою тіотриазоліну та ацетилцистеїну. Український біофармацевтичний журнал, (5-6), 42-45.

Посохова, К. А., Вольська, А. С., & Чернухіна, О. О. (2013). Зміни гістологічної будови печінки при її ураженні парацетамолом та призначенні тіотриазоліну та ацетилцистеїну. Вісник морфології, (19,№ 2), 302-306.

Посохова, К. А., Вольська, А. С., & Шевчук, О. О. (2014). Зміни гістологічної будови печінки при її ураженні парацетамолом і призначенні тіотриазоліну та ацетилцистеїну. Медична хімія, 16(4)., 112-123.

Фармакопея України, Д. (2015). ДП «Український науковий фармакопейний центр якості лікарських засобів». 2-е вид. Харків: ДП «Український науковий фармакопейний центр якості лікарських засобів, 1, 1128.

Chiew, A. L., Reith, D., Pomerleau, A., Wong, A., Isoardi, K. Z., Soderstrom, J., & Buckley, N. A. (2020). Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. The Medical journal of Australia, 212(4), 175–183. https://doi.org/10.5694/mja2.50428

Kang, A. M., Padilla-Jones, A., Fisher, E. S., Akakpo, J. Y., Jaeschke, H., Rumack, B. H., Gerkin, R. D., & Curry, S. C. (2020). The Effect of 4-Methylpyrazole on Oxidative Metabolism of Acetaminophen in Human Volunteers. Journal of medical toxicology : official journal of the American College of Medical Toxicology, 16(2), 169–176. https://doi.org/10.1007/s13181-019-00740-z

Koppen, A., van Riel, A., de Vries, I., & Meulenbelt, J. (2014). Recommendations for the paracetamol treatment nomogram and side effects of N-acetylcysteine. The Netherlands journal of medicine, 72(5), 251–257.

Rollstin, A. D., & Seifert, S. A. (2013). Acetaminophen/diphenhydramine overdose in profound hypothermia. Clinical toxicology (Philadelphia, Pa.), 51(1), 50–53. https://doi.org/10.3109/15563650.2012.748195

Wong, A., & Graudins, A. (2017). Risk prediction of hepatotoxicity in paracetamol poisoning. Clinical toxicology (Philadelphia, Pa.), 55(8), 879–892. https://doi.org/10.1080/15563650.2017.1317349

Wong, A., Sivilotti, M. L. A., & Graudins, A. (2017). Accuracy of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity in modified-release paracetamol overdose. Clinical toxicology (Philadelphia, Pa.), 55(5), 346–351. https://doi.org/10.1080/15563650.2017.1290253

Обґрунтування вибору допоміжних речовин для отримання таблеток на основі тіотриазоліну та парацетамолу

Хомин Наталія, Грошовий Тарас, Васенда Мар'яна, Пласконіс Юлія

Кафедра управління та економіки фармації з технологією ліків
ТНМУ імені І. Я. Горбачевського МОЗ України, м. Тернопіль, Україна

Address for correspondence:

Vasenda Marjana

E-mail: vasenda@tdmu.edu.ua

ISSN 2786-6661
eISSN 2786-667X

Анотація: *одним з найбільш часто вживаних анальгетиків та антипіретиків у світі є парацетамол, незважаючи на його гепатотоксичність. Аналіз наукових праць показав, що при спільному застосуванні парацетамолу з тіотриазоліном є суттєве зниження його гепатотоксичності. Фармакологами пропонується комбінований лікарський засіб, що вміщує анальгетик–антипіретик парацетамол та гепатопротектор – тіотриазолін. Для вказаної комбінації парацетамолу з тіотриазоліном необхідно створити раціональну лікарську форму – таблетки. Для цього необхідно підібрати допоміжні речовини, дослідити їх вплив на технологічні показники таблеток основі тіотриазоліну та парацетамолу, обґрунтувати вибір кращих допоміжних речовин при розробці таблетованого лікарського засобу. З метою розробки оптимального складу таблеток парацетамолу з тіотриазоліном вологою грануляцією було використано наступні технологічні операції: просіювання, зважування, змішування, зволожування, гранулювання, висушування, повторне гранулювання опудрювання та пресування. Використовували допоміжні речовини, які відповідають вимогам ДФУ і забезпечують виконання всіх технологічних показників якості таблетованих препаратів. Для реалізації експерименту використовували математичне планування, а саме п'яти факторний план на основі гіпер-греко латинського квадрату. У процесі досліджень визначили залежність усіх досліджуваних показників (однорідність маси, стираність, стійкість таблеток до роздавлювання та час розпадання) від допоміжних речовин, які водилися в склад таблеток на основі тіотриазоліну та парацетамолу згідно вибраного плану експерименту. На основі аналізу було відібрано для подальших досліджень допоміжні речовини, які чинили максимальний ефект на основні технологічні показники якості отриманих таблеток, а саме МКЦ 101, арбоцель Р 290, натрій кроскармельоза, аеросил 200, кислота стеаринова, як зв'язуючи розчин – 5% крохмальний клейстер.*

Ключові слова: таблетки, парацетамол, тіотриазолін, дисперсійний аналіз, допоміжні речовини.