УДК 615.014.07:615.225.2:615.014.47:519.237.4
DOI: 10.32352/0367-3057.2.22.06

M. B. DEMCHUK [1] (https://orcid.org/0000-0002-9105-2302),
Yu. Ya. MELNYK [2] (https://orcid.org/0000-0002-8516-9926),
N. V. MALANCHYK [1] (https://orcid.org/0000-0002-0175-7502),
T. A. GROSHOVYI [1] (https://orcid.org/0000-0002-6427-2158),
V. Y. SKOROKHODA [2] (https://orcid.org/0000-0002-2352-5964)
[1] *Horbachevsky Ternopil National Medical University*
[2] *Lviv Polytechnic National University*

RESEARCH THE INFLUENCE OF EXCIPIENTS ON THE TECHNOLOGICAL PROPERTIES OF CAPTOPRIL FAST DISSOLVING FILMS

Key words: fast dissolving film, captopril, polymer, plasticizer, variance analysis

М. Б. ДЕМЧУК [1] (https://orcid.org/0000-0002-9105-2302), канд. фарм.наук, доцент,
Ю. Я. МЕЛЬНИК [2] (https://orcid.org/0000-0002-8516-9926),
Н. В. МАЛАНЧУК [1] (https://orcid.org/0000-0002-0175-7502),
Т. А. ГРОШОВИЙ [1] (https://orcid.org/0000-0002-6427-2158), д-р фарм. наук, проф.,
В. Й. СКОРОХОДА [2] (https://orcid.org/0000-0002-2352-5964), д-р техн. наук, проф.
[1] *Тернопільський національний медичний університет імені І. Я. Горбачевського*
[2] *Національний університет «Львівська політехніка»*

ВИВЧЕННЯ ВПЛИВУ ДОПОМІЖНИХ РЕЧОВИН НА ТЕХНОЛОГІЧНІ ВЛАСТИВОСТІ ШВИДКОРОЗЧИННИХ ПЛІВОК КАПТОПРИЛУ

Ключові слова:швидкорозчинна плівка, каптоприл, полімер, пластифікатор, дисперсійний аналіз

Fast dissolving drug-delivery systems were first developed as an alternative to conventional dosage forms for pediatric and geriatric patients having problems with swalloving. This system can be defined as a dosage form for oral administration, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva. This dosage form rapidlydisintegrates and/or dissolves to release the active pharmaceutical ingredient and can be swallowed in the form of liquid [1, 2].

Using polymeric films as a fast dissolving drug-delivery system has greatly developed nowadays. The administration of oral dissolving films has numerous advantages including easy transportation and accurate dosing [3, 4]. The films are convenient for dysphasic patients having difficulties with swallowing tablets and capsules. They provide rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect[5–8].

Oral films as fast dissolving drug-delivery systemsare used for management of acute conditions such as pain, vomiting, migraine, hypertension, congestive heart failure, asthma etc [9].

Captopril is an antihypertensive drug used for the hypertension therapy and heart failure through reduction of angiotensin II and increase of bradykinin production. The systemic bioavailability of captopril is approximately 60–65% [10, 11]. When captopril is taken under the tongue, its antihypertensive effect occurs within 5–15 minutes [12]. According to these facts captopril can be considered as a suitable candidate for developing

fast dissolving oral films.

The aim of our study was to prepare captopril fast dissolving films(FDFs) by solvent casting method and analyze the influence of groups of excipients on technological parameters of the films using Latin hypercube design[13].

Materials and Methods

The formulations were designed according to the method of 3*3*3 Latin hypercube. In this design, fourgroups of factorswere evaluatedand experimental trials were performed in 27 possible combinations (Table 1). The three factors including factor A (type of disitegrant), factor B (type of plasticizer) and factor C (type of sweetener) were studied on three levels. The factor D (type of polymer) was studied on nine levels. All linear effects of the factors established on n levels are determined with the same maximum accuracy for all experiments. The effect of factor D on n^2 levels is determined with the accuracy which is n-times less.

Table 1

Independent variables and their levels selected to perform Latin hypercube design

Independent variables (factors)	Level of factor
A – type of disintegrant	a_1 – sodium croscarmellose
	a_2 – Polyplasdone XL-10crospovidone
	a_3 – sodium starch glycolate (SSG)
B – type of plasticizer	b_1 – propylene glycol
	b_2 – glycerol
	b_3 – polyethylene glycol (PEG) 400
C – type of sweetener	c_1 – sucralose
	c_2 – sorbitol
	c_3 – mannitol
D – type of polymer	d_1 – HPMC Metolose®90 SH 100 000
	d_2 – HPMC Metolose® 65 SH 50
	d_3 – HPMC Vivapharm® E3
	d_4 –HPMC Vivapharm® E15
	d_5– Kollicoat® IR
	d_6–polyvinyl alcohol (PVA)
	d_7 – combinationHPMC + PEG 4000
	d_8 – combinationHPMC + PEG 6000
	d_9 – hydroxypropyl cellulose (HPC)

The captopril fast dissolving oral films were prepared by a solvent casting method. The weighed quantity of polymer was kept for swelling in hot distilled water and dissolved.The captopril, sweetener and disintegrant were dissolved in distilled water and added to previously received chilled polymer solution along with a plasticizer, mixed thoroughly to form a homogenous mixture. Entrapped air bubbles were removed by applying vacuum.

The casting solution (25 ml) was poured into petridish and dried at 40°C in the oven for 24 h for solvent evaporation. The dried films werecarefully removed from petridish andcut into square dimensions of 2.3cm×2.3 cm (5.3 cm^2). These films were kept in a desiccator for 2 days for further drying and packed intoair tight plastic bags till further use.

The films were evaluated for uniformity of weight, thickness [14], swelling index[15], mechanical properties [16, 17] and disintegration time [18, 19].

Uniformity of weight. Each film was individually weighed on analytical balance (Shimadzu Electronic Balance, Japan) and average weight of 10 films was found. It is considered that the film stood the test if none of individual masses differs from the average mass more than ±10%. If one of the films didn't stand the test the determination was carried out on 20 films in addition [14]. A large difference in weight denotes the nonuniform distribution of the drug in the film.

The thickness of different films was measured using a calibrated thickness gauge (Campak, Poland) with an accuracy of 0.001 mm[14]. The thickness was measured by placing each film between the anvil and the presser foot of the dial gauge at 5 different points (center and 4 corners) on the film to ensure the uniformity of the film thickness and the mean value was calculated.

The swelling index. The film sample was weighed and placed on a preweighed stainless steel wire mesh. The wire mesh was then submerged into the petridish containing 20 ml distilled water. The increase ofthe film's weight was determined at regular time intervals until the constant weight was obtained [15].

Mechanical properties of films were evaluated by test bursting machines (Kimura Machinery type 050/RT-601U) at the movable traverse's transference speed of 25 mm/min.The determination of physical and mechanical properties of polymer films by the break method was carried out. It is based on deformation of the sample which is effected by a pin indenter to determine the tensile strength and elongation at the break [16–19].

Tensile strength is an indicator of the film's toughness. Captopril films were cut into specimens of round shape with a diameter 17 mm. The geometric dimensions of the films were measured atthe accuracy of 0.01 mm using caliper «Microtech» at 5 different positions. Film thickness was measured by means of manual thickness gauge with an accuracy of 0.001 mm at 5 different positions. The maximum load at the moment of the film's break at the accuracy of 0.001 kgf was fixed on the scale of the device. The elongation of the sample at the moment of its break with measurement error up to 0.1 mm was determined on the clock type indicator.

Tensile strength (σ_x) was calculated using the formula (1):

$$\sigma_x = \frac{F_p}{A_0} \quad (1)$$

where «F_p» is the maximum force at breakage,kgf;

«A_0» is the initial cross sectional area of the sample, cm^2.

The reported data is themean of 3 individual determinations.

Elongation of films. For the determination of films' elongation, the indenter'smoving from the moment of its collision with the sample to its breakthrough was measured [16, 17].

The percentage elongation of the films wascalculated using the formula (2):

$$\varepsilon = 257 \cdot \frac{l}{D} - 25 \quad (2)$$

where «*l*» is the movement of the indenter from the moment of contact with the sample to its breakthrough;

«*D*» is the diameter of the hole of the clamping ring.

The research results are presented as an average value. Statistical analysis was performed using Student's t-test. The value of $p < 0.05$ was taken as the level of significance [20].

Results and Discussion

Fast-dissolving films of captopril were prepared by a solvent casting method according to the matrix given in Table 2. The obtained films were evaluated according to the following indicators: uniformity of weight, thickness, swelling index,tensile strength, elongation of filmsand disintegration time. The results of the study of these indicators are shown in Table 2.

The obtained results of the study were subjected to variance analysis.The verification of the influence of factors on significance was carried out with the help of F – value. The test was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant if the $F_{test} > F_{0.05}$.

The results of comparative design show that 3 groups of factor shave a significant influence on the weight variation of captopril FDFs: D > A > B. The comparison of excipients from the group of polymers (D) gives the following benefits: HPC (d_9) > Kollicoat IR (d_5) > HPMC Vivapharm® E15 (d_4) > HPMC+PEG 6000 (d_8) = PVA (d_6) = HPMC Vivapharm® E3 (d_3) > HPMC+PEG 4000 (d_7) > HPMC Metolose®90 SH 100 000 (d_1) > HPMC Metolose® 65 SH 50 (d_2).

Polymers of PVA and Kollicoat IR provided the formation of slightly rough in texture, less flexible, translucent, harder and inelastic films with a larger mass. Films which were formed using polymersHPC, or HPMC or combinations HPMC with PEG 4000 or PEG 6000 were characterized by close values of the average weight, which ranged from 130 to 160 mg.These films were smooth, flexible and transparent. The films obtained from HPMC Metolose® were very thin and light with an average weight of 60 and 70 mg.

Among the investigated samples of disintegrants Polyplasdone XL-10 crospovidone (a_2) and SSG (a_3) had better influence on the average weight of captopril FDFs. The value of this indicator was improved due to such plasticizers as glycerol (b_2) and PEG 400 (b_3).

The results of the variance analysis show that 3 groups of factors are significant and influence on thickness of captopril FDFs. The effect of different groups of excipients may be placed in the following rank order: factor D > factorA > factorB.

However, the influence of factor D (the type of polymer) on the thickness of the films is the most significant. The optimal value of this indicator is provided by the combination of HPMC with PEG 4000 and the combination HPMC with PEG 6000, when using them the thickness of the films is 0.25 and 0.22 mm, respectively (Fig. 1).

Table 2

Design of formulations and results of technological parameters of captopril fast dissolving films

№ formula	Factor				Weight, mg	Thickness, mm	Swelling index, %	Disintegration time, s	Tensile strength, MPa	Elongation,%	The desirability function
	A	B	C	D							
1	a_1	b_1	c_1	d_1	60 ± 2.640	0.17 ± 0.0051	696 ± 31.32	80 ± 2.032	0.88 ± 0.0210	71.40 ± 1.6065	0.718
2	a_1	b_2	c_1	d_5	180 ± 2.340	0.26 ± 0.0039	72 ± 2.592	75 ± 3.180	0.10 ± 0.0016	39.25 ± 1.2756	0.181
3	a_1	b_3	c_1	d_9	130 ± 3.250	0.20 ± 0.0040	274 ± 11.508	65 ± 2.353	0.34 ± 0.0109	110.50 ± 4.6521	0.468
4	a_2	b_1	c_1	d_2	50 ± 1.650	0.20 ± 0.0060	757 ± 28.766	33 ± 1.072	0.49 ± 0.0208	55.30 ± 1.4157	0.607
5	a_2	b_2	c_1	d_6	310 ± 3.720	0.50 ± 0.0075	202 ± 5.655	900 ± 41.040	0.68 ± 0.0180	100.40 ± 3.5642	0
6	a_2	b_3	c_1	d_7	132 ± 2.904	0.28 ± 0.0070	255 ± 7.650	30 ± 1.275	0.71 ± 0.0230	56.30 ± 1.4413	0.733
7	a_3	b_1	c_1	d_3	110 ± 2.750	0.17 ± 0.0037	375 ± 13.500	53 ± 1.886	2.40 ± 0.0987	86.40 ± 2.808	0.987
8	a_3	b_2	c_1	d_4	190 ± 3.610	0.30 ± 0.0060	303 ± 12.335	46 ± 1.186	1.60 ± 0.0200	39.30 ± 1.0060	0.955
9	a_3	b_3	c_1	d_8	210 ± 5.040	0.21 ± 0.0050	276 ± 9.665	23 ± 0.915	0.88 ± 0.0285	39.30 ± 1.2615	0.799
10	a_1	b_1	c_2	d_4	100 ± 4.100	0.21 ± 0.0063	410 ± 15.580	54 ± 1.447	1.88 ± 0.0480	86.40 ± 2.1168	0.959
11	a_1	b_2	c_2	d_8	120 ± 4.320	0.22 ± 0.0075	317 ± 14.265	10 ± 0.285	0.63 ± 0.0225	39.30 ± 0.5698	0.699
12	a_1	b_3	c_2	d_3	170 ± 6.460	0.34 ± 0.0095	282 ± 10.715	80 ± 3.400	0.82 ± 0.0316	55.30 ± 1.7807	0.746
13	a_2	b_1	c_2	d_5	170 ± 5.950	0.36 ± 0.0115	256 ± 9.005	30 ± 1.368	0.44 ± 0.0188	71.40 ± 1.8278	0.236
14	a_2	b_2	c_2	d_9	200 ± 4.640	0.22 ± 0.0055	289 ± 7.514	45 ± 1.152	0.36 ± 0.0148	70.40 ± 2.5203	0.468
15	a_2	b_3	c_2	d_1	65 ± 2.470	0.12 ± 0.0038	904 ± 32.544	88 ± 3.212	2.23 ± 0.1050	87.40 ± 2.3423	0.943
16	a_3	b_1	c_2	d_6	260 ± 5.460	0.22 ± 0.0048	238 ± 10.472	600 ± 15.480	0.65 ± 0.0209	55.30 ± 1.7419	0
17	a_3	b_2	c_2	d_7	160 ± 5.200	0.30 ± 0.0095	259 ± 12.430	23 ± 0.823	0.46 ± 0.0214	23.20 ± 0.9303	0.522
18	a_3	b_3	c_2	d_2	70 ± 2.660	0.12 ± 0.0042	428 ± 20.115	65 ± 2.938	1.81 ± 0.0695	87.40 ± 3.3998	0.967
19	a_1	b_1	c_3	d_7	100 ± 2.650	0.17 ± 0.0075	94 ± 3.755	49 ± 2.293	0.13 ± 0.0017	5.10 ± 0.1708	0.351
20	a_1	b_2	c_3	d_2	70 ± 2.815	0.12 ± 0.0055	560 ± 21.840	26 ± 1.190	3.00 ± 0.1435	35.30 ± 1.2885	0.990
21	a_1	b_3	c_3	d_6	100 ± 3.820	0.21 ± 0.0048	94 ± 3.755	300 ± 10.74	3.04 ± 0.1420	135.60 ± 4.0409	0
22	a_2	b_1	c_3	d_8	120 ± 4.320	0.22 ± 0.0055	346 ± 8.650	32 ± 1.488	0.52 ± 0.0186	23.20 ± 0.7076	0.615
23	a_2	b_2	c_3	d_3	160 ± 3.840	0.40 ± 0.0168	440 ± 15.840	132 ± 6.006	1.52 ± 0.0326	100.60 ± 3.1689	0.902
24	a_2	b_3	c_3	d_4	200 ± 5.195	0.31 ± 0.0078	140 ± 5.005	55 ± 1.936	0.84 ± 0.0108	71.40 ± 1.8278	0.786
25	a_3	b_1	c_3	d_9	110 ± 3.320	0.17 ± 0.0051	365 ± 11.680	48 ± 1.368	0.83 ± 0.0140	55.30 ± 1.5760	0.789
26	a_3	b_2	c_3	d_1	70 ± 2.745	0.15 ± 0.0063	540 ± 15.120	120 ± 3.900	1.67 ± 0.0296	65.40 ± 1.7330	0.881
27	a_3	b_3	c_3	d_5	210 ± 7.560	0.38 ± 0.0135	50 ± 2.005	48 ± 0.744	0.32 ± 0.0083	40.30 ± 1.2694	0.430

N o t e: $n = 5$, $p = 95\%$.

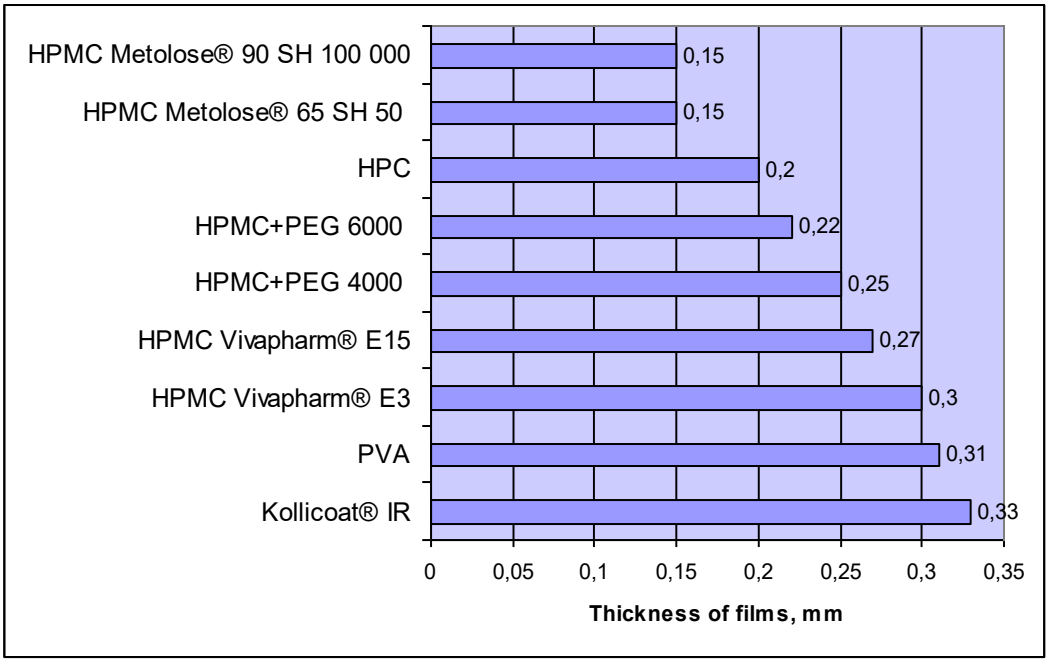

Fig. 1. **The effect of polymers on the films' thickness**

The lowest values of films' thickness were obtained by using sodium croscarmellose (a_1) and SSG (a_3) as disintegrants. Glycerol (b_2) and PEG 400 (b_3) prevailed over propylene glycol (b_1) in the group of plasticizers.

The rank order of the influence of the studied factors on the swelling index has the following form: D > A > B > C. The largest percentage of swelling was observed by using HPMC Metolose®90 SH 100 000 and HPMC Metolose® 65 SH 50 which prevailed over other polymers. High values of swelling index were also obtained by using HPMC Vivapharm® E3 (365%), or combination of HPMC with PEG 6000 (313%) or HPC (310%). In disintegrants' group, Polyplasdone XL-10 crospovidone (a_2) had the benefits over SSG (a_3) and sodium croscarmellose(a_1). Among plasticizers propylene glycol (b_1) or glycerol (b_2) had significant influence on the value of swelling index. The group of sweeteners showed the slightest influence on the results of this indicator: sorbitol(c_2) > sucralose(c_1) > mannitol(c_3).

One of the most important technological indicators of FDFs is its disintegration time. It is the time at which the film breaks or disintegrates when brought in contact with water or saliva. This test is carried out by placing the film in the phosphate buffer. The disintegration time should be up to 3 min.There is no official guidelines available for fast disintegrating oral films.

The disintegration time less than 3 min which was observed in all formulations except #5, 16 and 21, met the requirements for fast dissolving systems. The most significant effect on the disintegration time of captopril FDFswas made by the group of polymers.Films containing HPMC in combination with PEG 6000 or PEG 4000 disintegrated the fastest. Films containing HPMC Metolose® 65 SH 50 or Kollicoat IR also disintegrated fairly quickly (Fig. 2).

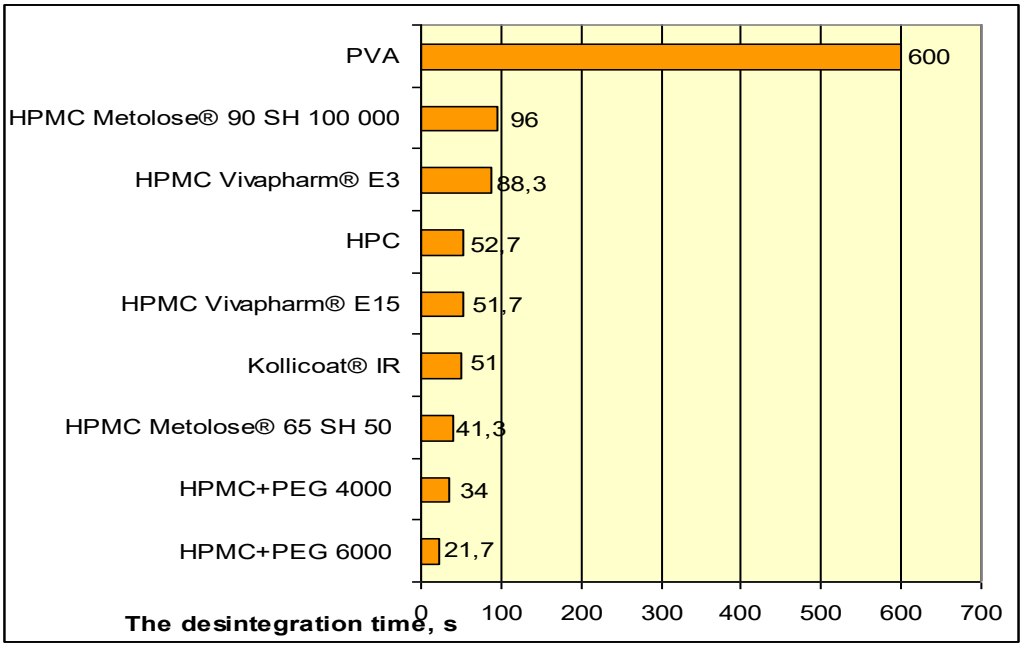

Fig. 2. **The effect of polymers on the disintegration time of captopril FDFs**

The mechanical properties of the film give ideas about abilities to withstand the force during processing, packaging, transport and handling. The tensile strength and elongation of captopril FDFs were also investigatedfor characteristics of the physical and mechanical properties of the films.Only the group of factors D (type of polymers) is statistically significant for the impact of captopril films on the tensile strength.The highest value of tensile strength for captopril FDFs was observed when using HPMC Metolose® 65 SH 50 (1.77 MPa) or HPMC Metolose®90 SH 100 000 (1.59 MPa). HPMC Vivapharm® E3 (1.58 MPa), HPC (1.46 MPa) and HPMC Vivapharm® E15 (1.44 MPa) have shown better influence on this indicator too.

The most significant effect on the elongation of captopril FDFs has been made by the group of polymers and the group of plasticizers. The rank order among polymers according to the influence on the elongation of films is as follows: PVA >HPMC Vivapharm® E3 > HPC > HPMC Metolose®90 SH 100 000 > HPMC Vivapharm® E15 > HPMC Metolose® 65 SH 50 > Kollicoat® IR > HPMC+PEG6000 > HPMC+PEG4000. PEG 400has the most significant impact on the elongation prevailing over glycerol (b_2) and propylene glycol (b_1).

Since, different factors have better influence on different indicators according to the variance analysis. So, it is necessary to transfer them into dimensionless quantities, using the desirability function, a generalized quality indicator [20].

The results were subjected to dispersion analysis. Emerging influence on the descriptive function indicators was shown by polymers. In regard to the influence on the desirability function, the samples of polymers can be placed in the following sequence: HPMC Vivapharm® E15 > HPMC Vivapharm® E3 > HPMC Metolose® 65 SH 50 > HPMC Metolose®90 SH 100 000 > HPMC+PEG6000 > HPC > HPMC+PEG4000 > Kollicoat® IR > PVA.The leading role in this group is given to HPMC Vivapharm® E15, which was selected for future research.

The second place in the ranking was taken by the group of disintegrants. According to dispersion analysis, SSG has an advantage over Polyplasdone XL-10 crospovidone and significantly exceeds sodium croscarmellose. Therefore, SSG was chosen for further research.

So, in the group ofplastisizers, PEG 400 has an advantage over glyceroland propylene glycol according to the results of the average values of the calculated response.

There is no «leader» among sweeteners in terms of impact on the generalized quality indicator. Mannitol has a slight advantage over sorbitol.

A promising area of further research is the development of the final composition of new captopril fast dissolving films. The results of this study are the basis for determining the optimal composition of drug-loaded films using a regression analysis to find out the quantitative ratio of excipients, as well as using a Quality by Design approach for detailed analysis of major risks that can happen during manufacturing conditions.

Conclusions

Fast dissolving films are a novel approach in oral drug delivery systems. Oral films have many advantages related to disintegration, dissolution and bioavailability over traditional dosage forms. In addition to this, they can also be used when quick action is required.For the present study, captopril was selected as a model drug candidate. When captopril is taken under the tongue, its antihypertensive effect occurs within 5–15 minutes.

The experimental series of captopril FDFs were obtained by solvent casting method. Formulations were designed according to the method of 3*3*3 Latin hypercube.The physical and technologicalproperties of captopril FDFs were studied. Based on the obtained results related to the choice of excipients, the best excipients were chosen for the development of captopril FDFs. According to the results of desirability function, the best values of technological parameters of captopril FDFs were obtained when using HPMC Vivapharm® E15 as a polymer, PEG 400 as a plasticizer, sodium starch glycolate and sorbitol.These excipients in film formulations showed more rapid disintegration and better mechanical properties.

References

1. *Mushtaque M., Muhammad I. N., Ali S. K. et al.* Novelty and compliance of oral fast dissolving thin film – apatient friendly dosage form // Clin. Pharmacol. Biopharm. – 2021. – V. 10, N 2. – P. 211.

2. *Rédai E., Antonoaea P., Todoran N. et al.* Development and evaluation of fluoxetine fast dissolving films: an alternative for noncompliance in pediatric patients // Processes. – 2021. –V. 9, N 5. – P.778. https://doi.org/10.3390/pr9050778

3. *Yelave A., Bhagwat G.* Mucoadhesive buccal films: a novel approach for the delivery of anti-hypertensive drugs //Asian J. Pharmac. Clin. Res. – 2021. – V. 14, N 4. – P. 12–21.https://doi.org/10.22159/ajpcr.2021.v14i4.40654

4. *Lodhi D. S., Verma M., Golani P. et al.* Fast-dissolving oral film of anti-migraine drug: a rewiew // National J. Pharmac. Sci. – 2021. – V. 1, N 2. – P. 40–48.

5. *Pavliuk B., Chubka M., Hroshovyi T.*The development of composition and characterization of biodegradable hemostatic and absorbable sponges for medical application// Farmacia. – 2020. – V. 68, N 3. – P. 419–425. https://doi.org/10.31925/farmacia.2020.3.6

6. *Gupta M.K., Priya S., Singh S. et al.* Formulation and evaluations of mouth dissolving film using natural excipients // Inter.J. Current Pharmac. Rev. Res. – 2021. – V. 13, N 3. – P.28–37.

7. *Gosavi D.S., Akarte A.M., Chaudhari P.M. et al.* Mouth dissolving films: a review // World J.Pharmac. Res. – 2021. – V. 10, N 3. – P.187–209.

8. *Zhu Y., You X., Huang K. et al.* Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability // Nanotechnology. – 2018. – V. 29, N 30. – P. 304001.https://doi.org/10.1088/1361-6528/aac010

9. *Demchuk M. B., Hroshovyi T. A., Malanchuk N. V.* Porivnialni doslidzhennia asortymentu likarskykh plivok, shcho predstavleni na farmatsevtychnykh rynkakh Ukrainy, SSHA ta Polshchi // Farmats. zhurn. – 2020. – T. 75, № 1. – S. 12–19. https://doi.org/10.32352/0367-3057.1.20.02

10. *Dawoud M., Hashem F.*Formulation and in-vitro evaluation of oral captopril bioadhesive delivery system // Indian J. Pharmac. Education and Res. – 2020. – V. 54, N 2s. – P. 200–209.https://doi.org/10.5530/ijper.54.2s.76

11. *Kamyshnyi A., Krynytska I., Matskevych V. et al.* Arterial hypertension as a risk comorbidity associated with Covid-19 pathology // Inter. J. Hypertension. – 2020. – P. 1–7. https://doi.org/10.1155/2020/8019360

12. *Akdeniz Y. S., Alay M. T.* Management and treatment of hypertensive emergencies // Phnx Med. J. – 2020. – V. 2, N 1. – P.58–65.

13. E-Handbook of Statistical Methods / Ed. by *Heckert N., Filliben J., Croarkin C., Hembree B., Guthrie W., Tobias P., Prinz J.* – 2002. – Режим доступу: https://www.nist.gov/publications/handbook-151-nistsematech-e-handbook-statistical-methods

14. *Davtyan L., Voronkina A.* The study of properties of the matrix for periodontal films based on metronidazole, chlorhexidine and glucosamine // Inter. J. PharmTech Res. – 2016. – V. 9, N 2. – P.9–12.

15. *Karthik D. R., Keerthy H. S., Rajkumar Prasad Yadav*. A review on fast dissolving oral films // Asian J. Pharmac. Res. Dev. – 2021. – V. 9, N 3. – P. 122–128.https://doi.org/10.22270/ajprd.v9i3.969

16. *Skorokhoda V., Melnyk Y., Semenyuk N. et al.* Film hydrogels on the basis of polyvinylpyrrolidone copolymers with regulated sorption-desorption characteristics // Chemistry and Chemical Technol. – 2017. – V. 11, N 2. – P. 171–174. https://doi.org/10.23939/chcht11.02.171

17. *Melnyk Yu., Stetsyshyn Yu., Skorokhoda V. et al.* Polyvinylpyrrolidone-graft-poly(2-hydroxyethylmethacrylate) hydrogel membranes for encapsulated forms of drugs // J. Polymer Res. – 2020. – V. 27, N 11. – P. 1–11.https://doi.org/10.1007/s10965-020-02335-7

18. *Tamer M. A., Hammid S. N. A. A., Ahmed Balqis.* Formulation and *in vitro* evaluation of bromocriptine mesylate as fast dissolving oral film // Int. J. App. Pharm. – 2018. – V. 10, N 1. – P. 7–20.https://doi.org/10.22159/ijap.2018v10i1.22615

19. *Singh S., Virmani T., Virmani R. et al.* Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation // Universal J. Pharmac. Res. – 2018. – V. 3, N 4. – P.60–69.https://doi.org/10.22270/ujpr.v3i4.185

20. *Hroshovyi T. A., Martseniuk V. P., Kucherenko L. I. ta in.* Matematychne planuvannia eksperymentu pry provedenni naukovykh doslidzhen v farmatsii. – Ternopil: Ukrmedknyha, 2008. – 367 s.

Список використаної літератури

1. *Mushtaque M., Muhammad I.N., Ali S.K. et al.* Novelty and compliance of oral fast dissolving thin film – apatient friendly dosage form // Clin. Pharmacol. Biopharm. – 2021. – V. 10, N 2. – P. 211.

2. *Rédai E., Antonoaea P., Todoran N. et al.* Development and evaluation of fluoxetine fast dissolving films: an alternative for noncompliance in pediatric patients // Processes. – 2021. –V. 9, N 5. – P. 778. https://doi.org/10.3390/pr9050778

3. *Yelave A., Bhagwat G.* Mucoadhesive buccal films: a novel approach for the delivery of anti-hypertensive drugs //Asian J. Pharmac. Clin. Res. – 2021. – V. 14, N 4. – P. 12–21.https://doi.org/10.22159/ajpcr.2021.v14i4.40654

4. *Lodhi D. S., Verma M., Golani P. et al.* Fast-dissolving oral film of anti-migraine drug: a rewiew // National J. Pharmac. Sci. – 2021. – V. 1, N 2. – P. 40–48.

5. *Pavliuk B., Chubka M., Hroshovyi T.* The development of composition and characterization of biodegradable hemostatic and absorbable sponges for medical application// Farmacia. – 2020. – V. 68, N 3. – P. 419–425. https://doi.org/10.31925/farmacia.2020.3.6

6. *Gupta M. K., Priya S., Singh S. et al.* Formulation and evaluations of mouth dissolving film using natural excipients // Inter. J. Current Pharmac. Rev. Res. – 2021. – V. 13, N 3. – P. 28–37.

7. *Gosavi D. S., Akarte A. M., Chaudhari P. M. et al.* Mouth dissolving films: a review // World J. Pharmac. Res. – 2021. – V. 10, N 3. – P. 187–209.

8. *Zhu Y., You X., Huang K. et al.* Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability // Nanotechnology. – 2018. – V. 29, N 30. – P. 304001. https://doi.org/10.1088/1361-6528/aac010

9. *Демчук М. Б., Грошовий Т. А., Маланчук Н. В.* Порівняльні дослідження асортименту лікарських плівок, що представлені на фармацевтичних ринках України, США та Польщі // Фармац. журн. – 2020. – Т. 75, № 1. – С. 12–19. https://doi.org/10.32352/0367-3057.1.20.02

10. *Dawoud M., Hashem F.* Formulation and in-vitro evaluation of oral captopril bioadhesive delivery system // Indian J. Pharmac. Education and Res. – 2020. – V. 54, N 2s. – P. 200–209. https://doi.org/10.5530/ijper.54.2s.76

11. *Kamyshnyi A., Krynytska I., Matskevych V. et al.* Arterial hypertension as a risk comorbidity associated with Covid-19 pathology // Inter. J. Hypertension. – 2020. – P. 1–7. https://doi.org/10.1155/2020/8019360

12. *Akdeniz Y. S., Alay M. T.* Management and treatment of hypertensive emergencies // Phnx Med. J. – 2020. – V. 2, N 1. – P. 58–65.

13. E-Handbook of Statistical Methods / Ed. by*Heckert N., Filliben J., Croarkin C., Hembree B., Guthrie W., Tobias P., Prinz J.*– 2002. – Режим доступу: https://www.nist.gov/publications/handbook-151-nistsematech-e-handbook-statistical-methods

14. *Davtyan L., Voronkina A.* The study of properties of the matrix for periodontal films based on metronidazole, chlorhexidine and glucosamine // Inter. J. PharmTech Res. – 2016. – V. 9, N 2. – P. 9–12.

15. *Karthik D. R, Keerthy H. S., Rajkumar Prasad Yadav.* A review on fast dissolving oral films // Asian J. Pharmac. Res. Dev. – 2021. – V. 9, N 3. – P. 122–128. https://doi.org/10.22270/ajprd.v9i3.969

16. *Skorokhoda V., Melnyk Y., Semenyuk N. et al.* Film hydrogels on the basis of polyvinylpyrrolidone copolymers with regulated sorption-desorption characteristics // Chemistry and Chemical Technol. – 2017. – V. 11, N 2. – P. 171–174. https://doi.org/10.23939/chcht11.02.171

17. *Melnyk Yu., Stetsyshyn Yu., Skorokhoda V. et al.* Polyvinylpyrrolidone-graft-poly(2-hydroxyethylmethacrylate) hydrogel membranes for encapsulated forms of drugs // J. Polymer Res. – 2020. – V. 27, N 11. – P. 1–11.https://doi.org/10.1007/s10965-020-02335-7

18. *Tamer M. A., Hammid S. N. A. A., Ahmed Balqis.* Formulation and *in vitro* evaluation of bromocriptine mesylate as fast dissolving oral film // Int. J. App. Pharm. – 2018. – V. 10, N 1. – P. 7–20. https://doi.org/10.22159/ijap.2018v10i1.22615

19. *Singh S., Virmani T., Virmani R. et al.* Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation // Universal J. Pharmac. Res. – 2018. – V. 3, N 4. – P. 60–69. https://doi.org/10.22270/ujpr.v3i4.185

20. *Грошовий Т. А. та ін.* Математичне планування експерименту при проведенні наукових досліджень у фармації. – Тернопіль: Укрмедкнига, 2008. – 367 с.

Надійшла до редакції 8 лютого 2022 р.
Прийнято до друку 19 лютого 2022 р.

M. B. Demchuk [1] (https://orcid.org/0000-0002-9105-2302)
Yu. Ya. Melnyk [2] (https://orcid.org/0000-0002-8516-9926)
N. V. Malanchyk [1] (https://orcid.org/0000-0002-0175-7502)
T. A. Groshovyi [1] (https://orcid.org/0000-0002-6427-2158),
V. Y. Skorokhoda [2] (https://orcid.org/0000-0002-2352-5964)
[1] *Horbachevsky Ternopil National Medical University*
[2] *Lviv Polytechnic National University*

RESEARCH THE INFLUENCE OF EXCIPIENTS ON THE TECHNOLOGICAL PROPERTIES OF CAPTOPRIL FAST DISSOLVING FILMS

Key words: fast dissolving film, captopril, polymer, plasticizer, variance analysis

A B S T R A C T

Drug-loaded films are of great interest among fast-dissolving drug-delivery systems. The creation of fast-dissolving films for the treatment of cardiovascular diseases is important.The first inhibitor of angiotensin-converting enzyme to appear on the world market was captopril, which is used to treat hypertension, chronic heart failure and others. Captopril has an antihypertensive effect, which manifests itself within 5–15 minutes after sublingual administration.

The aim of our study was to develop the technology of captopril fast dissolving films by solvent casting method and analyze the influence of groups of excipients on technological properties of the films.

The influence of the character of polymers, plasticizers, disintegrants and sweeteners on the technological properties of experimental batches of captopril fast dissolving films was studied. Such technological indicators as uniformity of weight, thickness, swelling index,tensile strength, elongationand disintegration time were studied.

The influence of excipients' composition on the technological indicators of captopril fast dissolving films has been researched. It was found out that the effect of the type of polymer had the decisive influence on all parameters of films.The selected plasticizer determined the elasticity (films' elongation), film thickness and weight variation. Optimal values of the average weight and thickness of captopril films are provided by the use of a polymer in the combination of HPMC with PEG 4000 or a combination of HPMC with PEG 6000, as a plasticizer – glycerin or PEG 400. The best results of films' swelling were obtained with the introduction of HPMC brands Metolose® 90 SH 100 000 or Metolose® 65 SH 50, Polyplasdone XL-10 crospovidone, propylene glycol and sorbitol. The disintegration time less than 3 min was observed in all investigated film compositions, except those containing PVA. The highest value of tensile strength for captopril films was obtained using HPMC brand Metolose® 65 SH 50 or Metolose®90 SH 100 000.

Using the desirability function, the optimal excipients within the studied groups were selected.It has been established that the optimal values of the technological parameters of captopril films can be achieved using Hydroxypropyl MethylcelluloseVivapharm® E15, polyethylene glycol 400, sodium starch glycolate and sorbitol.

М. Б. Демчук [1] (https://orcid.org/0000-0002-9105-2302),
Ю. Я. Мельник [2] (https://orcid.org/0000-0002-8516-9926),
Н. В. Маланчук [1] (https://orcid.org/0000-0002-0175-7502),
Т. А. Грошовий [1] (https://orcid.org/0000-0002-6427-2158),
В. Й. Скорохода [2] (https://orcid.org/0000-0002-2352-5964)
[1] Тернопільський національний медичний університет імені І. Я. Горбачевського
[2] Національний університет «Львівська політехніка»

ВИВЧЕННЯ ВПЛИВУ ДОПОМІЖНИХ РЕЧОВИННА ТЕХНОЛОГІЧНІ ВЛАСТИВОСТІ ШВИДКОРОЗЧИННИХ ПЛІВОК КАПТОПРИЛУ

Ключові слова:швидкорозчинна плівка, каптоприл, полімер, пластифікатор, дисперсійний аналіз

А Н О Т А Ц І Я

Серед швидкорозчинних систем доставки лікарських засобівзначнузацікавленість викликають лікарські плівки.Актуальним є створення швидкорозчинних лікарських плівок для лікування серцево-судинних захворювань. Першим інгібітором ангіотензин-перетворюючого ферменту, що з'явився на світовому ринку, став каптоприл, який застосовують для лікування гіпертонічної хвороби, хронічної серцевої недостатності та ін. Каптоприл виявляє антигіпертензивний ефект, який проявляється протягом 5–15 хв після прийому під язик.

Мета нашої роботи – розроблення технології швидкорозчинних плівок каптоприлу методом поливу з випаровуванням розчинника та дослідження впливу груп допоміжних речовин на їхні технологічні властивості.

Досліджено вплив природи полімерів, пластифікаторів, розпушувачів та підсолоджувачів на технологічні властивості експериментальних серій швидкорозчинних плівок каптоприлу. Досліджували такі технологічні показники: однорідність маси, товщина плівок, ступінь набрякання, границя міцності під час прориву, відносне видовження під час прориву, час розпадання.

Вивчено вплив різних груп допоміжних речовин на технологічні властивості швидкорозчинних плівок каптоприлу. Встановлено, що вплив виду полімеру є визначальним на усі показники плівок. Від обраного пластифікатора залежить еластичність (відносне видовження під час прориву), а також товщина та маса плівки. Оптимальні значення середньої маси та товщини плівок каптоприлу забезпечує використання як полімеру комбінації ГПМЦ із ПЕГ 4000 або комбінації ГПМЦ із ПЕГ 6000, як пластифікатора– гліцерину або ПЕГ 400. Кращі результати набухання плівок одержано у разі введення до їх складу ГПМЦ марок Metolose® 90 SH 100 000 або Metolose® 65 SH 50, Polyplasdone XL-10 кросповідону, пропіленгліколю та сорбіту. Час розпадання менше 3 хв отримали для всіх досліджуваних складів плівок, за винятком тих, які містили ПВС. Найбільше значення

міцності при прориві для швидкорозчинних плівок каптоприлу було отримано при застосуванні ГПМЦ марки Metolose® 65 SH 50або Metolose®90 SH 100 000.

За допомогою функції бажаності обрано оптимальні допоміжні речовини в межах вивчених груп.Встановлено, що оптимальні значення технологічних параметрів плівок каптоприлу можна досягнути, використовуючи гідроксипропілметилцелюлозу Vivapharm® E15, поліетиленгліколь 400, натрію крохмаль гліколят та сорбіт.

М. Б. Демчук [1] (https://orcid.org/0000-0002-9105-2302),
Ю. Я. Мельник [2] (https://orcid.org/0000-0002-8516-9926),
Н. В. Маланчук [1] (https://orcid.org/0000-0002-0175-7502),
Т. А. Грошовой [1] (https://orcid.org/0000-0002-6427-2158),
В. Й. Скорохода [2] (https://orcid.org/0000-0002-2352-5964)
[1] Тернопольский национальный медицинский университет имени И. Я. Горбачевского
[2] Национальный университет «Львовская политехника»

ИЗУЧЕНИЕВЛИЯНИЯВСПОМОГАТЕЛЬНЫХ ВЕЩЕСТВ НА ТЕХНОЛОГИЧЕСКИЕ СВОЙСТВА БЫСТРОРАСТВОРИМЫХ ПЛЕНОК КАПТОПРИЛА

Ключевые слова: быстрорастворимая плёнка, каптоприл, полимер, пластификатор, дисперсионный анализ

А Н Н О Т А Ц И Я

Среди быстрорастворимых систем доставки лекарственных средств значительную заинтересованность вызывают лекарственные пленки. Актуальным является создание быстрорастворимых пленок для лечения сердечно-сосудистых заболеваний. Первым ингибитором ангиотензин-превращающего фермента, появившемся на мировом рынке, стал каптоприл, который применяют для лечения гипертонической болезни, хронической сердечной недостаточности и т. д. Каптоприл оказывает антигипертензивный эффект, который проявляется в течение 5–15 мин после приема под язык.

Цель нашей работы – разработка технологии быстрорастворимых пленок каптоприла методом литья с испарением растворителя и исследования влияния групп вспомогательных веществ на технологические показатели пленок.

Исследовано влияние природы полимеров, пластификаторов, разрыхлителей и подсластителей на технологические свойства экспериментальных серий быстрорастворимых пленок каптоприла. Исследовали такие технологические показатели: однородность массы, толщина, степень набухания, предел прочности при прорыве, относительное удлинение при прорыве, время распада.

Изучено влияние компонентов составов на технологические свойства быстрорастворимых пленок каптоприла. Установлено, что влияние вида полимера является определяющим на все показатели пленок. От выбранного пластификатора зависит эластичность (относительное удлинение при прорыве), толщина и масса пленки. Оптимальные значения средней массы и толщины пленок каптоприла обеспечивают использование в качестве полимера комбинации ГПМЦ с ПЭГ 4000 или комбинации ГПМЦ с ПЭГ 6000, как пластификатора – глицерина или ПЭГ 400. Лучшие результаты набухания пленок получены при введении в их состав ГПМЦ марок Metolose® 90 SH 100 000 или Metolose® 65 SH 50, Polyplasdone XL-10 кросповидона, пропиленгликоля и сорбита.Время распада менее 3 мин получили для всех изучаемых составов пленок, за исключением тех, которые содержали ПВС. Наибольшее значение прочности при прорыве для быстрорастворимых пленок каптоприла было получено при применении ГПМЦ марки Metolose® 65 SH 50 или Metolose®90 SH 100 000.

С помощью функции желательности избрали оптимальные вспомогательные вещества в пределах изученных групп.Установлено, что оптимальные значения технологических параметров пленок каптоприла можно достичь, используя гидроксипропилметилцеллюлозу Vivapharm® E15, полиэтиленгликоль 400, натрия крахмалгликолят и сорбит.

Електронна адреса для листування з авторами: pavljukm@tdmu.edu.ua
(Демчук М.Б.)