RESEARCH ARTICLE

The Development of Tablets containing Vinpocetine and *Ginkgo biloba* L. Extract

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ABSTRACT

The release rate of active pharmaceutical ingredients (APIs) from tablet dosage forms is significantly influenced by the composition of the formulation, in particular filler composition. In this work, we analyzed the impact of the ratio of excipients on the release rate of vinpocetine from a tablet containing *Ginkgo biloba* L. extract as the second API. Microcrystalline cellulose (MCC), hydroxypropylcellulose (L-HPC) mixed with MCC (up to 16% of HPC), and partially pregelatinized starch were used in different ratios as excipients. Moreover, tween-80 was used to study the effect of introduction of emulsifier on the APIs' release rates. According to our findings, optimal APIs' release rates are achieved when using the combination of MCC with HPC at a ratio of 2:3.

Keywords: *Ginkgo biloba* L. extract, Vinpocetine, Dissolution test, Disintegration test.

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INTRODUCTION

Tablets are one of the most popular pharmaceutical dosage forms nowadays.[1] Although this dosage form has been produced for a long time, problems are often encountered in the development of new formulations, such as adherence of powder onto tablet tooling and unsatisfactory release rates of the active pharmaceutical ingredients (APIs).[2] Achieving optimal conditions for API release is especially problematic when developing tablet forms of water-insoluble extracts, for example, *Ginkgo biloba* L. extract.[3] We have previously proposed a solution to this problem by using a mixture of MCC and low-substituted HPC (L-HPC) as a filler and wet granulation of the tablet mass.[4] However, the release rate of the active ingredients from such formulations has not been evaluated.

This work also examines other ways of improving the APIs' release profiles including the use of excipients to improve disintegration time of the tablets. Delayed water penetration through tablet pores is considered one of the reasons for slower disintegration times and thus poorer APIs' release rates. Pregelatinized starch show to improve tablet disintegration by increasing water penetration into the pores.[5]

Solubilizers are another class of excipients used to improve the release of APIs. Several papers have described examples of the successful use of tween for this purpose.[6,7]

There is also evidence that binders may affect the properties of fillers in a formulation. For example, pregelatinized starch is described to vary in elasticity and mechanical strength depending on the moisture content in tablet formulation.[8]

The purpose of the work to develop the composition of a combined tablet form containing a dry extract of *G. biloba* and vinpocetine.

MATERIALS AND METHODS

Materials

Vinpocetine containing 98.8% of Vinpocetine was purchased from Covex®. Dry *G. biloba* leaf extract was obtained from the commercial manufacturer, Finzelberg. Content of terpene trilactones is 6.1% (according to the regulatory documentation, it should be over 6%), flavonoids 24.2% (should be over 24%). 96% of the substance passes through a 0.3 mm sieve and moisture content is no more than 5% determined by the Fischer method.

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(a) MCC for granulation (FLOCEL® 101), (b) hydroxypropylcellulose (HPC, L-HPC-21®), (c) hydroxypropylmethylcellulose (HPMC) (PHARMACOAT® 603), (d) crospovidone (Polyplasdone XL and XL-10), (e) partially pregelatinized starch (Starch® 1500), (f) tween-80 (Polysorbate 80) were obtained from the following manufacturers accordingly: (a) GMW JRS Pharma Pvt. Ltd., (b, c) Shin-Etsu Chemical Co., Ltd., (d) ISP Pharaceutical technology, (e) Colorcon Inc., (f) PanReac AppliChem. The active ingredients and excipients were not past their expiry date at the time of the study.

Drying equipment - drying cabinet LF-25/350-VG1, LOIP, Russia Set of woven sieves 1.5, 0.67, 0.4, 0.1, 0.05 mm, Russia

Methods

Preparation of model tablets

To prepare the granules vinpocetine 1.61 g, dry *Ginkgo* extract 10.00 and 33.00 g the excipient or mix of the excipients (detailed composition is given in Table 1) were blended until homogenous powder. The powder was mixed with 2.3 mL binder solution (23% of total tablet mass) continuously until enlarged particles appeared homogenous. The wet granules mixture was hand-sieved through 1.5 mm sieve screen and dried by hot air stream (60°C**)** to a 5% residual moisture. Dried granules were hand-sieved again using the sieve with 1-mm mesh size and lubricated with 0.96 g polyplasdone XL-10 and 0.48 g magnesium stearate. Flowability of the granules was assessed using the conventional method.[9] Obtained granules were compressed using manual hydraulic tablet press (PGR-10, Russia) fitted with 9 mm round flat face bevel edge punches with a bisection line at a pressure 90 kg/cm^2 (or 8MPa). See Table 1 for the detailed composition of model tablets.

Preparation of model tablets with different MCC: HPC ratio

Model tablets were prepared using the method described above. The tablet mass containing the active ingredients and one of the excipient variants was divided into two parts. Granules were obtained using 0.5 or 1% HPC solution as a binder solution for the first and second parts of the tablet mass. respectively. The tablet formulations are shown in Table 2.

Flowability of the granules was assessed after lubricating. The tablets were prepared using a manual hydraulic tablet press. During the compression process. such characteristics as adherence of the granules to the tooling and presence/absence of chips on the surfaces of obtained tablets were monitored and noted. The disintegration test was performed for obtained tablets according to the conventional method.[9]

The dissolution test was performed according to the conventional method described at[10] using 0.1M hydrochloric acid as the dissolution medium. Samples were taken using 1000 µL automated pipette at the following time intervals: every minute for the first 10 minutes and every 5 minutes from the 10 to 30th minutes of the test. The samples were placed in air-tight 5 mL vials, labelled and then analyzed by spectrophotometry. It should be noted that during the test, the volume of solvent withdrawn for sampling was not replenished resulting in a systematic error in the quantification of vinpocetine leading to overestimation of its content. The vinpocetine concentration was calculated by recalculating the residual volume of solvent in the dissolution flask and then systematic error was taken into account.

Table 1: Tablet formulations used to test the effect of various excipients on vinpocetine release rates, %tablet mass

Composition:	*1 (%)*	*2 (%)*	*3 (%)*	*4 (%)*
G. biloba L. extract.	21.7	20.8	20.7	21.8
Vinpocetine	3.5	3.4	3.3	3.5
MCC FLOCEL® 101	71.6	62.0	72.5	36.0
HPC	-	-	-	36.0
starch (Starch 1500)	-	10.9	-	-
Tween 80	-	-	0.5	-
Hypromellose (HPMC) 0.05% solution (Pharmcoat 603). on a dry basis	0.0025	0.0024	0.0024	0.0025
magnesium stearate	1	1	1	1
PVP (Polyplasdone XL-10)	2	2	2	2

The obtained optical density values were converted to vinpocetine concentration, using the equation (1):

$$C_{vin} = \frac{A_x * C_{st}}{A_{st}} \qquad (1)$$

Obtained data were then used to plot the concentration of vinpocetine (mg/mL) versus time of the sampling graph.

RESULTS AND DISCUSSION

Previously,[4] a basic composition was proposed for tablets containing a mixture of vinpocetine and *ginkgo* extract: vinpocetine 10 mg (3.5%), *ginkgo* extract - 62 mg (21.7%), filler - 219 mg (72%), disintegrant 6 mg, magnesium stearate 3 mg and binder solution added to obtain a sufficiently moist mass.

In addition to the use of the MCC and HPC mixture as a filler, the following technological methods were proposed which, in our opinion, could lead to a higher API's release rate from the tablet form while maintaining the flowability of the tablet mass. These include the use of an additional disintegrant (Starch 1500 pregelatinized starch) blended in during the stage of lubricating the granules and the use of tween 80 as a solubilizer.

Although the previously proposed composition (considered as a base in this article, see composition 1, Table 1) allowed the disintegration of tablets at the level required by regulatory documentation,[9] it should be noted that the composition with HPC (composition 4, Table 1) showed better flowability and increased a disintegration rate of tablets. Compared to these compositions, formulations with partially pregelatinized starch (composition 2, Table 1) and tween-80 (composition 3, Table 1) did not increase the rate of disintegration of tablets and the flowability of the tablet mass.

Table 2: Tablet formulations containing the combination of vinpocetine and *G. biloba* L. extract with different MCC:HPC ratio, % of tablet weight

Composition:		*5*	*6*	*7*	*8*
G. biloba L. extract.		42.9	42.8	38.1	38.3
Vinpocetine		6.9	6.9	6.2	6.2
MCC FLOCEL® 101		35.4	35.4	31.5	31.6
HPC		11.8	11.8	21	21.1
Hypromellose (HPMC) solution (Pharmcoat® 603). on a dry basis	0.5	0.09	-	0.11	-
	1	-	0.28	-	0.14
Lubricating:					
Magnesium stearate		1	1	1	1
PVP (Polyplasdone® XL-10)		2	2	2	2

In order to identify the reason for the positive effect of the mixture of MCC and HPC, we studied the release of active substances from tablets of model mixtures given in Table 2. The following parameters were chosen to assess and compare the model formulations: flowability of the granules (after lubricating), the absence of adhesion to punches, the absence of chips on the surfaces of tablets, disintegration time of the tablets according to the conventional method. Results are presented in Table 3.

Spectroscopy in the UV region was used as an analytical technique to evaluate the release of active ingredients. The method chosen was spectrophotometric analysis. Method specificity was assessed by comparing the absorption spectra in the UV region (Figure 1). To estimate the concentration of vinpocetine, it was necessary to subtract the contribution of the extract from the intensity of absorption.

Additionally, the linearity of the response was checked over the analytical range of the techniques (Figure 2). The results show a high value of approximation coefficients for the key absorption wavelengths of vinpocetine (0.998 and 0.999 for 270 and 314 nm, respectively).

The high correlation coefficients for the specific wavelengths of vinpocetine (270 and 314 nm) show the acceptability of the methodology for the analysis of vinpocetine release rate over time if the intensity of absorption due to the *ginkgo* extract (mainly flavonoids in its composition) is taken into account. Lack of specificity can be considered a conditional assumption in this study due to the comparison of values for the same tablet at different sampling points.

Thus, the proposed methodology meets the basic requirements for the quantification methods.[4] Further on, this methodology was used to identify the effect of excipients and their ratios on the release rate curves. For this purpose, the plot of vinpocetine concentration versus sampling time was produced. Figure 3 shows the obtained curves at a detection wavelength of 314 nm. The appearance of the plot at a wavelength of 270 nm matched the one obtained for the wavelength of 314 nm.

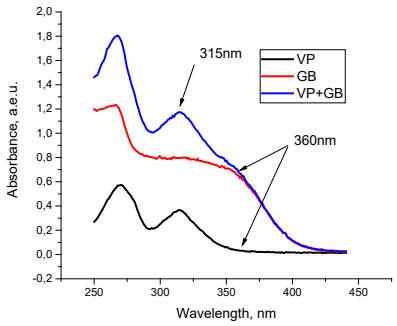

Figure 1: Absorption spectra of vinpocetine (red), ginkgo extract (black) and their sum (blue) in 0.1 M hydrochloric acid

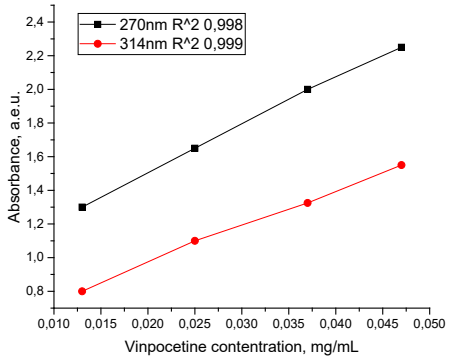

Figure 2: Dependence of optical density on the concentration of vinpocetine in the model mixture at wavelengths of 270 and 314 nm. The correlation coefficient at 270 and 314 nm was 0.998 and 0.999, respectively

Figure 3 shows that the vinpocetine release curves obtained within the first 5 minutes of the experiment match almost perfectly for all formulations (containing MCC only or in combination with HPC, Tween 80 or pregelatinized starch). Neither the partial replacement of MCC with pregelatinized starch nor the addition of Tween 80 yielded any significant changes within the first 10 minutes of the experiment. However, the addition of HPC to the formulation produced a clear increase in vinpocetine release rates within the first 10 minutes with it reaching maximum concentration in solution just after 15 minutes of the experiment. The results demonstrate that the release profile of formulation 3 (containing Tween 80) is not significantly different from formulation 1. Formulations 2 and 4, however, have shown faster release of vinpocetine from tablets. The main difference between the release rates for the formulations in question can be explained by the nature of the excipients. Pregelatinized starch and HPC have good wettability[11] whereas Tween 80 is a representative of neutral surfactants - a solubilizer designed to increase the solubility of hydrophobic components. Based on this, we can conclude that the main reason for decreased release rates in studied compositions lays in limited wettability rather than solubility of APIs.

The maximum concentration of vinpocetine released from tablets with HPC (formulation 4) was at 18–20th minutes of the experiment, with 75% released in less than 10 minutes.

Table 3: Pharmaceutical and technological properties of obtained granules and tables intended to detect the effect of hydrophilic polymers in model formulations

	1	*2*	*3*	*4*
Disintegration, min	Over 40	Over 40	26.7 ± 9.6	9.25 ± 0.25
Free flow, g / s	11.6 ± 2.0	10.7 ± 1.2	11.4 ± 1.3	11.2 ± 2.0
Chips on tablets' surfaces	Not detected (a tablet 9 mm in diameter, the cylindrical shape with the bevel edge and a bisection line, the surface is smooth without chips and cracks)			
Adhesion of the tablet mass to the press tooling	Absent			
Delamination of the tablet when ejected from press	Absent			

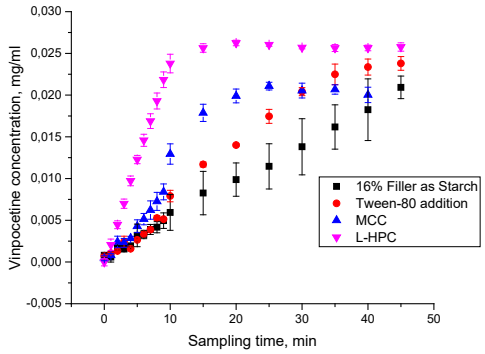

Figure 3: Vinpocetine concentration versus sampling time plot. The graph presents the results of one experiment per each of the formulations 1-4

Whereas for formulation 2 (with pregelatinized starch), it took 25 and 20 minutes, respectively to reach these marks (maximum release and 75% release).

The formulation containing only MCC as a filler had the longest period before reaching the plateau on the diagram. As a result, it was possible to evaluate how the release process depends on the chosen hydrophilic polymer. The calculation of the similarity coefficient and difference coefficients ii, iii showed a complete inconsistency between the curves (criteria f_1<15 and f_2>50 were not satisfied). This indicates a significant difference between the different formulations.

The experiments show the unsuitability of use of microcrystalline cellulose without additives, or with the replacement of 16% of it with pregelatinized corn starch. The reason for this is most likely in the difficulty of water penetration into the tablet due to the formation of a gel-layer on the surface. At the same time, formulations with HPC added to MCC and also upgraded by adding tween-80 to the granulate, result in a step-by-step, accurate increase in concentration of vinpocetine released from tablets. However, the gradual increase in vinpocetine concentration is different between the two formulations: for formulation 3 the increase starts at the 7th minute, while for formulation 4 it starts at minute 1.

For interpretation, the possibility of approximating the release curves with respect to a linear and polynomial (degree 2) mathematical model was assessed. The results are presented in Figure 4 and Table 4.

The curve obtained for composition 1 (with MCC only as a filler) on the vinpocetine release plot degenerates into a straight line due to prolonged wetting and disintegration times.

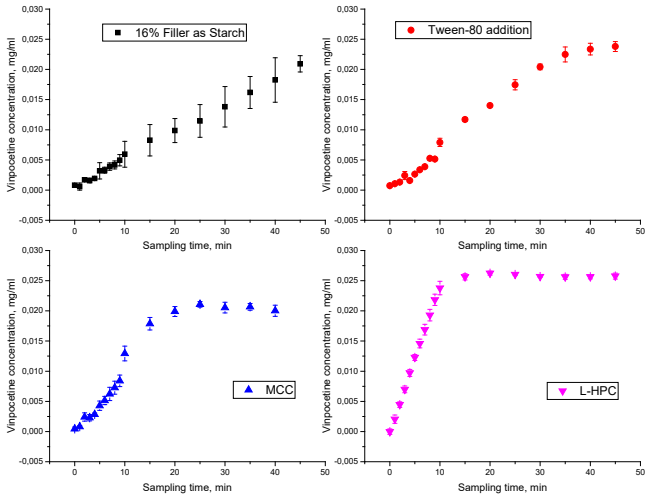

Figure 4: Scatter plots of vinpocetine release from tablets of formulations 1-4. The data represented by the rectangle corresponds to quartiles 25 and 75%, the closed segment corresponds to the scatter from the minimum to the maximum values.

Table 4: The approximation of release curves to functions: linear and polynomial of degree 2

Composition	*Distribution type*	*Approximation coefficient*
22 MCC	Linear	0.9965
23 16% replaced with starch	Polynomial of degree 2	0.9827
		0.9684
24 Tween-80	Polynomial of degree 2	0.9703
25 HPC	Linear	0.9990

Compositions 2 and 3 have more pronounced disintegration and wetting stages. Mixture 4 has practically no wetting plateau, proceeding immediately to disintegration and deaggregation. The addition of pregelatinized starch (Starch 1500) should have promoted water penetration into the tablet mass by increasing porosity. However, the disintegration time of the tablets containing Starch 1500 did not change. It can be concluded from the analysis of the release curve that vinpocetine dissolution could be accelerated by increasing the disintegration rate, without significant changes to the wetting time of the tablet over its entire volume.

Similar changes in the dissolution process can be observed with the addition of tween 80. Due to the solubilizing and

Table 5: Pharmaceutical and technological properties of formulations 5-8

Compositions	*5*	*6*	*7*	*8*
Disintegration time (minutes)	30	30	20	25
Flowability (g/s)	5.28 ± 0.08	5.07 ± 0.05	4.75 ± 0.16	4.67 ± 0.12
Chips on tablets' surfaces	Not detected	Not detected	Not detected	Not detected
Adhesion on the press tooling	Absent	Absent	Absent	Absent
Delamination of the tablet when ejected from the press	Absent	Absent	Absent	Absent

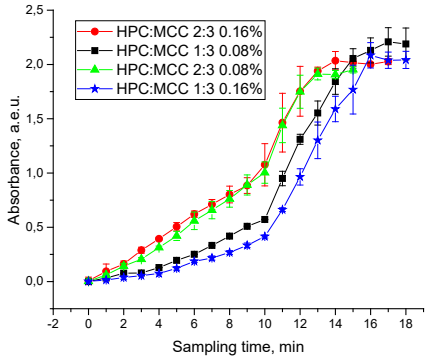

Figure 5: Effect of HPC:MCC ratio on vinpocetine release curves from tablets formulations 5-8

emulsifying effect of the component, the disintegration and dissolution of the active substances are improved. Furthermore, the dissolution experiments show better reproducibility within a series. This can largely be attributed to a more homogeneous distribution of tween in the tablet mass.

The analysis of the release curves provides explanation for the reduced disintegration time of the formulation with the partial replacement of MCC with HPC. Only this combination provided a linear, sharp increase in vinpocetine concentration at the beginning of the test. The other compositions, under the same conditions, provided a smooth rise which only turned into a sharp increase after 10 minutes of experiment. The reason for this phenomenon, in our opinion, is the increased wettability of the tablet.

Thus, the introduction of HPC has resulted in the improved release of vinpocetine from the tablets due to shortening of wetting and deaggregation times. However, the resulting tablet mix had a low bulk density. That is why we proceeded with evaluating the effects of various amounts of HPC (as a filler) and hypromellose (HPMC) solution (as a binding solution) on both the vinpocetine release rates and bulk density of the tablet mix.

Compositions 5–8 have all been shown to produce satisfactory flowability of the tablet mix.

The values of the main pharmaceutical processing properties are presented in Table 5.

The results indicate that the addition of such excipients as HPC to formulation produces shorter disintegration times compared to formulations containing no such excipients.

Hydroxypropyl methylcellulose (Pharmcoat 603) has shown no significant effect on the API release rate, however, we noted a better reproducibility of the dissolution results into a batch. The experiments also show that HPC:MCC ratio affects API release rates, but a further increase in the fraction of HPC does not improve the release rate. The dependence of dissolution on the excipient content is presented in Table 5.

The use of 1% HPMC solution (Pharmcoat 603) as a binder should have contributed to the improved dissolution and disintegration rates. However, the disintegration time of the tablets did not change. As a result of the curve analysis, a delayed API release can be observed.

The analysis of the dissolution curves (Figure 5) shows a decrease in the disintegration time for the formulation containing a mixture of HPC and MCC at a ratio of 2:3 as a filler.

The calculation of similarity and difference coefficients ii, iii showed a complete inconsistency of the curves (criteria $f_1<15$ and $f_2>50$ were not satisfied).

CONCLUSION

This study optimized the composition of tablets containing ginkgo extract and vinpocetine by changing the excipients in the original formulation. The initial formulation contained microcrystalline cellulose as a filler. This composition did not provide the required rate of disintegration and dissolution. Therefore, the options of replacing part of the MCC with pregelatinized starch, tween 80 or low-substituted hypromellose were considered. Based on the improved dissolution rates observed in formulations containing the MCC:HPC ratio of 1:1, formulations with other ratios of these fillers were studied as well. MCC: HPC ratios of 3:1 and 3:2, as well as varying amounts of binder, were considered. Taking into account the results of bulk density and dissolution tests, the following composition should be considered as optimal: a mixture of hydroxypropyl cellulose and microcrystalline cellulose the ratio of 2:3 as a filler, and 1% hydroxypropylmethylcellulose solution as a binder.

AUTHOR'S CONTRIBUTION

Slovesnova N.V. – Investigation, Writing - Original Draft,, Petrov A.Yu. – Methodology, Glavatskih S. A. – Data Curation, Supervision, Writing - Review & Editing,, Bolotova A.V. – Visualization, Writing - Review & Editing

REFERENCES

1. Sethuraman S, Radhakrishnan K. Analytical method development and validation of caffeine in tablet dosage form by using UV-spectroscopy. International Journal of Novel Trends in Pharmaceutical Sciences. 2013:3:4:82-86. Available from: https://

docplayer.net/21875127-Analytical-method-development-and-validation-of-caffeine-in-tablet-dosage-form-by-using-uv-spectroscopy.html

2. Bejugam N K, Mutyam,S K, Shankar G N. Tablet formulation of an active pharmaceutical ingredient with a sticking and filming problem: direct compression and dry granulation evaluations. Drug development and industrial pharmacy. 2015:41:2:333-341. Available from: doi:10.3109/03639045.2013.859266
3. Epshtein N. A. Validation of analytical methods: graphical and computational criteria for assessing the linearity of methods in practice. J Development and registration of medicines. 2019:2:8:122-130. Available from: DOI:10.33380/2305-2066-2019-8-2-122-130
4. Slovesnova N.V., Petrov A. Yu., Glavatskikh S. A., Boyko V. I., Kinev M. Yu., Kuznetsov A. V. Obtaining tablets with a combination of ginkgo extract and vinpocetine. J Development and registration of medicines. 2018:2:23:32-37. Available from: https://www.pharmjournal.ru/jour/article/view/574/569 Jubril I, Muazu J, Mohammed G T. Effects of phosphate modified and pregelatinized sweet potato starches on disintegrant property of paracetamol tablet formulations. Journal of applied pharmaceutical science 2012:2:2:32-36. Available from: https://www.researchgate.net/publication/265219787_Effects_of_Phosphate_Modified_and_Pregelatinized_Sweet_Potato_Starches_on_Disintegrant_Property_of_Paracetamol_Tablet_Formulations
5. Jaya S, Chowdary K P R, Rajeswara Rao P. Effect of superdisintgrants and solubilizers on the dissolution rate and dissolution efficiency of ritonavir tablets . International Research Journal of Pharmaceutical and Applied Sciences 2012:2:5:224-229. Available from: https://www.scienztech.org/index.php/irjpas/article/view/464
6. Attivi D, Ajana I, Astier A, Demoré B, Gibaud S. Development of microemulsion of mitotane for improvement of oral bioavailability. Drug development and industrial pharmacy, 2010:36:4:421-427. Available from: DOI:10.3109/03639040903225083
7. Van der Voort Maarschalk K, Vromans H, Groenendijk W, Bolhuis . K, Lerk C F. Effect of water on deformation and bonding of pregelatinized starch compacts. European journal of pharmaceutics and biopharmaceutics, 1997:44:3:253-260. Available from: https://doi.org/10.1016/s0939-6411(97)00128-8
8. OPS.1.4.2.0013.15 Disintegration of tablets and capsules [Electronic resource] Available from: https://docs.rucml.ru/feml/pharma/v14/vol2/345/ (accessed 04.11.21).
9. OPS.1.4.2.0014.15 Dissolution for solid dosage forms Electronic resource] Available from: https://docs.rucml.ru/feml/pharma/v14/vol2/349/ (accessed 04.11.21).
10. Sizyakov S A, Alekseev K V, Suldin A S, Alekseeva S K. Modern auxiliary substances in direct pressing technology. J Pharmacy. 2008:4:52-56. Available from: https://pharmaciyajournal.ru/ru/contents/2008/4?ysclid=lpng4gguoq467983292. Mimura K, Kanada K, Uchida S, Yamada M, Namiki N. Formulation study for orally disintegrating tablet using partly pregelatinized starch binder. J Chemical and Pharmaceutical Bulletin. 2011:59:8:959-964. Available from: DOI: 10.1248/cpb.59.959
11. Chakma S, Khadka P, Jo K, Kim H, Ro J, Park K et al. Solubility enhancement of celecoxib using solidified Tween 80 for the formulation of tablet dosage forms. Journal of Pharmaceutical Investigation. 2015:45:5:449-460. Available from: DOI:10.1007/s40005-015-0192-1