Bulletin of the Chemists and Technologists of Macedonia, Vol. **17**, No. 1, pp. 33–39 (1998)
GHTMDD – 304 ISSN 0350 – 0136
Received: February 22, 1998 UDC: 615.222.073/.074
Accepted: May 15, 1998
Original scientific paper

DRUG DISSOLUTION PROFILES AND PHYSICO-CHEMICAL STABILITY EVALUATION OF CONTROLLED-RELEASE SOLID DISPERSION GRANULES

Katerina Goračinova[1], Ljiljana Klisarova[2], Angel Simov[1], Emilija Fredro-Kumbaradži[1], Kristina Mladenovska[1], Marija Glavaš[1]

[1]Institute of Pharmaceutical Technology, Faculty of Pharmacy, The "Sv. Kiril & Metodij" University, Vodnjanska 17, 91 000 Skopje, Republic of Macedonia
[2]Institute of Chemistry, Faculty of Natural Sciences and Mathematics, The "Sv. Kiril & Metodij" University, P.O.B. 162, 91 001 Skopje, Republic of Macedonia

Physico-chemical stability and drug dissolution profiles of the prepared solid dispersions containing Verapamil HCl as active substance were evaluated using different experimental methods during 60-months real-time stability studies. During the stability studies no drug decomposition or changes in the active substance content appeared. Physical characterization of the solid dispersions showed no changes in the drug/polymer network during ageing. The initial amorphous appearance of the drug substance in the solid dispersions was maintained during ageing. Although the drug dissolution profiles showed differences compared to series tested immediately after preparation, the drug release dependence upon HPMCP HP 55 was maintained even more pronounced at higher pH values.

Key words: solid dispersions; stability studies; controlled release; Verapamil HCL; ethyl cellulose; HPMCP HP 55

INTRODUCTION

Solid dispersions of the drug substance Verapamil HCl and different polymers were prepared using the solvent evaporation method in order to formulate a controlled release dosage form with increased pharmaceutical availability at higher pH values. The continuous drop of the drug dissolution rate is characteristic for substances with decreasing solubility at higher pH values incorporated in conventional sustained release dosage forms. Also precipitation of poorly soluble free base may occur within formulation in the intestinal fluids. The precipitated drug is no longer capable of release from formulations. Formulation of dosage forms with ensured pharmaceutical availability will result in increased bioavailability especially for substances that undergo intense first-pass metabolism incorporated in modified release dosage forms [1–6].

Verapamil HCl solid dispersion granules containing ethyl cellulose and hydroxyl propyl cellulose as release-controlling polymers showed no quantitative drug release at higher pH values. The drug release rate depended upon the percentage of hydroxypropyl cellulose in the formulation, it decreased as the pH medium increased and was followed by an interruption of release at pH 6.8. Increased percentage of hydroxypropyl cellulose in the formulations resulted in the abrupt release of Verapamil HCl at pH 1.5 [7].

To achieve the goal of preparing a controlled release dosage form containing Verapamil HCl as the active substance with even increased release rate at higher pH values, solid dispersion granules containing ethyl cellulose (EC), hydroxypropyl cellulose LF (HPC), hydroxypropyl methylcellulose phthalate HP 55 (HPMCP HP 55) as polymer substances for controlling the drug release rate were prepared. Dissolution rate studies showed that with the incorporation of HPMCP HP 55 in the controlled-release formulation, an increased release rate of the active substance at higher pH values was achieved without causing abrupt drug release at lower pH values. So, slow and continuous decrease of the drug dissolution rate at higher pH values was avoided with the prepared dosage forms. The alteration of the physical properties of the active

teration of the physical properties of the active substance (particle size, crystal structure) as well as drug/polymer interactions participates in the mechanism of controlled drug release [6, 7].

Physical instability is a major problem in solid dispersions. Precipitation of the drug substance out of the polymer network with subsequent changes of physico-chemical properties of solid dispersions might occur during ageing. These would induce changes in the polymer network structure and dissolution rate profiles [9–11].

The aim of this study was to evaluate the stability of the prepared dosage forms using different experimental methods (HPTLC studies, IR spectroscopy, UV spectroscopy, X-ray diffraction method, dissolution rate studies) for evaluating if the drug molecules remain interlaced with the polymer molecules and enslaved within the polymer network during 60-months real-time stability studies.

EXPERIMENTAL

Materials

The following chemicals were used in this study: Verapamil hydrochloride and Norverapamil (Fischer Chemicals AG, Germany), hydroxypropyl methylcellulose phthalate HP 55 (HPMCP HP 55, Shin Etsu Chemical Co., Ltd.,) Ethyl cellulose 10 cp (EC 10cp, Colorcon, UK), Hydroxypropyl cellulose LF (HPC, Hercules, U.S.) and absolute ethanol (Merck, Germany).

Methods

Preparation of solid dispersion granules

Solid dispersions containing Verapamil HCl, EC 10cp, HPC and various concentrations of HPMCP HP 55 (Table I) were prepared by the solvent evaporation technique. After dissolving or suspending the drug substance and the polymers in absolute ethanol the solvent was evaporated under vacuum at 55°C. Solid dispersion granules were prepared by grounding and sieving. Fractions between 25 and 40 mesh were used for further investigations.

Table I

Composition of mixtures for preparation of solid dispersions

Series	Verapamil HCl (parts)	EC 10cp (parts)	HPC (parts)	HPMCP HP 55 (parts)
A	1.00	1.55	0.45	0.65
B	1.00	1.55	0.45	1.05
C	1.00	1.55	0.45	1.15
D	1.00	1.55	0.45	1.25

Stability studies were carried out using the following experimental methods:

HPTLC studies

HPTLC studies (Camag applicator, Camag scanner II, plate material silica gel Merck $60F_{254}$, solvent system cyclohexane : diethylamine 85 : 15) were carried out for quantitative determination of the active substance and detection of possible decomposition that may have occurred during the preparation of the solid dispersion granules and during the stability studies. Verapamil HCl and Norverapamil were used as standard substances. Densitometric analysis of Verapamil HCl and Norverapamil was carried out at 278 nm. The calibration curves of Verapamil HCl in chloroform were obtained in the range 1–10μg. The mean values of the correlation coefficient, slope and intercept for Verapamil HCl were 0.9983, 0.0214 and 0.3353. Also calibration curves in chloroform in the range of 0.2–5 μg were obtained for Norverapamil. The linear regression analysis showed these values for correlation coefficient, slope and intercept: 0.9978, 0.0314 and 0.5041. Rf values for Verapamil HCl and Norverapamil were 0.638 and 0.378, respectively.

Dissolution rate studies

Samples of solid dispersion granules equivalent to 240 mg Verapamil HCl were tested in 1000 ml buffer solutions at pH 1.5 composed of NaCl and HCl and pH 6.8 composed of KH_2PO_4 and NaOH (USP XXII rotation basket method, apparatus Erweka DZT, at 100 rpm). Also half-change dissolution method, by Gaudy [12], was carried out during 24 hours by changing the pH of the dissolution medium from 1.2 (during 1 hour), to 2.5 (for 2 hours), to 5.5 (for an additional 2 hours), to 7.5 (until the end of the dissolution test). The withdrawn aliquots were analysed spectrophotometrically (Perkin Elmer UV/Vis Lambda 16).

X-ray diffraction studies

The physical nature of the drug substance in solid dispersion granules was determined using the X-ray diffraction method (Jeol diffractometer, model JDX-7E, goniometer model DX-60-F). Powdered samples of Verapamil HCl and physical mixtures were examined for comparison.

IR spectroscopy studies

IR spectra of the drug substance, polymers, physical mixtures and solid dispersions were obtained using a Perkin-Elmer System 200 FT-IR spectrophotometer (KBr tablet).

UV spectroscopy studies

UV absorption spectroscopy studies of Verapamil HCl in solid dispersions (paraffini oleum) were carried out using HP 8452 diode array spectrophotometer Hewlett Packard. Verapamil HCl and physical mixtures of the drug substance and polymers were examined for comparison.

The above experiments were carried out periodically during 60-months stability studies (formulations were held in Kottermann chamber at 26 °C and relative humidity 65 %).

RESULTS AND DISCUSSION

No differences in the HPTL-chromatograms and no other peaks except Verapamil HCl peaks were detected in the chromatograms, which eliminates the possibility for decomposition of the drug substance during preparation of the solid dispersions or during stability studies (Verapamil HCl and Norverapamil were used as standard substances). Also, no significant changes of the drug content in the solid dispersions were noticed following 60-months stability studies (Table II).

Table II

Verapamil hydrochloride content in freshly prepared solid dispersion granules and after 60-months stability studies

Series	Mean weight ±SD (g), $n = 20$	Mean drug content ±SD (mg), initial content, $n = 5$	Mean weight ±SD (g), $n = 20$	Mean drug content ±SD (mg), after 60 months ($n = 5$)	F-ratio for experimental data during 60-months stability studies (df/df' = 2.76; $P = 0.05$)	t-values ($P = 0.05$) (initial and content after 60 months)
A	0.876 ± 0.003	240.0 ± 5.0	0.876 ± 0.002	239.0±4.3	2.01	0.3039
B	0.972 ± 0.002	241.5 ± 4.9	0.972 ± 0.003	241.0±3.2	2.04	0.1706
C	0.996 ± 0.003	239.5 ± 4.0	0.995 ± 0.003	238.0±4.5	1.79	0.4983
D	1.020 ± 0.003	237.6 ± 3.8	0.999 ± 0.005	237.0±3.4	1.87	0.2362

In the our previously published results from the IR spectroscopy evaluation it was shown that all characteristic bands of Verapamil HCl were present in physical mixtures of the drug substance and the polymers. In the case of solid dispersion changes in the area of νC–O–C skeletal vibrations (1200–1000 cm^{-1}) in glucose units in cellulose polymers appeared, showing differences in glucose bond orientation in solid dispersions. Basically, no changes in the frequency and shape of Verapamil HCl bands were noticed, which leads to the conclusion that no significant redistribution of the electronic density in the structure of the organic molecules appeared. This indicates that there is no strong interaction between the drug and the polymers, so interactions of van der Waal's type and/or dipole-dipole interactions exist in solid dispersions [7, 8]. Drug/polymer network structural characterisation showed that drug molecules were entrapped in the polymer's network in the prepared solid dispersions. During the stability studies no changes in the IR spectra of the solid dispersions appeared (Fig 1). Previously reported changes in the area of skeletal vibrations among the physical mixtures and solid dispersions due to the differences in glucose bond orientation in the drug/polymers network were also present in the IR spectra of solid dispersions during the stability studies (area of νC–O–C skeletal vibrations, 1200–1000 cm^{-1}, Fig. 2). This is proof that the drug substance was enslaved in the polymer network and no separation appeared during the stability studies. This was further confirmed with other experimental

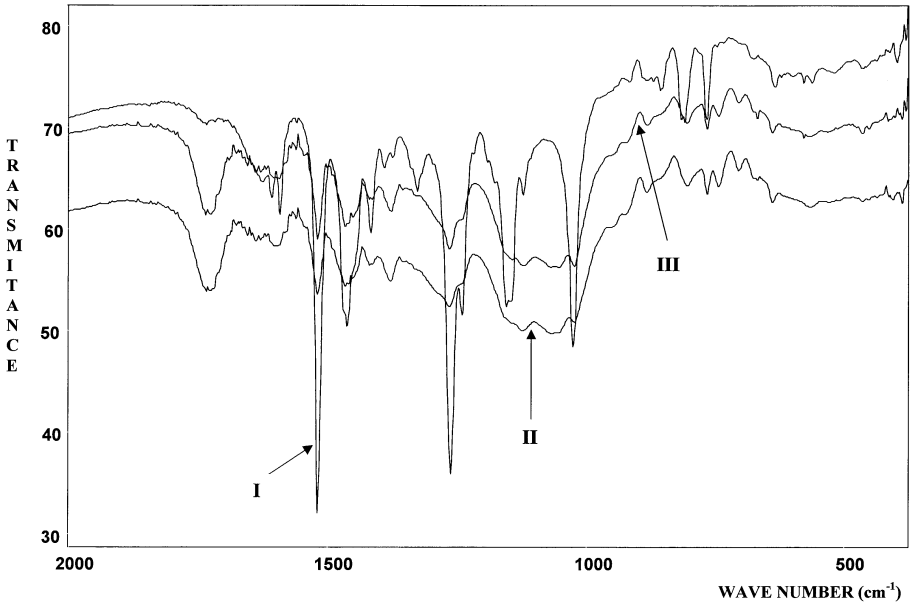

Fig. 1. IR spectra of physical mixture (I), solid dispersion C – immediately after preparation (II) and solid dispersion C – after ageing (III)

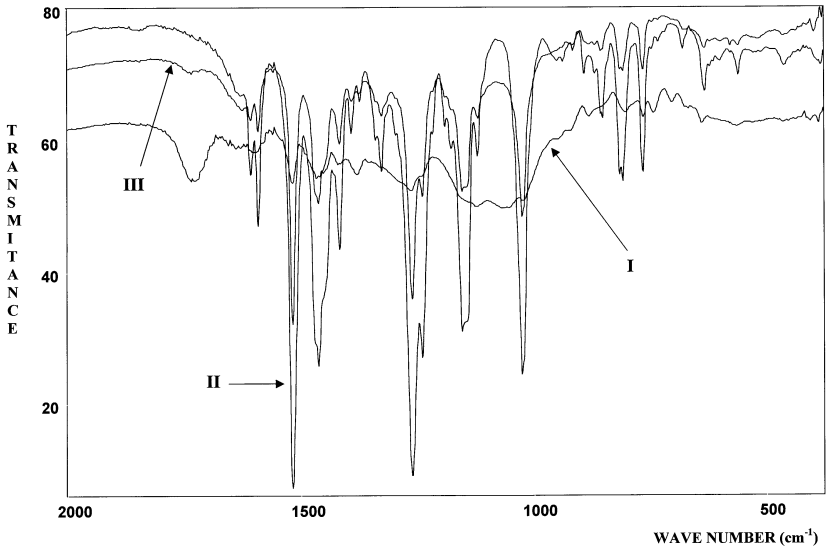

Fig. 2. IR spectra of solid dispersion C – after ageing (I), Verapamil HCl (II) and physical mixture (III)

methods. Also, in our following investigations studies concerning further spectral analysis (band shape analysis, derivative spectroscopy) will be carried out [14].

During the preparation of solid dispersions and splicing among the drug molecules with the polymer molecules, change of the crystal form of the drug substance appeared. The diffraction pattern of pure Verapamil HCl showed that the drug substance is highly crystalline in nature and in spite of the small proportion of the drug substance in the physical mixtures the X-ray diffractograms possessed all characteristic Verapamil.HCl diffraction lines. Previously reported amorphous state of the drug phase in freshly prepared solid dispersions was confirmed during the stability studies using X-ray diffraction method (Fig. 3).

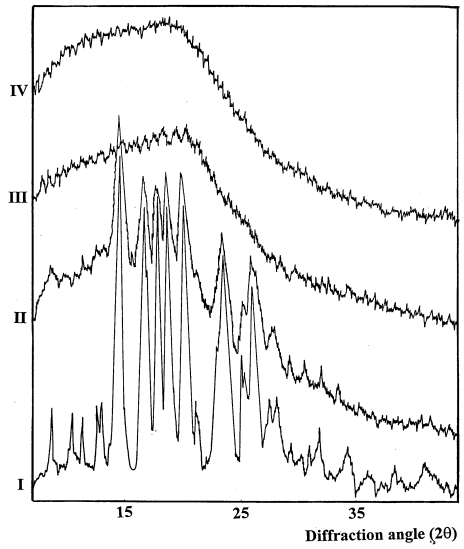

Fig. 3. X-ray spectra of Verapamil HCl (I), physical mixture (II), solid dispersion C – immediately after preparation (III) and solid dispersion C – after ageing (IV)

The UV absorption maximum of Verapamil HCl in solid dispersions, resembles that of the drug substance dissolved in organic solvents (chloroform, 280.5 nm), but not that of Verapamil HCl particles (292 nm). Opposed to the drug substance absorption maximum in the solid dispersions, the absorption maximum of the drug substance in physical mixtures was unchanged compared to solid Verapamil.HCl (Fig. 4). The UV spectroscopy studies results confirmed that the shift of the Verapamil HCl absorption maximum in solid dispersions toward the lower wavelengths (281 nm) was also present during the stability studies. These might be another proof that the drug is dispersed and embedded inside the polymer network.

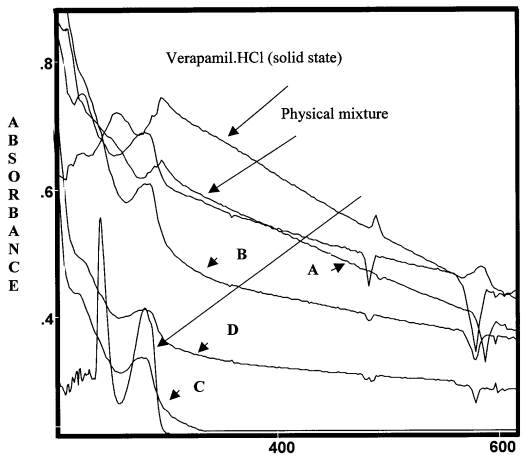

Fig. 4. UV spectra of Verapamil HCl, physical mixture and solid dispersions A, B, C and D

Despite the low solubility of the drug substance at neutral pH values (Verapamil HCl solubility decreases from 0.156 g/cm^3 at pH 5.0 to 0.025 and 0.010 g/cm^3 at pH 6.0 and 7.0, respectively), incorporation of HPMCP HP 55 in the formulation resulted with faster drug release rate of the drug substance at higher pH values.

No changes in the drug release rate from the examined formulations was noticed during the first 36 months of stability evaluation. But after 60-months stability studies statistically significant changes (two sample comparison, $\alpha = 0.05$) in the drug release rate from series A and B at pH 1.5 and from series C and D at 6.8 appeared (Figs. 5, 6). As was expected the half-change dissolution testing also point to a statistically significant increase of the drug release rate from all series (Fig. 7). The drug release rate from series with lower content of HPMCP HP 55 at pH 1.5 was increased but no abrupt release was noticed from either series. The release rate at pH 1.5 from series C and D with higher content of HPMCP HP 55 was not significantly changed. The dissolution studies results at pH 6.8 during the stability evaluation point that the release rate of the drug substance was increased from all series (statistically significant increase was noticed from series C and D). The main role of this polymer to improve the drug release at higher pH values where the solubility of drug substance is problematical, was maintained and even more pronounced. This is another proof that the drug substance is highly dispersed within the structure of solid dispersion and no recrystalization and separation appeared during ageing. The results from the half change dissolution testing were in accordance with the previous investigations at pH 1.5 and 6.8, as increased release was noticed from all series during this test.

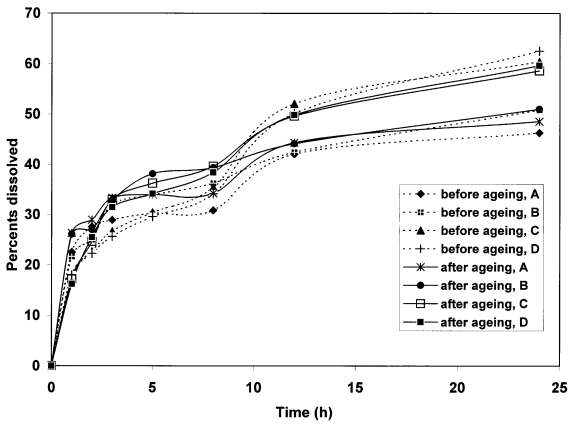

Fig. 5. Cumulative amounts (%) of Verapamil HCl released from solid dispersion granules (pH 1.5; $n = 5$)

The diffusion mechanism of the drug release rate was not changed as another proof that the network structure was maintained. The release mechanism was most approximate to that of the leaching type for the matrix (Table III), first presented by T. Higuchi [13].

Channels were formed in the solid dispersion granules after the dissolution of the soluble polymers and Verapamil HCl was diffused and dissolved into the dissolution medium in the channels in the ethylcellulose network.

Table III

Kinetic parameters for series A, B, C and D before and after ageing

Series	Diffusion model			
	Before ageing		After ageing	
	R	k (%h$^{-1/2}$)	r	k (%h$^{-1/2}$)
A	0.9901	7.7031	0.9567	12.8710
B	0.9951	14.3550	0.9761	20.2900
C	0.9924	18.0910	0.9805	21.06140
D	0.9920	21.1010	0.9851	22.4546

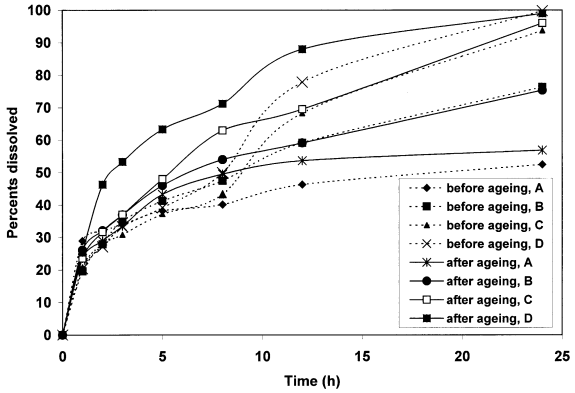

Fig. 6. Cumulative amounts (%) of Verapamil HCl released from solid dispersion granules (pH 6.8; $n = 5$)

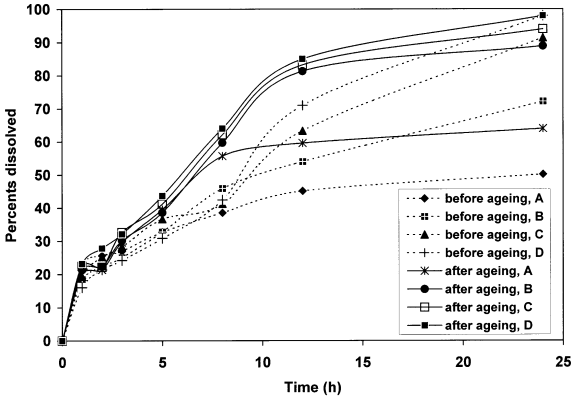

Fig. 7. Cumulative amounts (%) of Verapamil HCl released from solid dispersion granules (half-change method, $n = 5$)

CONCLUSIONS

Physical characterisation of the prepared solid dispersions during the stability studies by the above mentioned methods show that no changes in the structure of solid dispersions appeared and the drug molecules remained enslaved in the polymer's network. During the stability studies an increased release rate was noticed from all the series. Despite the different release rate the main role of the incorporated HPMCP HP 55 was maintained as no abrupt release was noticed from either serie at pH 1.5 and as the dissolution rate at pH 6.8 was even more increased after ageing. Although these systems generally didn't appeared to lose their controlled release they are not recommended as stable during 60 months as differences in the drug release rate appeared during stability studies.

REFERENCES

[1] N. Kohri, H. Yatabe. K. Iseki, K. Myazaki , *Int. J. Pharm.*, **68**, 255 (1991).

[2] P. Santi, P. L. Catellani, P. Colombo, C. Ringard-Lefebvre, C. Barthelemy, A-M. Guyot-Hermann, *Int. J. Pharm.*, **68**, 34 (1991).

[3] S. N. Tenjarla, R. Allen , A. Borazani, *Drug. Dev. Ind. Pharm.*, **20** (1), 49 (1994).

[4] K. Thoma, T. Zimmer, *Int. J. Pharm.*, **58**, 197 (1990).

[5] M. S. Kislaliogly, M. A. Khan, C. Blount, R. W. Goettisch, S. Bolton, *J. Pharm. Sci.*, **80** (8), 799 (1991).

[6] D. B. Beten, A. J. Moes, *Int. J. Pharm.*, **103**, 243 (1994).

[7] K. Goracinova, Lj. Klisarova, A. Simov, E. Fredro-Kumbaradzi, L. Petrusevska-Tozi, *Drug. Dev. Ind. Pharm.*, **22** (3), 255 (1996).

[8] K. Goracinova, Lj. Klisarova, A. Simov, *Drug. Dev. Ind. Pharm.*, **21** (3), 383 (1995).

[9] M. R. Jenquin, J. W. Mc Ginity, *Int. J. Pharm.*, **101**, 23 (1994).

[10] H-K. Chan, I. Gonda, *Int. J. Pharm.*, **68**, 179 (1991).

[11] H. Yuasa, T. Ozeki., Y. Kanaya, K. Oishi, T. Oyake, *Chem. Pharm. Bull.*, **39** (2), 465 (1991).

[12] C. Brossard, D. Wouessidjewe, *S. T. P. Pharma*, **6**, 728 (1990).

[13] T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).

[14] M. W. Mackenzie, *Advances in Applied Fourier Transform Infrared Spectroscopy*, John Wiley & Sons Ltd, 1988, England.

Р е з и м е

ФИЗИЧКО-ХЕМИСКА СТАБИЛНОСТ НА ЦВРСТИ ДИСПЕРЗИИ СО ВЕРАПАМИЛ-ХИДРОХЛОРИД И НЕГОВО КОНТРОЛИРАНО ОСЛОБОДУВАЊЕ

Катерина Горачинова[1], Љиљана Клисарова[2], Ангел Симов[1], Емилија Фредро-Кумбараџи[1], Кристина Младеновска[1], Марија Главаш[1]

[1]Институт за фармацевтска технологија, Фармацевтски факултет, Универзитет „Св. Кирил и Методиј“, Водњанска 17, 91 000 Скопје, Република Македонија
[2]Институт за хемија, Природно-математички факултет, Универзитет „Св. Кирил и Методиј“, п. фах 161, 91001 Скопје, Република Македонија

Клучни зборови: цврсти дисперзии; испитување на стабилноста; контролирано ослободување; верапамил-хидрохлорид; етилцелулоза; хидроксипропил-метил-целулоза фталат

Беше испитувана стабилноста на подготвените цврсти дисперзии со верапамил-хидрохлорид со употреба на различни експериментални методи (IC спектроскопија, UV спектроскопија, дифракција со X-зраци, тенкослојна хроматографија под висок притисок, тестови на дисолуција) во тек на 60 месеци. За време на испитувањата на стабилноста не беше забележан распад и/или промена на квантитативниот состав на активната супстанција. Физичкото карактеризирање на цврстите дисперзии покажа дека не доаѓа до промени во структурата на цврстите дисперзии за време на стареењето. Исто така беше зачувана аморфноста на вклопената активна супстанција во цврстите дисперзии. Иако ослободувањето на верапамил-хидрохлоридот за време на стареењето се разликува од почетното, сепак зависноста на ослободувањето на активната супстанција од полимерот HPMCP HP 55 беше задржана, а дури и понагласена при повисоки pH вредности.