ORIGINAL ARTICLE

THERMAL STABILITY ASSESMENT OF AMIODARONE HYDROCHLORIDE IN POLYMERIC MATRIX TABLETS

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Abstract

Amiodarone, an antiarrhythmic agent with low bioavailability caused by its low water solubility, is currently used in the form of conventional release tablets (200 mg/tablet). In order to develop new solid oral dosage forms with prolonged release, we analysed the stability of pure amiodarone and amiodarone complexed with hydroxypropyl-β-cyclodextrin (HP-β-CD), in association with matrix forming agents (Kollidon®SR and chitosan), during direct compression. The stability assessment and the identification of potential interactions between amiodarone and the auxiliary substances were established by spectrophotometric and thermal analysis. The thermal profile of the tablet formulation containing amiodarone and excipients (abbreviated F1) showed the conservation of the crystalline form of the active substance following direct compression. In the thermogram of the formulation containing complexed amiodarone (abbreviated F10), the melting point of the crystalline form disappeared, which indicated the amorphous nature of the active substance caused by its interactions with the polymers. FT-IR spectra for the two tablet formulations revealed characteristic bands of the tertiary amine bond in the amiodarone structure. The band attributed to the aromatic C=C bond stretching is frequently displaced/bent in the presence of excipients, due to the interactions between amiodarone and polymers. The complete disappearance of the absorption bands characteristic of amiodarone (2580 - 2455 cm^{-1}) in the FT-IR spectrum for the formulation with the inclusion complex showed the formation of chemical bonds between the OH groups of HP-β-CD and the tertiary amine of the active substance.

Rezumat

Amiodarona, un antiaritmic cu biodisponibilitate scăzută datorită solubilității scăzute, este folosită sub forma comprimatelor convenționale (200 mg/comprimat). Scopul acestui studiu a fost de a formula noi forme farmaceutice, cu eliberare prelungită, pornind de la stabilitatea amiodaronei ca atare și a complexului format de aceasta cu hidroxipropil-β-ciclodextrină, prin combinare cu un agenți formatori de matriță (Kollidon®SR și chitosan) prin combinare directă. Evaluarea stabilității identificarea interacțiunilor posibile între amiodaronă și substanțele auxiliare a fost determinată prin intermediul analizelor spectrofotometrice și termice. Profilul termic al comprimatelor formulate conținând amiodaronă și excipients (notate F1) au accentuat prezența formei cristaline a substanței active. În termograma comprimatelor formulate cu complexul format de amiodaronă cu hidroxipropil-β-ciclodextrină (notate F10), punctul de topire al formei cristaline a dispărut, indicând natura amorfă a substanței active, datorită interacțiunilor polimerice. Spectrele în infraroșu înregistrate pentru formulările prezentate au dezvăluit benzi caracteristice ale legăturii amino- terțiare din structura amiodaronei, iar banda atribuită legăturii aromatice C=C este deplasată în prezența excipienților. Dispariția completă a benzilor caracteristice amiodaronei (2580 – 2455 cm^{-1}) în spectrul în infraroșu înregistrat pentru formularea ce conține complexul de incluziune permite interpretarea formării unor noi legături între grupările OH din hidroxipropil-β-ciclodextrină și amina terțiară a substanței active.

Keywords: amiodarone, controlled release, structural changes, polymeric matrix tablets

Introduction

The low oral bioavailability of amiodarone (AMD) caused by its low water solubility catalogues it in BCS class II of active ingredients, whose solubility is a critical factor in achieving optimal therapeutic outcomes [1]. The mechanism of action of AMD prolongs the myocardial cell-action potential duration and total refractory period especially in the atrium and in the His-Purkinje system, but also in the ventricular myocardium. Moreover, it depresses sinus node automaticity [2].

The development of sustained release systems that contain poorly soluble pharmaceutical substances is carried out with the controlled release tablet formulation technology [3], in order to control the release rate during residence in the gastrointestinal tract [4-6]. To this end, it is necessary to include the active substance in hydrophilic polymer matrix tablets [7].

Our study aimed to assess the stability of free or hydroxypropyl-β-cyclodextrin (HP-β-CD) complexed

AMD in association with Kollidon®SR (KOL) and chitosan (CHT) and the use of direct compression [8]. AMD stability and compatibility with HP-β-CD has previously been investigated and data showing the compatibility of these substances have been published [9].

In the first stage of the research, we focused on the optimization of biopharmaceutical properties of AMD by formulating and preparing 9 formulations of oral modified release AMD tablets based on KOL in variable amounts (40 - 60%) and CHT (3 - 7%), by direct compression. Concentrations of 40% KOL and 3% CHT were found to be optimal for the pharmacotechnical characteristics of the prepared tablets [1]. A KOL:CHT ratio of 13.33:1 was consequently considered optimal for obtaining matrix systems. This mixture of matrix forming excipients was associated with AMD or AMD/HP-β-CD in order to develop two matrix system formulations with extended release of AMD [10].

Spectrometric and thermal analysis methods were used to identify structural changes in the substances utilized for the preparation of AMD matrix tablets, during the compression process, and to detect potential interactions between them.

Thus, we used Fourier transform infrared spectroscopy (FT-IR), as it provides information on the chemical bonds and establishes the molecular structure of the sample. The method relies on the fact that the bonds and the groups of bonds vibrate at certain frequencies, thus providing information on the chemical structure of the sample [11, 12].

The stability of the crude materials was also investigated using dynamic differential scanning calorimetry (DSC), a method used for the measurement of thermal transitions and physicochemical processes in the study sample [13]. The DSC curve allows the characterization of an exothermic or endothermic process, defines the types of transitions involved, the final purpose being the identification of potential structural changes that have an impact on the AMD release characteristics in modified-release tablets and on the pharmacodynamic effect of this active substance [14, 15].

Materials and Methods

Materials. HP-β-CD/AMD complex ("P. Poni" Institute of Macromolecular Chemistry, Iași, Romania), Kollidon®SR (KOL), (BASF, Germany), chitosan practical grade (CHT) (BASF, Germany), Avicel® PH Microcrystalline Cellulose (Chemtrec, USA & Canada), Aerosil® 200 (Degussa, Germany), magnesium stearate (Union Derivan SA, Spain), potassium bromide (Sigma Aldrich, Germany), amiodarone hydrochloride (reference substance, Sigma Aldrich), were of analytical grade.

Methods

Preparation of matrix tablets. Two formulations of AMD matrix tablets were formulated and prepared by direct compression, using a Korsch EK0 tablet press (punch diameter of 9 mm at a compression pressure of 8 - 10 kN). The formulation containing free AMD was labelled F1 and the formulation containing AMD/HP-β-CD complex was labelled F10. The ratio of matrix forming agents was 13.33:1 KOL:CHT in both formulations.

FT-IR analysis. The measurement of IR absorption spectra was made with a VERTEX 70 spectrophotometer (Bruker, Germany) for powdered samples, obtained by the trituration of a set of 4 tablets for the formulations F1 and F10, as well as for samples using only the active substance in the matrix tablets. The samples for analysis were obtained by the trituration of 2 mg sample with 500 mg KBr, subsequently subjected to tableting. Before using it for sample preparation, KBr was activated for 3 hours at 200°C, in order to remove the absorbed water that might have influenced the results. The samples were measured in the spectral range of 4000 - 500 cm^{-1}, with a resolution of 4 cm^{-1}. The spectra were recorded at room temperature.

DSC analysis. The 5 - 8 mg samples were delivered in aluminium crucibles which were not tightly closed; they were analysed in a dynamic mode at a rate of 10°C min^{-1} in the range of 50 - 300ºC; a nitrogen flow of 20 mL/min was passed through the measuring cell using a Netzsch DSC 200F3 calorimeter (Germany). Before starting the measurement, the calorimeter was calibrated with indium as a standard for temperature and energy.

Results and Discussion

The compared spectra of samples F1 and F10 are shown in Figures 1 and 2.

The spectra of the samples F1 and F10 are shown comparatively in Figure 1. For illustration purposes, we inserted the spectrum recorded for HP-β-CD. The IR spectrum obtained for HP-β-CD exhibits a wide absorption band in the wave number range 3600 - 3100 cm^{-1}, characteristic for the stretching vibrations of the OH groups. The intense absorption bands can be found at the wavenumbers 2970, 2931 and 2875 cm^{-1}, characteristic for the stretching vibration of the aliphatic CH groups. The absorption bands located at 1480 - 1350 cm^{-1} are characteristic for the rocking vibrations of the aliphatic CH groups, whereas the bands observed at 1300 - 1000 cm^{-1} (1160 - 1040 cm^{-1}) are provided by the stretching vibrations of the CO ether groups [15]. The FT-IR spectrum recorded for the sample F10 showed characteristic absorption bands for both HP-β-CD and AMD. There were not found bonds between AMD and the cyclodextrin support. The complete disappearance of the characteristic

absorption bands of AMD (2580 - 2455 cm^{-1}) indicates the formation of the chemical bonds between the OH groups of HP-β-CD and the tertiary amine group of AMD [9]. In the spectrum recorded for the F10 sample containing the HP-β-CD/AMD complex, the intensity of the peaks in this spectral region is significantly lower as compared to the F1 sample. Moreover, as compared to the F1 sample, F10 has a broad IR absorption band which is much more intense in the spectral region of 3000 - 3600 cm^{-1} due to the large number of OH groups in the composition of the HP-β-CD/AMD complex. A very weak band can be observed at 1650 cm^{-1}, characteristic for the stretching vibration of the carbonyl group of amiodarone. In addition, very weak or medium peaks, characteristic for the vibrations in the AMD molecule, are found only in the "footprint" region. For example, very weak peaks are visible at 1631 cm^{-1} and 1556 cm^{-1}, the peaks recorded at 1241 cm^{-1} and 1219 cm^{-1} are flattened, forming a broad IR absorption band, and the peaks in the spectral region 600 - 900 cm^{-1}, characteristic for amiodarone, are not visible in the F10 sample spectrum, except for a very weak peak, at 750 cm^{-1}. The intensity decrease in the absorption bands in the spectral region 3200 - 3600 cm^{-1} is evident when the IR spectra of the F1, F10 samples are compared.

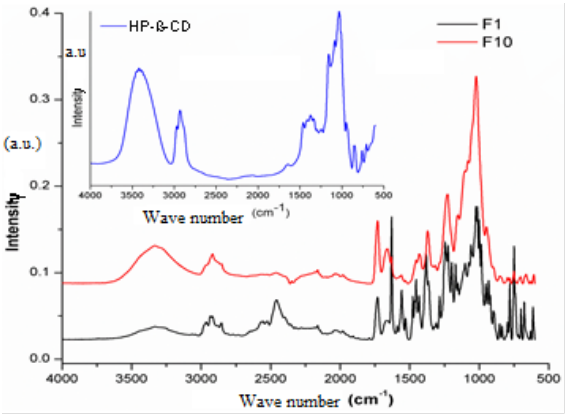

Figure 1.
Comparative representation of FT-IR spectra recorded for samples F1 and F10 as compared to HP-β-CD

Chitosan (CHT) has a broad absorption band in the region 3600 - 3200 cm^{-1}, characteristic for the stretching vibration of O-H bonds in the composition of polymer chains. In this region, there is a broad band centred at 3333 cm^{-1}, including both absorption bands characteristic for the stretching vibrations of the O-H bonds in the polymeric structure of CHT and for the stretching vibrations of the N-H bond at 1652 cm^{-1}, 1592 cm^{-1} and 1372 cm^{-1}, characteristic for the amides I, II, III [16] and also involving the presence of the intermolecular H bonds. Proportionally, with the increase of the amount of KOL, it is noted a decrease in the intensity of this band and the appearance of weak bands cantered at 3247, 3442 and 3454 cm^{-1}, characteristic of the vibrations of "normally" polymeric and dimeric O-H bonds. Furthermore, in the spectral region 1580 - 1780 cm^{-1}, the intensity of the absorption bands at 1668 cm^{-1} and 1729 cm^{-1}, characteristic for the stretching vibrations of the alkenyl bond and for the vibration of the keto group in KOL, respectively, increases proportionally with the increase of the KOL amount used in sample preparation. The same observation can be noted for the bands found at 1365 cm^{-1}, 1245 cm^{-1}, 1224 cm^{-1}, 1120 cm^{-1} and 1020 cm^{-1} originating from the rocking vibration of the C-H vinyl bond ($-CH=CH_2$) in the plane of the bond, the stretching vibration of the CN bond, the stretching of Aryl-O aromatic ether, the stretching of the CN group in the tertiary amines, the stretching of the etheric C-O bond, the stretching vibration of the CN bond in the KOL structure [17, 18]. In fact, the absorption band at 1120 cm^{-1}, which is characteristic for the stretching of the etheric C-O bond in the KOL structure, is almost unremarkable in the IR spectrum of the F1, F10 samples that contain the smallest amount of KOL. The IR characteristic absorption bands for KOL at 2926 cm^{-1} for the C-H bond, at 1665 cm^{-1} for the C=O bond and at 1732 cm^{-1} for the ether group [19] are slightly more intense in the F10 sample spectrum as compared to the F1 sample spectrum.

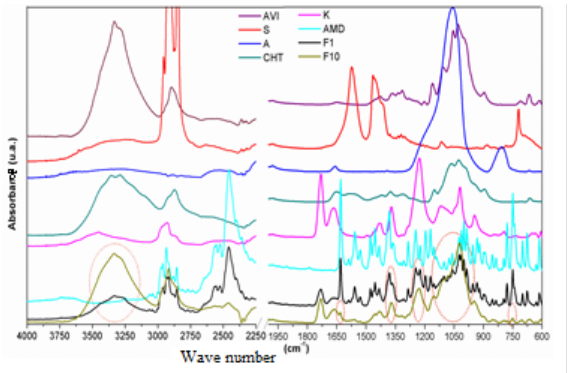

Figure 2.
FT-IR spectra of samples F1 and F10 as compared to the constituent crude materials
(AVI – Avicel® PH microcrystalline cellulose, A – aerosil, S – magnesium stearate, CHT – chitosan, K – Kollidon SR®)

Avicel (AVI), as a sort of microcrystalline cellulose, has an IR spectrum with characteristic bands due to the stretching vibrations of the O-H bond in the region 3600 - 3100 cm^{-1}, at 1429 cm^{-1}, for the symmetric stretching vibrations of the CH_2 group, at 1161 cm^{-1} for the asymmetric stretching vibrations of the C-O-C bond, at 1055 cm^{-1} for the C-O bond

and at 897 cm^{-1} for the C-O-C of the β-(1,4) glycosidic bond [20].

Aerosil (A), also known as pyrogenic silica, exhibits in the recorded IR spectrum two absorption bands characteristic for the vibration of the Si-O bond: a very intense band at 1060 cm^{-1} and a less intense band at 810 cm^{-1} [21].

Due to its structure, *magnesium stearate (S)* also exhibits an IR spectrum with very intense absorption bands characteristic for the asymmetric and symmetric stretching vibrations of the C-H bond of the methylene group (at 2916 and 2850 cm^{-1}, respectively), an absorption band at 1570 cm^{-1} characteristic for the asymmetrical stretching vibration of the metal - carboxylate group, an intense absorption band at 1470 cm^{-1} attributable to the rocking vibration of the C-H bond from the methylene group (-CH_2-) [22].

The peaks, characteristic of Aerosil and magnesium stearate, are overlaid by the intense peaks given by the vibrations of the AMD and the KOL bonds.

Figure 2 shows IR spectra recorded for F1 and F10 samples as compared to those recorded using the crude materials. The changes found when comparing the two spectra are highlighted by circles.

Figure 3 shows the DSC thermal analyses of AMD as compared to KOL, CHT and Avicel, while Figure 4 shows the DSC thermograms for F10, F1 as compared to AMD, the reference substance and the inclusion complex HP-β-CD/AMD.

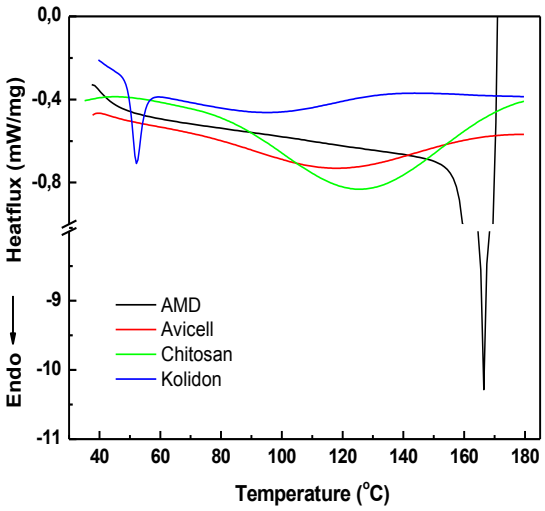

Figure 3.
The DSC thermograms of AMD as compared to the ones of KOL, CHT and Avicel

Figure 4 shows comparatively the thermal analysis of the active ingredient AMD, the HP-β-CD/AMD complex, and the F1 and F10 formulations. The most relevant result of these DSC analyses is the decrease of the intensity of the complexed AMD melting process, as actually it could be observed a weak endothermic process, with two peaks, performed at ~ 150°C and 166°C, respectively. The result confirms the formation of an inclusion complex HP-β-CD/AMD [9], in which the morphology of the active ingredient is conserved in the cavity. Therefore, the dual nature of the melting process shows that the active ingredient exhibits two distinct crystal morphologies. Overall, however, the inclusion complex HP-β-CD/AMD exhibits an amorphous nature as compared to the pure active ingredient.

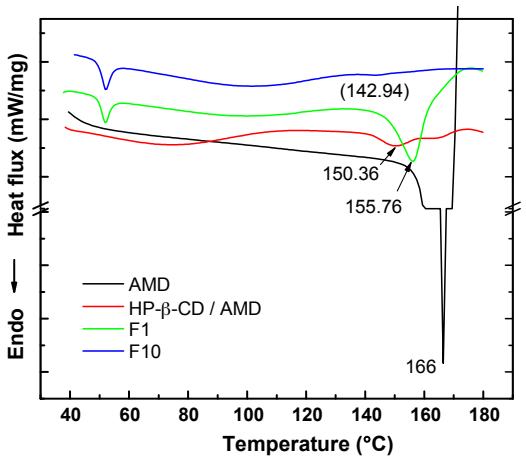

Figure 4.
The DSC thermograms for F10, F1 as compared to AMD, the reference substance and the inclusion complex HP-β-CD/AMD

The DSC curves for the two formulations in Figure 4 show significant differences concerning the melting process of complexed AMD. The thermal profile of F1 formulation shows the polymer and the active ingredient characteristics, indicating the conservation of the crystalline form of AMD after compression, in the presence of the excipients. Moreover, the KOL, present in the mixture, triggers yet another melting process at a much lower temperature (52°C), but it does not affect the morphology of AMD [23, 24]. As expected, the F1 formulation (containing the active ingredient in free form) shows a melting process of AMD at around 155.8°C, whereas for the F10 formulation (containing the HP-β-CD/AMD complex instead of AMD) there is a much weaker melting process, at around 143°C. The differences between the melting point and the intensity of the process show the presence of interactions between AMD and polymers. They are due to the complexed state of the active ingredient that was physically mixed in those formulations. In the thermogram of the F10 formulation, the melting point of the AMD crystalline form disappears, thus indicating an amorphous nature. Furthermore, the melting processes for both the HP-β-CD/AMD complex and the two formulations, F1 and F10, occur at temperatures much lower than for AMD pure substance.

Conclusions

The FT-IR spectrum recorded for the F10 sample showed absorption bands characteristic for both HP-β-CD and AMD, while the complete disappearance of the characteristic AMD absorption bands (2580 - 2455 cm^{-1}) indicated the possibility of the chemical bond formation between the OH groups of HP-β-CD and the tertiary amine of AMD. The F10 sample showed a broad IR absorption band which was more intense in the spectral region 3000 - 3600 cm^{-1} as compared to F1, due to the large number of OH groups included in the HP-β-CD/AMD complex.

The IR characteristic KOL absorption bands, at 1730 cm^{-1} and 1665 cm^{-1} are slightly more intense in the F10 sample spectrum as compared to the F1 sample spectrum. The peaks characteristic recorded for the other crude materials are underlined by the intense peaks due to the vibrations bonds in AMD and KOL.

The melting process and the other processes associated with the dehydration of the constituents are significant, but they do not affect the morphology of AMD.

DSC curves showed that the thermal stability of AMD increases by complexation, which is evident, both in the curve of the inclusion complex and in the F10 formulation tablet containing this complex. This feature is a clear advantage in the tableting process. The results of this study showed that AMD, in both its free and complexed form, can be formulated as matrix tablets, based on KOL and CHT, without undergoing physicochemical changes that might adversely affect its *in vivo* bioavailability.

References

1. Kawabata Y., Wada K., Nakatani M., Yamadaa S., Onoue S., Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *Int. J. Pharm.*, 2011; 420(1): 1-10.
2. Popa D.E., Lupuliasa D., Stănescu A.A., Bârcă M., Burcea-Dragomiroiu G.T.A., Miron D.S., Rădulescu Ș.F., Simulation of the *in vivo* exposure to ibuprofen based on *in vitro* dissolution profiles from solid dosage forms. *Farmacia*, 2014; 62(3): 483-493.
3. Klüppel Riekes M., Piazzon Tagliari M., Granada A., Kuminekb G., Segatto Silvab M.A., Stulzer H.K., Enhanced solubility and dissolution rate of amiodarone by complexation with β-cyclodextrin through different methods. *Mat. Sci. Eng. C*, 2010; 30(7): 1008-1013.
4. Streubel A., Siepman J., Bodmeier R., Gastro-retentive drug delivery system. *Expert. Opin. Drug Deliv.*, 2006; 3(2): 217-233.
5. Chourasia M.K., Jain S.K., Pharmaceutical approaches to colon targeted drug delivery systems. *J. Pharm. Sci.*, 2003; 6(1): 33-66.
6. Basit A.W., Advances in colonic drug delivery. *Drugs*, 2005; 65(14): 1991-2007.
7. Maderuelo C., Zarzuelo A., Lanao J., Critical factors in the release of drugs from sustained release hydrophilic matrices. *J. Control Release*, 2011; 154: 2-19.
8. Challa R., Ahuja A., Ali J., Khar R.K., Cyclodextrins in drug delivery: an updated review. *AAPS Pharm. Sci. Tech.*, 2005; 6(2): E329-E357.
9. Păduraru O.M., Bosînceanu A., Țântaru G., Vasile C., Effect of hydroxypropyl-β-cyclodextrin on the solubility of an antiarrhytmic agent. *Ind. Eng. Chem. Res*., 2013; 52(5): 2174-2181.
10. Gligor-Vonica A.L., Casian T., Reznek A., Tomuță I., Gligor F., Simultaneous quantification of atorvastatin and amlodipine in powder blends for tableting by NIR spectroscopy and chemometry. *Farmacia*, 2015; 63(3): 381-387.
11. Naşcu H.I., Jantschi L., Chimie Analitică şi instrumentală. Academic Press & Academic Direct, Cluj Napoca, 2004; 83-91.
12. Socrates G., Infrared and Raman Characteristic Group Frequencies, 3rd ed. John Wiley & Sons, New York, 2004; 109-135.
13. Yoshida M.I., Gomes E.C., Soares C.D., Oliveira M.A., Thermal behavior study and development kinetics of amiodarone hydrocloride under isotermal conditions. *Drug Dev. Ind. Pharm.*, 2011; 37(6): 638-647.
14. McCauley J.A., Brittain H.G., Thermal methods of analysis. In: Brittain G. (ed.): Physical characterization of pharmaceutical solids, M. Dekker Inc., New York, 1995; 238-243.
15. Silverstein R.M., Webster F.X., Kiemle D.J., Spectrometric Identification of Organic Compounds. John Wiley & Sons Inc., New York, 2005.
16. Rokhade A.P., Shelke N.B., Patil S.A., Aminabhavi T.M., Novel interpenetrating polymer network micro-spheres of chitosan and methylcellulose for controlled release of theophylline. *Carbohyd. Polym.*, 2007; 69(4): 678-687.
17. Coates J., Interpretation of infrared spectra. In: Meyers R.A. (ed.). A practical approach in Encyclopedia of Analytical Chemistry. John Wiley & Sons Ltd., Chichester, 2000; 10815-10837.
18. Kim H.J., Lee S.H., Lim E.A., Kim J.S., Formulation optimization of solid dispersion of mosapride hydro-cloride. *Arch. Pharm. Res.*, 2011; 34(9): 1467-1475.
19. Ciolacu D.E., Ciolacu F., Popa V.I., Amorphous cellulose-structure and characterization. *Cell. Chem. Technol.*, 2011; 45(1): 13-21.
20. Păduraru O.M., Ciolacu D., Darie R.N., Vasile C., Synthesis and characterization of polyvinyl alcohol/ cellulose cryogels and their testing as carriers for a bioactive component. *Mat. Sci. Eng. C*, 2012; 32(8): 2508-2515.
21. Yuan H.N., Yao S.J., Shen L.Q., Mao J.W.. Preparation and Characterization of Inclusion Complexes of beta-Cyclodextrin-BITC and beta-Cyclodextrin-PEITC. *Ind. Eng. Chem. Res.*, 2009; 48(10): 5070-5078.
22. Phaechamud T., Charoenteeraboon J., Mahadlek J., Characterization and *in-vitro* drug release of a chitozan-magnesium stearate monolithic matrix system. *Asian J. Pharm. Sci.*, 2009; 4(5): 265-276.

23. Alhhatib K.S., Hamed S., Mohammad M.K., Bustanji Y., Akhalidi B., Aiedeh K.M., Najjar S., Effects of Thermal Curing Conditions on Drug Release from Polyvinyl Acetate-Polyvinyl Pyrrolidone Matrices. *AAPS Pharm. Sci. Tech.*, 2010; 11(1): 253-266.

24. Gonzalez Novoa G.A., Heinämäki J., Mirza S., Antikainen O., Colarte A.I., Paz A.S., Yliruusi J., Physical solid-state properties and dissolution of sustained-release matrices of polyvinylacetate. *Eur. J. Pharm. Biopharm.*, 2005; 59(2): 343-350.