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Application of Different Analytical Methods for Characterization of Pharmaceutical Materials

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Abstract: Many of the analytical methods can be used to characterization of pharmaceutical materials. Some of them were used to describe hybrid organic-inorganic materials applied in sustained drug delivery composed of Ibuprofen as a model drug, polyethylene glycol (PEG 10000) as polymer and two different fillers (AEROSIL® 200V and AEROSIL® R816). Influence of the type of employed filler and the temperature of experiment on the surface properties and bulk interactions was estimated. Inverse gas chromatography (IGC) has been applied to observe the interactions in that system. Flory-Huggins interaction parameters, the dispersive component of surface free energy and acid-base characteristic of the surface were used to assess the behaviour of the composites in terms of drug release. The temperature affects the magnitude of the interactions and thus the release of the drug from the hybrid matrix. Fourier transform infrared (FTIR) spectra were collected for all investigated materials and their components. The quantity of the released drug from the hybrid materials was measured using Ultraviolet-visible spectroscopy (UV/VIS) spectrophotometer. The executed experiments allowed the estimation of the properties of prepared composites. Prepared materials present properties required in sustained drug release and may be successfully applied as drug delivery systems.

Key words: Inverse gas chromatography, pharmaceutical materials' characterization, Flory-Huggins parameters.

1. Introduction

The research of pharmaceutical materials is carried out in many laboratories all around the world. The investigation of the structure, properties, nature and strength of the interactions occurring plays a key role in the development of pharmaceutical systems. To achieve this, many analytical methods can be used. From these methods, you can choose the one that provides the most information.

The authors proposed to use three techniques to characterize materials that can be applied to the controlled drug release. These are IR (FTIR), UV and IGC. The UV and FTIR techniques are well known and are used in pharmacy. The last one is the most recent one used in this area.

The first used technique is Infrared Spectroscopy, an exactly FTIR. Most molecules absorb IR light, converting it to a molecular vibration. This absorption is characteristic for the nature of the chemical bonds presented in a sample. Each component spectrum shows absorption bands that enable to determine if certain functional groups are presented in a molecule [1].

UV spectroscopy identifies conjugated molecules and it is also a well-known technique [1]. In our investigation, we used it to determine the concentration of a drug in solution. This technique can be also used to determine a drug release profiles (RD) [1, 2].

The last used technique is inverse gas IGC. This is a method where the material of interest is placed in a chromatographic column as a stationary phase and the behavior of carefully selected test solutes is studied [3-5]. Retention parameters and the shapes of chromatographic peaks of these solutes are affected by the nature and magnitude of interactions between them and the examined material. So it is possible to use IGC for characterizing surface and bulk properties of many materials: powders, particulates, fibers, films

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and semi-solids. IGC experiments can be performed with a standard commercial gas chromatograph. In our case, we use dedicated equipment SEA–IGC (*Surface Measurement Systems* - United Kingdom). The main value obtained from the IGC chromatogram is retention time of each individual solvent, which can be recalculated to specific retention volume (V_g). For the further researches, it is the crucial retention parameter.

$$V_g = \left(\frac{(t_R - t_o) \cdot j \cdot F_c \cdot 273.15}{w_l \cdot T_c}\right) \quad (1)$$

where: t_R is the retention time for the adsorbing probe; t_o is the mobile phase hold-up time (dead time); j is the James-Martin pressure drop correction; T_c is the column temperature; w_l is the sample mass; F_c is the exit flow rate.

At the base of IGC retention parameters, we can characterize materials. We can determine a wide range of surface (i.e. heats of sorption) and bulk properties (i.e. glass transitions and Flory-Huggins parameters).

The surface energy is an important parameter for the characterization of surface properties. It can provide a useful picture of the energetic situation on the surface and shows therefore a strong dependency on various macroscopic properties.

Surface energy can be correlated to adhesion properties and also can be correlated to bulk powder behavior.

Surface of solids is characterized by their activity, acid-based properties, surface area and porosity [6, 7].

$$\gamma_S = \gamma_S^D + \gamma_S^{SP} \quad (2)$$

The dispersive properties of the examined material are calculated from the IGC retention data of test solutes determined at infinite dilution and presented by dispersive component of the free surface energy γ_S^D . The two most common models for the determination of the dispersive surface energy were proposed by Schultz and Lavielle (Eq.3) and Dorris and Gray (Eq.4).

$$2 \cdot N \cdot a_L \cdot \sqrt{\gamma_S^D \cdot \gamma_L^D} + C = RT \cdot lnV_g \quad (3)$$

$$\gamma_S^D = \left(\frac{1}{4\gamma_{CH2}}\right) \cdot \left(\frac{-R \cdot T_c \cdot ln\frac{V_{g,n+1}}{V_{g,n}}}{N \cdot a_{CH2}}\right)^2 \quad (4)$$

Specific properties, described by K_A and K_D parameters, characterize surface ability to acid (acceptor of electrons) and basic (donor of electrons) interactions, accordingly and can be calculated at the base of equation:

$$\frac{\Delta G_{sp}}{AN^*} = K_A \cdot \frac{DN}{AN^*} + K_D \quad (5)$$

$$\Delta G_{sp} = RT \cdot ln\left(\frac{V_g}{V_{g,ref}}\right) \quad (6)$$

where: ΔG_{sp} is the specific component of free energy of adsorption of polar test solute; *DN* is the donor number of the polar test solute; *AN** is the acceptor number of the polar test solute.

Next group of properties evaluated by IGC are bulk properties. IGC can be used to probe phase transition where a change of properties occurs. All of them depend on the temperature of experiments. Above the glass transition temperature (T_g) of material, we can measure/determine bulk absorption properties.

First of all by using IGC we can determine the T_g, and then it is possible to estimate solubility δ_2 and Flory Huggins χ_{12}^{∞} or $\chi_{23}^{'}$ parameters. T_g can be determined from retention diagram – which is a plot of relationship of V_g from reciprocal of temperature. The minimum retention curve is observed as a T_g [5, 8-9].

The solubility parameter (Eq.7) reflects van der Waals interactions between molecules, forming a liquid.

$$\delta_1 = \sqrt{c.e.d.} = \sqrt{\frac{E_1^{coh}}{V_1}} = \sqrt{\frac{\Delta H - R \cdot T}{V_1}} \quad (7)$$

where δ_1 is the solubility parameter, E_1^{coh} is the cohesive energy, V_1 - the molar volume of a pure

liquid, *R* - the gas constant, *T* - the temperature.

For the polymeric materials we can use Hansen solubility equation:

$$\delta_T^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (8)$$

where each component corresponds to different interactions (dispersive, polar or hydrogen bonding) estimated from the slope of equation:

$$\frac{\delta_1^2}{RT} - \frac{\chi_{12}^{\infty}}{V_1^o} = \frac{2\delta_2}{RT} \cdot \delta_1 - \left(\frac{\delta_2^2}{RT} + \frac{\chi_s^{\infty}}{V_1^o}\right) \quad (9)$$

It is straight line equation. The left hand side contains the values of Flory-Huggins interaction parameter the test solute (see Eq.10), solubility parameter of test solute (δ_1) and its molar volume. Plotting the left hand side of such equation versus solubility parameter of test solute (δ_1) one obtains the slope ($a = 2\delta_2/RT$) enabling the calculation of the solubility parameter of the examined material (δ_2).

Flory-Huggins interaction parameter (χ) as an important factor of miscibility of polymer blends and solutions has been determined by a number of methods (e.g. SANS, DSC, IGC). It reflects interaction between low-molecular-weight solvent and high-molecular-weight polymer, and it has been considered as a Gibbs free energy parameter. At infinite dilution of the probe and for high molecular weight of the stationary phase the Flory-Huggins interaction parameter can be determined from:

$$\chi_{12}^{\infty} = \ln\left(\frac{273{,}15 \cdot R}{p_1^0 \cdot V_g \cdot M_1}\right) - \frac{p_1^0}{RT}(B_{11} - V_1^0) + ln\left(\frac{\rho_1}{\rho_2}\right) - 1 \quad (10)$$

where: *1* denotes the solute and *2* denotes examined material, M_1 is the molecular weight of the solute, p_1^0 is the saturated vapor pressure of the solute, B_{11} is the second virial coefficient of the solute, $V_1^0$is the molar volume, ρ_i is the density, *R* is the gas constant.

For multicomponent materials Flory-Huggins interaction parameter $\chi_{23}^{'}$ describes interaction of probe components (between first and second component of material) [5, 8, 10, 11]:

$$\chi_{23}^{'} = \frac{1}{\varphi_2 \cdot \varphi_3} \cdot (\chi_{12}^{\infty} \cdot \varphi_2 + \chi_{13}^{\infty} \cdot \varphi_3 - \chi_{1m}^{\infty}) \quad (11)$$

where φ_2 and φ_3 are the volume fractions of appropriate component "2" or "3".

Zhao and Choi calculated Flory-Huggins χ_{12}^{∞} and $\chi_{23}^{'}$ parameters for the blend, using instead of a molar volume of the polymer, so-called reference volume $V_2 = V_o$ (polymer segment volume) [8].

2. Methods and Materials

Pharmaceutical materials were composed with the use of ibuprofen as a model drug and hybrid inorganic-polymeric drug carriers. We prepared hybrid materials and mixed them with IBU (Polpharma - PL). PEG 10,000 (Sigma-Aldrich – MERCK - DE) was a polymeric component and Aerosil® R816 (AR 816), hydrophobic surface modified fumed silica, or Aerosil® 200V (AR 200), hydrophilic fumed silica were inorganic fillers (both from Evonik Industries - DE). All investigated materials – prepared samples were collected in table 1.

Table 1 Materials – prepared samples and sample names.

Materials (probes)	Samplenames
Ibuprofen	IBU
PEG 10,000	PEG
Aerosil® 200V	AR 200
Aerosil® R816	AR 816
Aerosil® 200V + PEG (200+100)	AR200-PEG
Aerosil® R816 + PEG (200+100)	AR816-PEG
IBU + Aerosil® 200V + PEG (200+200+100)	IBU-AR200-PEG
IBU + Aerosil® R816 + PEG (200+200+100)	IBU-AR816-PEG

Hybrids systems were created in two stages. In first active agent (IBU) was mixed with silica (AR) in ethanol and evaporated. In second stage the product was covered by polymer layer (PEG). Complex systems contained individual specimens in different ratios.

In IGC experiments used test solutes were: hexane -

purity 99% (Chempur), heptane - purity 99% (Sigma Aldrich), octane - 99% (Fluka), nonane - purity 99% (Acros Organics), chloroform - analytically pure (POCH S.A.), ethanol - purity 99% (POCH S.A.), 1,4-dioxane - purity 99% (Fluka), acetonitrile - analytically pure (POCH S.A.), ethyl acetate - purity HPLC (POCH S.A.).

IGC measurements were carried out by using SEA-IGC SMS Ltd. gas chromatograph equipped with a flame-ionization detector (FID). Chromatographic columns were from glass, I.D. 3 mm, length 30 cm. The injector was heated at 150 ℃ and FID detector at 150 ℃ and 37 ℃ column. Dry helium was used as carrier gas with a flow-rate of 15 ml/min. The investigated materials were mixed homogeneously with the glass beads. Measurements were carried out at infinite dilution which means that very small amount of test compounds was injected onto the chromatographic column with examined material. All columns were conditioned overnight at the flow-rate and temperature used later during IGC experiments.

FT-IR spectra were obtained on a JASCO 4600LE spectrophotometer and spectra was recorded in the frequency range 400–4000 cm^{-1}. The KBr discs (2 mg sample in 250 mg KBr) of different samples were prepared.

In vitro drug release studies from tablets were performed in 200 ml of phosphate buffer (pH 7.4) maintained at 37 ℃ and continuous stirring at Magnetic Stirrer (150 rpm). Tablets were prepared by pressing the mass of sample equivalent to 200 mg of IBU under pressure (5 MPa). Measurements of active medium concentration were done in triplicate, in predetermined time intervals, i.e. 5 min, 15 min, 30 min, 1 h, 2 h. Each time 5 ml of sample was collected by syringe with a 0.45 m filter. To assure constant volume of dissolution medium the collected samples were replaced with 5 ml of fresh buffer. The quantity of the released drug was measured using UV/VIS is spectrophotometer (V-630 spectrophotometer, Jasco) at 264 nm.

3. Results and Discussions

3.1 FTIR Results

To investigate the possible chemical interaction between drug and excipient FTIR spectra were obtained (Figs 1-6).

There are characteristic group bandwidths:

- 3500–3400 cm^{-1} band attributed to the OH group from the silica;
- 2977–2866 cm^{-1} bands that correspond to methylene and methyl groups;
- an intense band at 1742–1707 cm^{-1} representing the carbonyl vibration band;
- 1400 cm^{-1} coming from PEG O-H bending in-plane;
- 1300–1100 cm^{-1} band corresponding to the Si-O-Si bonding.

The formation of hydrogen bond may be observed in the spectra obtained for multicomponent probes as the move of band groups to lower frequencies, and change in intensity of the bands.

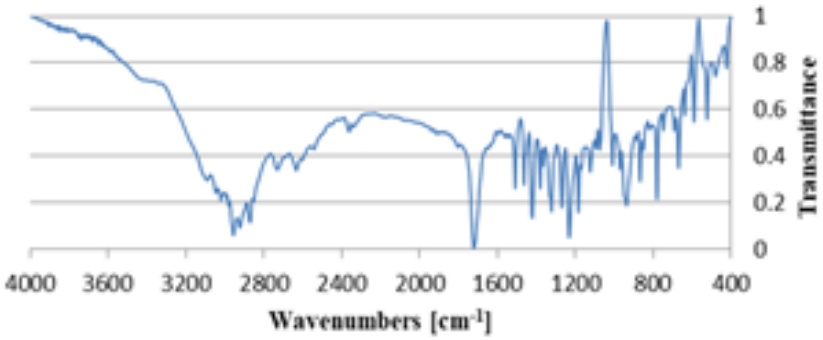

Fig. 1 FTIR spectrum for ibuprofen (KBr disk).

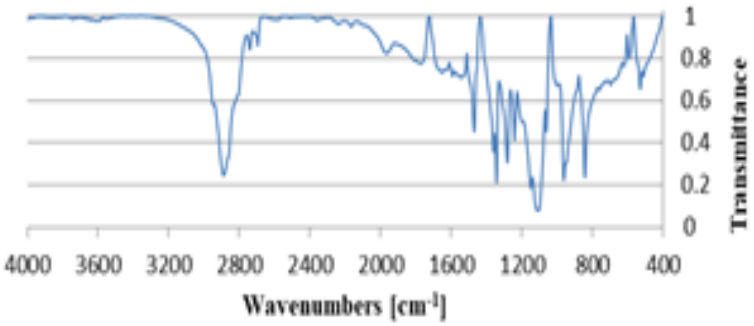

Fig. 2 FTIR spectrum for polyethylene glycol (KBr disk).

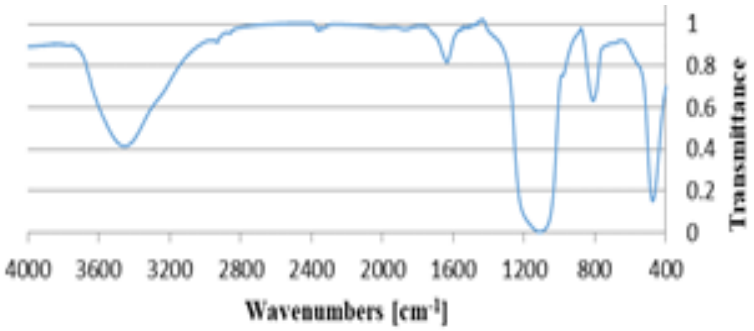

Fig. 3 FTIR spectrum for Aerosil R816 (KBr disk).

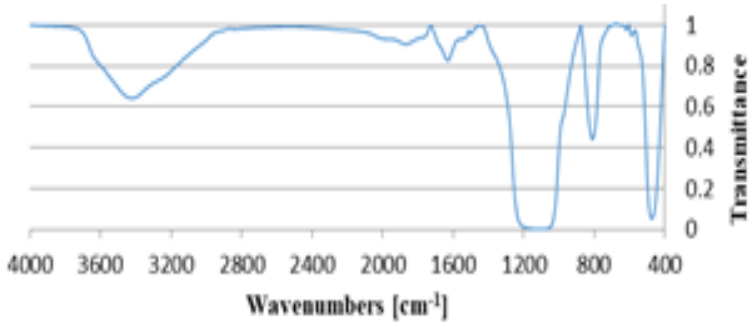

Fig. 4 FTIR spectrum for Aerosil 200V (KBr disk).

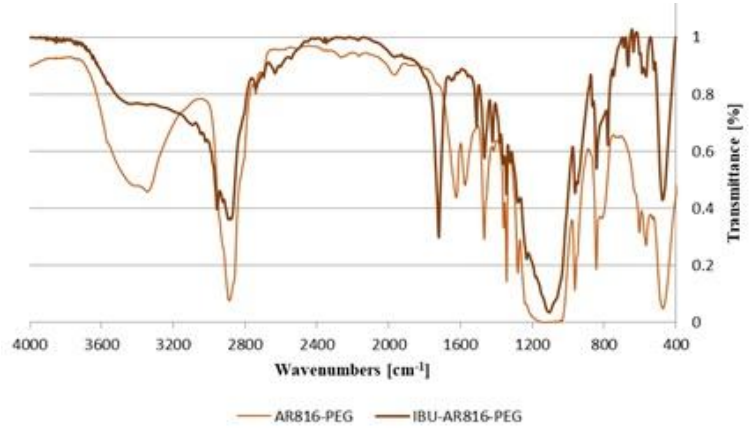

Fig. 5 FTIR spectra for Aerosil R816 compositions (KBr disk).

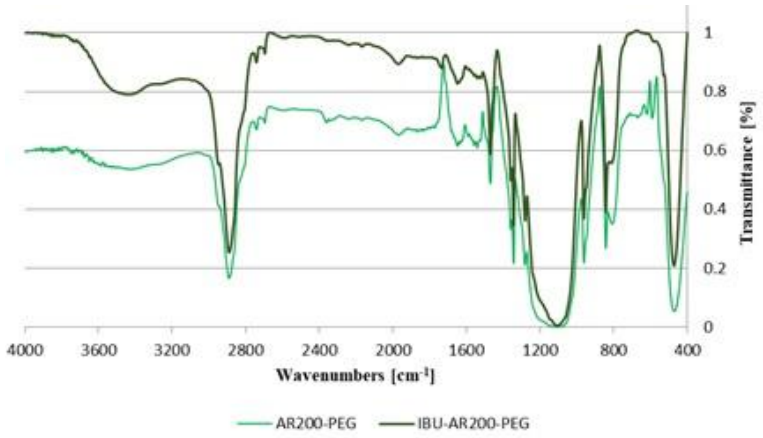

Fig. 6 FTIR spectra for Aerosil 200A compositions (KBr disk).

3.2 UV Results

Results from the UV were presented as a drug release profiles. Graphs (Figs 7-9) showed that Ibuprofen releases slightly faster from carrier composed with AR816 than with AR200. Both materials are good for controlling of the drug release.

3.3 IGC Results

Values of dispersive components of the surface free energy (γ_S^D) of the examined materials were presented in table 2.

Almost all of the examined materials have comparable values of γ_S^D ranged from 30 to 40 mJ/m^2, which is typical for materials of average activity. In the ternary hybrid materials values of γ_S^D are usually lower than for its single component, but in this study there were still in the range of average activity. It is probably caused by formation of hydrogen bonding between the active agent and the material.

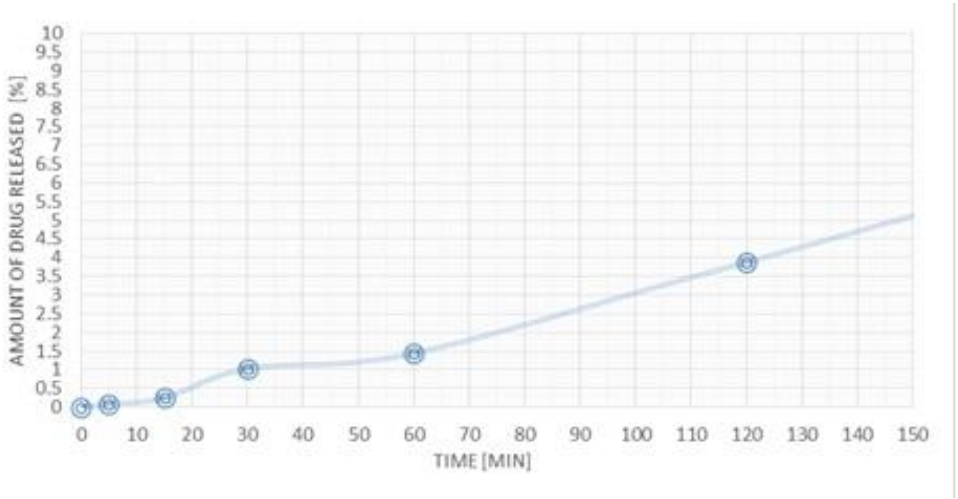

Fig. 7 Drug release profile for IBU-AR816-PEG composition.

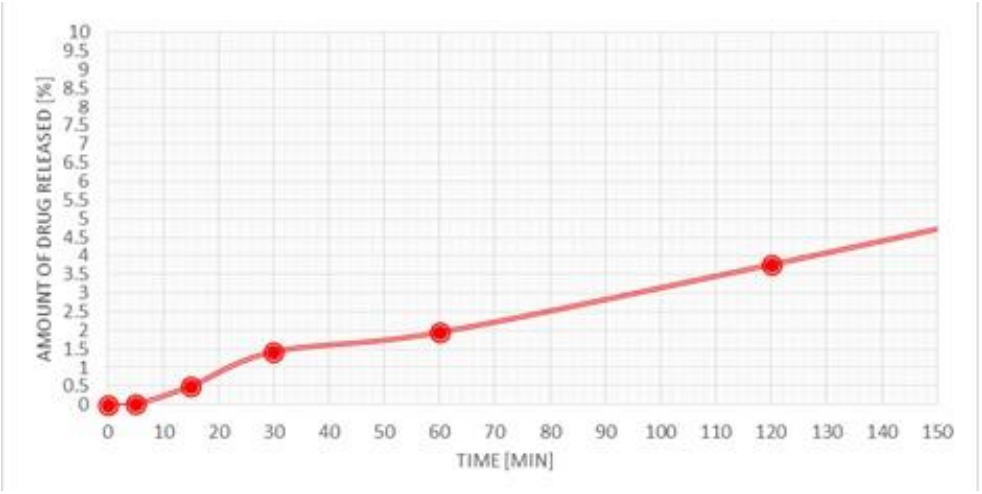

Fig. 8 Drug release profile for IBU-AR200-PEG composition.

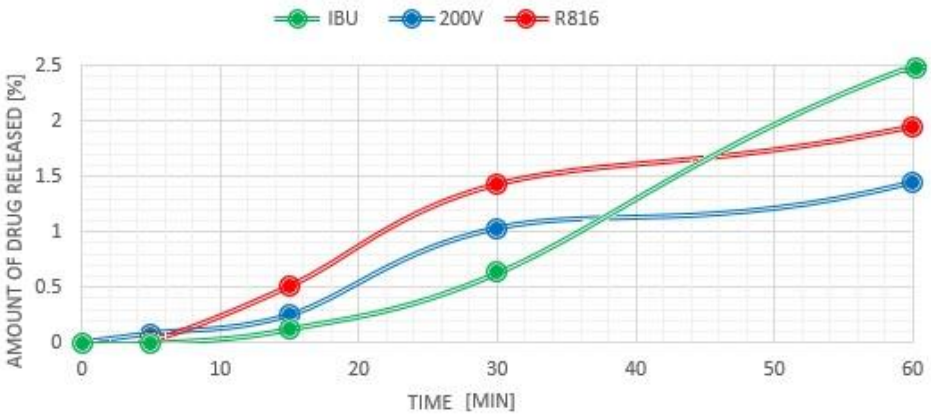

Fig. 9 Comparison of drug release profile for all probes in 60 minutes.

Table 2 Values of dispersive component of surface free energy γ_S^D.

Material	γ_S^D [mJ/m^2]	
	Dorris-Gray method	Schultz-Lavielle method
IBU	40.3	37.3
PEG	40.6	39.0
AR200	32.7	30.8
AR816	35.5	29.2
AR200-PEG	23.5	21.9
AR816-PEG	37.8	34.2
IBU-AR200-PEG	36.2	33.9
IBU-AR816-PEG	36.8	33.9

The surface properties of fillers (silica in this case) arise also from the ability to specific interactions resulting from the presence of polar functional groups on the surface of the material. Parameters K_A and K_D were applied for characterization of the acidity and basicity of the surface layer of hybrid materials. Values of these parameters were presented in Fig 10. Fumed silica exhibits a strong acceptor character due to the presence of silanol groups on the surface. Addition of the IBU causes a decrease of specific interactions between the test solutes and the IBU surface.

The strength of interactions between drug (IBU) and excipient (AR-PEG) was presented as Flory-Huggins χ'_{23} parameter. Value of this parameter depended on the type of test solute being used in IGC experiments. This dependence is connected with the non-ideality of interactions of the test solute with the components of examined mixture.

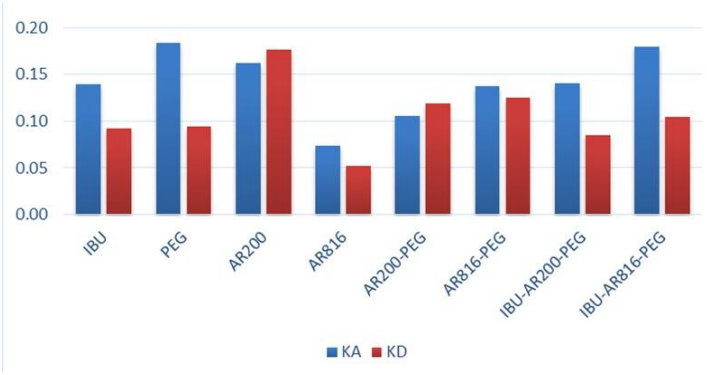

Fig. 10 Values of K_A and K_D parameters.

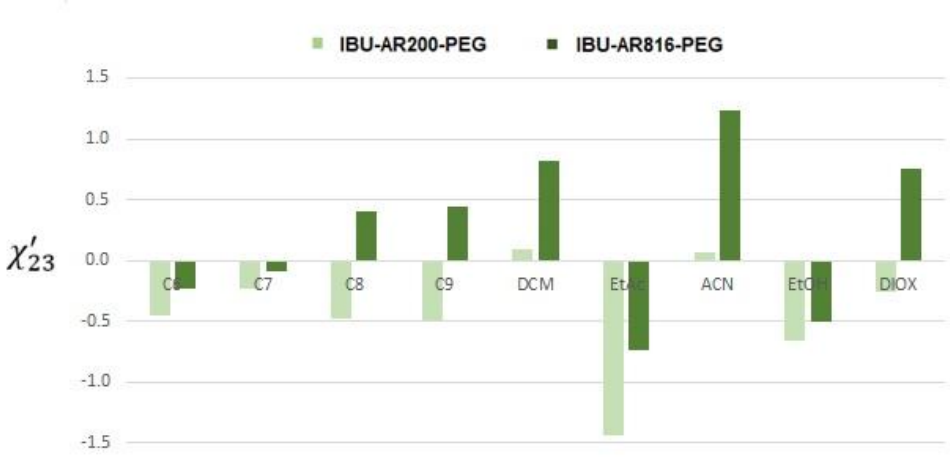

Fig. 11 Values of Flory-Huggins χ'_{23} parameter for drug-composition systems.

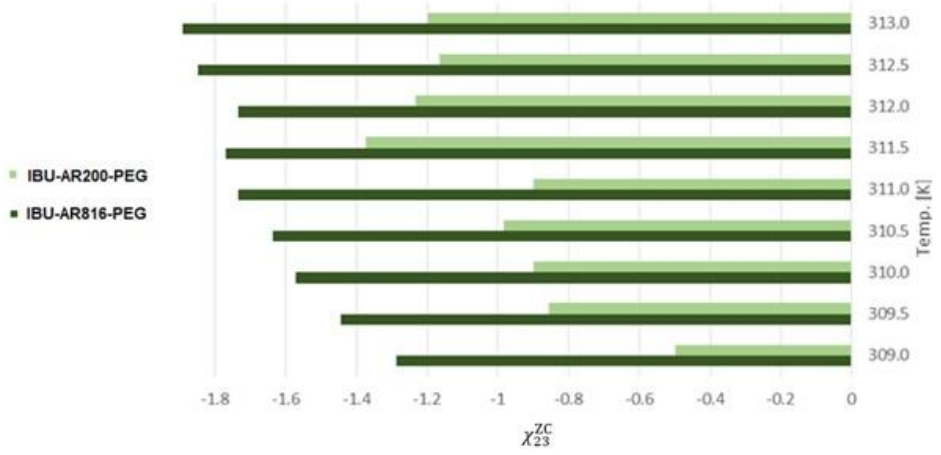

Fig. 12 Values of Flory-Huggins χ^{ZC}_{23} parameter for drug-composition systems.

You can see two graphs with the results obtained for investigated materials - calculated from classical (Fig. 11) and Zhao-Choi procedures [8] (Fig. 12). The first graph represent values for all used test solutes at temperature 37 ℃ and the second – illustrate the temperature dependence of the χ'_{23} parameter. The strength of interactions between drug (IBU) and excipient (AR-PEG) is higher for composites with

AR816.

4. Conclusions

The FTIR spectroscopy was used to investigate the possible chemical interaction between the drug and excipient. The bands characteristic for groups of the hybrid material can be expected to change after the incorporation of the active substance e.g., due to the formation of hydrogen bonds resulting in a shift of the bands of the respective groups. Hydrogen bonds were formed after incorporation of IBU resulting in a shift of the bands of proton donor group -OH as well as less visible bands of proton acceptor group -C=O.

The type of silica (hydrophilic vs. hydrophobic fumed silica) did not have significant influence on the IBU release (UV).

IGC method is a useful tool for estimation of the magnitude of interactions between the components of hybrid materials. Obtained values of γ_S^D, K_A, K_D and/or χ_{23}' values were used for preselection of the matrix material for a given API. Surface parameters might be used to monitor the changes of the properties caused by modification and to correlate with the amount and rate of drug release.

In this work, optimal hybrid material – drug interactions seemed to appear when the values of Flory-Huggins parameter were close to zero. In such case, IBU release remained gradual for a few hours with no significant burst effect.

Acknowledgments

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Disclosures of Interest

All authors are in agreement with the contents of article does not cause a conflict of interests in any of the areas of research.

References

[1] Fleming, I.., and Williams, D., 2019. *Spectroscopic Methods in Organic Chemistry*, 7th Edition: Springer, Print ISBN: 978-3-030-18251-9.

[2] Kołodziejek, J., Główka, E., Hyla, K., et al. 2013. "Relationship Between Surface Properties Determined by Inverse Gas Chromatography and Ibuprofen Release from Hybrid Materials Based on Fumed Silica." *International Journal of Pharmaceutics* 441 (1-2): 441-448.

[3] Lloyd, D. R., Ward, T., Schreiber, H., & Pizaña, C. C. 1989. "Inverse Gas Chromatography. Characterization of Polymers and Other Materials." In the ACS Symposium Series, DOI: 10.1021/bk-1989-0391.

[4] Milczewska, K., and Voelkel, A. 2008. "The Use of Flory-Huggins Parameters in Characterization of Polymer-Filler Compositions." *Journal of Applied Polymer Science* 107 (5): 2877-2882.

[5] Voelkel, A., Strzemiecka, B., Adamska, K., and Milczewska, K., 2009. "Inverse Gas Chromatography as a Source of Physiochemical Data." *J Chromatogr A* 1216 (10): 1551-66.

[6] Belgacem, M. N., and Gandini, A. 1999. "IGC as a Tool to Characterize Dispersive and Acid-base Properties of the Surface of Fibers and Powders." In: Pefferkorn, E. (Ed.), Interfacial Phenomena in Chromatography. Chap. 2, Marcel Dekker Inc., New York, pp. 42-85.

[7] Strzemiecka, B., and Voelkel, A. 2012. "Estimation of the Work of Adhesion by Means of Inverse Gas Chromatography for Polymer Complex Systems." *International Journal of Adhesion and Adhesives* 38: 84-88.

[8] Zhao, L., and Choi, P. 2002. "Measurement of Solvent-independent Polymer–polymer Flory–Huggins Interaction Parameters with the Use of Non-random Partitioning Solvents in Inverse Gas Chromatography." *Polymer* 43 (25): 6677-6681.

[9] Al-Saigh, Z. Y. 1997. "Review: Inverse Gas Chromatography for the Characterization of Polymer Blends." *Int J Polym Anal Charact* 3: 249-291.

[10] Huang, J-C. 2003. "Determination of Polymer–polymer Interaction Parameters Using Inverse Gas Chromatography" *J Appl Polym Sci* 90 (3): 671-680.

[11] Milczewska, K., Voelkel, A., and Pędzia, K. 2014. "Interactions in PEG/Aerosil® and PLA/Aerosil® Composites Described by IGC-determined Flory-Huggins χ_{23} Parameter." *J Polym Res* 21: 394-400.