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Surface modified poly (butyl cyanoacrylate) nanoparticles loaded with indomethacin: preparation and physicochemical characterization

V. Staneva[1], G. Ivanova[2], M. Simeonova[1*]

[1]*University of Chemical Technology and Metallurgy, Department of Polymer Engineering, 1756 Sofia, Bulgaria;*
[2]*REQUIMTE, Departamento de Quıımica, Faculdade de Ciěncias, Universidade do Porto, 4169-007 Porto, Portugal*

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Poly(butylcyanoacrylate) nanoparticles (PBCN) as biodegradable and biocompatible devices have gained interest as a colloidal drug delivery system. Their main technological advantage is the possibility of preparation by anionic polymerization in aqueous medium without addition of any initiator that could have undesirable side effects. Unfortunately, in such conditions arises a problem with the encapsulation of poorly water-soluble drugs.

Aiming to overcome this problem the modifying ability of hydroxypropyl-beta-cyclodextrin (HPBCD) in the preparation of PBCN loaded with indomethacin was investigated. Surface modified HPBCD-PBCN were prepared by anionic polymerization of the monomer in the presence of HPBCD. The loading of indomethacin was performed simultaneously with the formation of nanoparticles.

The physicochemical characterization of indomethacin loaded HPBCD-PBCN was made by Dynamic Light Scattering, laser Doppler electrophoresis, Infra Red and NMR spectroscopy. All of these verify the presence of the drug into the polymer matrix of nanoparticles.

Key words: *Poly(butylcyanoacrylate) nanoparticles, hydroxypropyl-β-cyclodextrin, indomethacin, drug delivery, NMR.*

INTRODUCTION

Indomethacin (Ind) (Fig 1), a non-steroidal anti-inflammatory drug is widely used in the treatment of arthritic diseases to reduce inflammation, pain and fever [1]. However it is well known to cause side effects including gastrointestinal disturbances. This can be avoided by delivering the drug to the targeted site of the body [2,3]. Indomethacin is poorly water-soluble drug and shows low bioavailability, but encapsulation of the drug within biodegradable polymer nanoparticles can increase its bioavailability.

Different types of polymer nanoparticles [4-7] were used as carriers for Ind aiming to improve its bioavailability and undesirable side effects. Complexes of soluble cyclodextrins and their derivatives with Ind were also prepared for improving drug bioavailability [8,9]. Different types of cyclodextrins are used in the preparation of poly(alkylcyanoacrylate) (PACA) nanoparticles, loaded with various poorly water-soluble drugs. The loading capacity of nanoparticles for poorly water soluble drugs is significantly increased as shown on a series of steroids and on saquinavir [10]. Hydroxypropyl-beta-cyclodextrin/Flurbiprofen (HPBCD/FP) inclusion complex was used for preparation of HPBCD/FP/PACA nanoparticles for improving the oral bioavailability of FP [11].

The aim of the present study was the preparation of hydroxypropyl-beta-cyclodextrin modified poly(butylcyanoacrylate) nanoparticles (PBCN) loaded with Ind and their physicochemical characterization.

EXPERIMENTAL

2.1. Materials

n-Butyl-2-cyanoacrylate (n-BCA) monomer was purchased from Specialty Polymers Ltd, Bulgaria. Hydroxypropyl-β-cyclodextrin, 97% was from ACRŌS ORGANICS (Belgium) and citric acid as monohydrate was from Auldrich. Indomethacin (Reagecon, Ireland) was a gift from Sopharma Ltd. Other chemicals were of laboratory grade purity and used as obtained.

2.2. Methods

2.2.1. Preparation of unloaded HPBCD modified poly(butylcyanoacrylate) nanoparticles (HPBCD-PBCN). HPBCD modified poly(butylcyanoacrylate) nanoparticles were prepared by an *in situ* anionic dispersion polymerization. Basically, the monomer, n-BCA

To whom correspondence should be sent.
E-mail: msimeonova@uctm.edu

(20 mg/ml) was instilled into aqueous polymerization medium, containing citric acid (2 mg/ml) and HPBCD (5 mg/ml) serving as

at room temperature with continuous magnetic stirring for 6 hours. The formed polymer suspension of nanoparticles was then adjusted to pH 7 by 1N sodium hydroxide.

2.2.2. Preparation of Indomethacin-loaded nanoparticles (HPBCD-PBCN-Ind). Nanoparticles-loading of Ind was accomplished during the interfacial polymerization simultaneously with formation of nanoparticles. Powdered Ind was dissolved (0.4 mg/ml) in 2 ml of acetone and the monomer was added to this organic phase. Then this organic phase was carefully added to the aqueous solution of HPBCD (5 mg/ml) and the polymerization was carried out under the same experimental conditions as the unloaded nanoparticles.

2.2.3. Photon Correlation Spectroscopy. The mean (hydrodynamic) diameters of unloaded and Ind-loaded nanoparticles were determined by photon correlation spectroscopy (PCS). The dynamic light scattering measurements were performed on a Zetasizer Nano ZS (Malvern Instruments, Malvern UK) using a detection angle of 173º at a temperature of 25ºC. Zeta-potential (ξ-potential) was measured by laser Doppler electrophoresis on the same apparatus using a detection angle of 17º of the scattered light at above temperature (25ºC). The analyzed samples were appropriately diluted with deionized water.

2.2.4. Fourier Transform Infrared Spectroscopy characterization. Fourier Transform Infrared (FTIR) spectroscopy was used as a preliminary tool to verify the presence of Ind into polymer matrix of HPBCD-PBCN. FTIR spectra of the nanoparticles both unloaded and Ind-loaded as well as of Ind were recorded in KBr pellets on a Varian Resolutions Pro spectrometer with resolution of 2 cm^{-1} over the range 4000–400 cm^{-1}.

Samples of the analyzed polymer suspensions were filtered over a 0.1 μm pore sized Cellulose nitrate membrane (Whatman, England) and the isolated wet nanoparticles were dried and used for characterization by FTIR and NMR spectroscopy.

2.2.5. NMR Spectroscopy. All NMR experiments were recorded on a Bruker Avance III 400 spectrometer, operating at 400.15 MHz for protons, equipped with pulse gradient units, capable of producing magnetic field pulsed gradients in the z-direction of 56 G/cm. The NMR spectra were acquired in DMSO-d_6 as a solvent at a temperature of 30°C. NMR spectra of Ind, HPBCD, HPCBD-PBCN, HPBCD-PBCN-Ind and physical mixture of acidifying agent and steric colloidal stabilizer, respectively. Polymerization was carried out

HPBCD-PBCN and Ind were measured. The solvent resonance peak at 2.49 ppm was used as a chemical shift reference in ^{1}H NMR spectra. ^{1}H NMR experiments were acquired with relaxation delay 1.5 s, 128 or more transients of a spectral width of 4000 Hz were collected into 64 K time domain points.

Two-dimensional ^{1}H/^{1}H correlation spectra (COSY) and gradient-selected ^{1}H/^{13}C heteronuclear single quantum coherence (HSQC) spectra were recorded using the standard Bruker software. 2D-COSY spectra were acquired with a multiple quantum filter, gradient pulses for selection, a gradient ratio of 16:12:40 and a relaxation delay of 1.5 s. A total of 2048 data points in F2 and 256 data points in F1 over a spectral width of 5000 Hz were collected. ^{1}H/^{13}C HSQC experiments (Bruker pulse program hsqcedetgpsisp2.2) [12-15] recorded in phase sensitive mode using echo/antiecho-TPPI gradient selection, with decoupling during acquisition time and multiplicity editing during selection were carried out with a spectral width of 6000 Hz for ^{1}H and 20000 Hz for ^{13}C, relaxation delay 1.5 s, Fourier transform (FT) size 2 K × 1K.

The two dimensional Nuclear Overhauser effect (NOE) spectroscopy (NOESY, ROESY) experiments were acquired in phase sensitive mode with gradient pulses in the mixing time, using the standard pulse sequences with optimized mixing time in the range between 200 and 800 ms. Generally, 64 scans and 512 F1 slices were obtained and the spectral width in both dimensions was 8000 Hz.

The Diffusion-ordered NMR (DOSY) experiments were acquired employing Bruker 2D pulse sequence (dstebpgp3s) with double stimulated echo for convection compensation and LED (Longitudinal Eddy Delay) using bipolar gradient pulses for diffusion [16,17] The experimental conditions (amount of the solute and the solvent, temperature, air flow, no sample rotation) for all DOSY experiments were kept constant. Before all NMR experiments, the temperature was equilibrated and maintained at 30°C, as measured using the spectrometer thermocouple system. All measurements were carried out in DMSO-d_6 and the diffusion coefficient of the residual water in DMSO-d_6 (1.2×10^{-9} m^2s^{-1}, calculated standard deviation of 1.4×10^{-3}) was used as an internal reference for the diffusion measurements. The spectra were recorded in 5 mm NMR tubes with an air flow of 535 l/h. Typically, in each experiment a

number of 16 spectra of 16K data points were collected, with values for the duration of the magnetic field pulse gradients (δ) of 3 for Ind and 3.6 ms for the rest of the samples, diffusion times (Δ) of 100 or 200 ms and an eddy current delay set to 5 ms. The pulse gradient (g) was incremented from 2 to 98% of the maximum gradient strength in a linear ramp. The spectra were first processed in the F2 dimension by standard Fourier transform and after baseline correction; the diffusion dimension was processed with the Bruker Topspin software package (version 3.2). The diffusion coefficients are calculated by exponential fitting of the data belonging to individual columns of the 2D matrix. The diffusion coefficients (D) were obtained by measuring the signal intensity at more than one place in the spectra and all scaled to the D value obtained for residual water in DMSO-d_6. At least two different measurements were done for the determination of each diffusion coefficient.

The amount of Ind included into the HPBCD-PBCN-Ind was determined by quantitative NMR analysis, using the relative quantitative method [18].

2.2.6. Drug Loading Determination. The amount of Ind included into the HPBCD-PBCN-Ind was determined by quantitative NMR analysis, using the relative quantitative method [18].

RESULTS & DISCUSSION

HPBCD-PBCN were prepared by an *in situ* anionic polymerization skilled as a dispersion polymerization process since a polymeric stabilizer (HPBCD) was used instead of an emulsifier. The loading of Ind into HPBCD-PBCN was performed during the interfacial anionic polymerization because of the insolubility of Ind in water. Alkylcyanoacrylate monomers are highly predisposed to anionic polymerization proceedings by initial addition of an anion to the strongly activated carbon-carbon double bond. Because of the presence of two powerful electron-withdrawing groups (ester, -COOBu and cyano,-CN), n-BCA monomer holds a remarkable reactivity toward nucleophiles (OH, NH_2, etc.), resulting in an extremely high polymerization rate. Due to its insolubility in the continuous aqueous phase the formed polymer precipitates into a new particulate phase stabilized by the polymeric stabilizer used. The aggregation of these precipitated growing polymer chains after their length exceeds a critical value resulted in formation of nanoparticles [19].

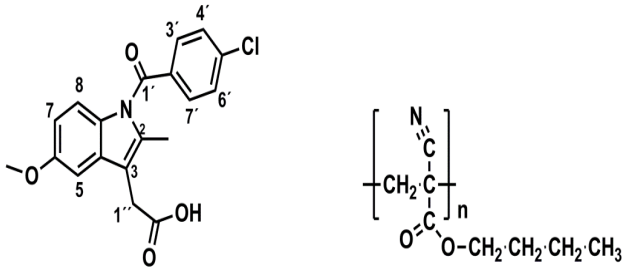

Fig.1. Chemical structure of Indomethacin (Ind) and poly(butylcyanoacrylate).

The obtained HPBCD-PBCN, unloaded and indomethacin loaded were characterized by size, size distribution, and ζ-potential, all considered as main colloid characteristics. Both nanoparticles show a narrow size distribution (polydispersity index, PDI<0.1). The mean hydrodynamic diameter of unloaded HPBCD-PBCN was 209 nm (PDI = 0.086), while those of indomethacin loaded ones was 197 nm (PDI = 0.044), (Fig. 2). A possible reason for the smaller mean diameter of Ind loaded nanoparticles could be an intermolecular interaction between the drug molecules and polymer chains leading to change in the particle compactness. Such behavior of the size of PBCN loaded with other drug molecules was described earlier [20]. The surfaces of both nanoparticles are negatively charged. The ζ-potentials of HPBCD-PBCN and HPBCD-PBCN-Ind in water were -42.3± 6.32 mV and -34.5±6.80 mV, respectively. The reduced surface negativity of Ind-loaded nanoparticles suggests that some of the drug molecules are located (adsorbed) on the nanoparticles surface.

FTIR studies were performed attempting to confirm drug inclusion into the nanoparticles. The comparative FTIR spectra of Ind, unloaded HPBCD-PBCN and drug loaded HPBCD-PBCN-Ind are present in Fig. 3.

In the FTIR spectrum of Ind (Fig. 3a), the characteristic C=O doublet at 1691.41 and 1715.14 cm^{-1}, and C-Cl band at 749.58 cm^{-1} are clearly observed (see molecular structure of Ind in Fig. 1). The FTIR spectrum of HPBCD-PBCN (Fig. 3b) shows the CH_3 at 2963.29 and 2875.96 cm^{-1}, and CH_2 at 2937.23 cm^{-1}. The characteristic CN stretching mode of the poly(butylcyanoacrylate) (see Fig. 1 for molecular structure) was observed at 2250.28 cm^{-1}. The prominent band at 1751.44 cm^{-1} corresponds to the C=O stretching mode of the polymer ester group, while the feature at 1257.75 cm^{-1} corresponds to the asymmetric C-O-C stretch. The C-CN band was observed at 1161.68 cm^{-1}. The wide OH band appears at 3463.23 cm^{-1}.

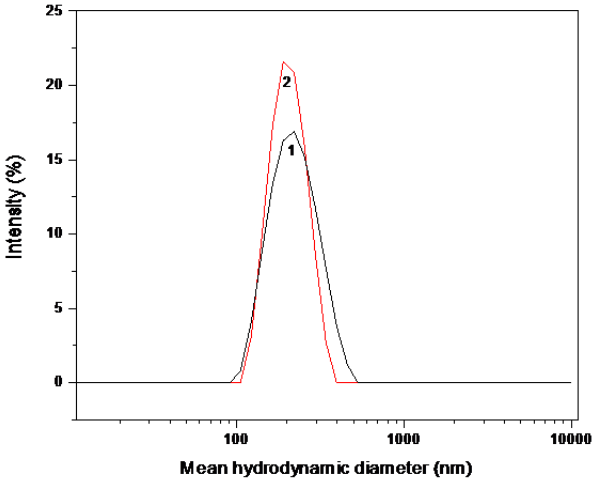

Fig. 2. Size distribution by intensity of HPBCD-PBCN (1) and HPBCD-PBCN-Ind (2)

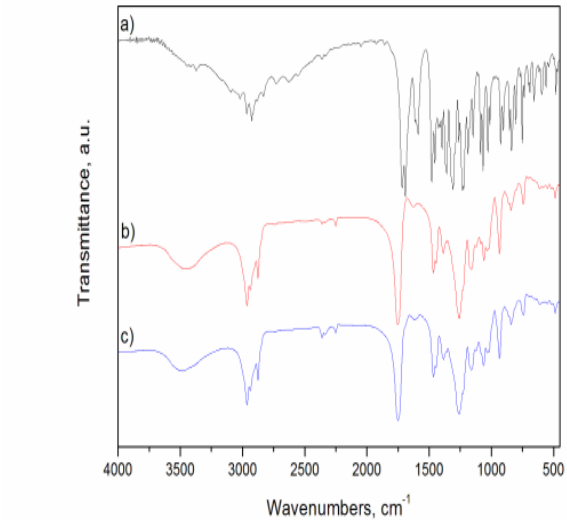

Fig. 3. FTIR spectra of Indomethacin (a), unloaded HPBCD-PBCN (b) and HPBCD-PBCN-Ind (c).

In the FTIR spectrum of HPBCD-PBCN-Ind (Fig. 3c) all characteristic bands of HPBCD-PBCN assigned to the CN stretching at 2250.20 cm^{-1}, C=O at 1750.22 cm^{-1} C-O-C at 1258.39 cm^{-1} and C-CN at 1159.97 cm^{-1} were observed. The characteristic OH band shifted significantly from 3463.23 to the 3482.41 cm^{-1} that evidenced some interactions of Ind molecules with the polymer matrix of nanoparticles.

The ability for inclusion of Ind into the polymer matrix of poly(butylcyanoacrylate) nanoparticles, prepared by an anionic polymerization of n-BCA in the presence of HPBCD was studied by proton NMR spectroscopy. The role of HPBCD in the polymerization process, the possible mechanisms of drug inclusion into the polymer matrix of HPBCD-PBCN and structural characterization of unloaded (HPBCD-PBCN) and Ind loaded (HPBCD-PBCN-Ind) nanoparticles were estimated by studying structurally important NMR parameters, such as chemical shifts, line shape and translational diffusion. For comparison, NMR spectroscopic investigations of Ind, HPBCD-PBCN and their physical mixture (HPBCD-PBCN+Ind) were carried out. The assignment of the resonance signals in ^1H NMR spectra of the samples studied was confirmed by an analysis of their $^1H/^1H$ COSY and $^1H/^{13}C$ HSQC spectra. Typical 400 MHz ^1H NMR spectra of HPBCD-PBCN, HPBCD-PBCN-Ind, Ind with assignment of the resonance signals are presented in Figure 4. The ^1H NMR spectrum of the physical mixture (HPBCD-PBCN+Ind) is included for comparison.

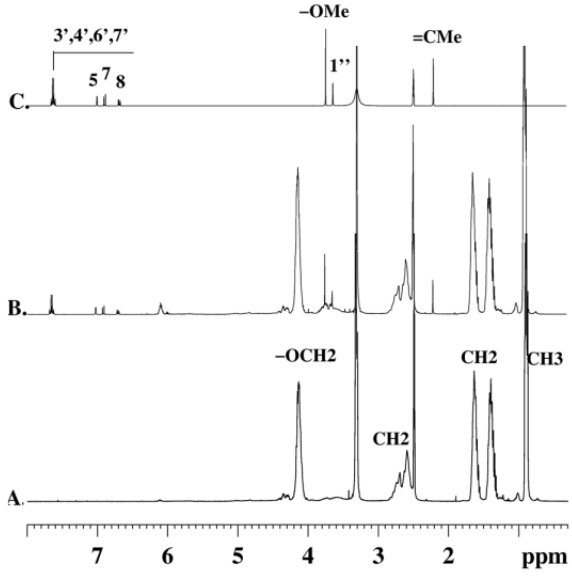

Fig. 4. 400 MHz ^1H NMR spectra of: HPBCD-PBCN (A), HPBCD-PBCN+Ind (B), HPBCD-PBCN-Ind (C) and Ind (D). The assignment of the resonance signals is included.

The ^1H NMR spectra of HPBCD-PBCN and HPBCD-PBCN-Ind are dominated by the intense resonance signals of protons belonging to poly(butylcyanoacrylate) (PBCA), i.e. resonances at 0.89 (CH_3), 1.40 (CH_2), 1.64 (CH_2), 4.14 (OCH_2) and 2.60 ppm (CH_2, main polymer chain). Weak and broad resonance signals characteristic for HPBCD at 5.1-4.8 ppm (anomeric protons), 3.9-3.4 ppm (-OCH and –OCH_2) and 1.04 ppm (CH_3) were additionally registered (Fig. 4). The line broadening of HPBCD resonance signals in ^1H NMR spectra of HPBCD-PBCN and HPBCD-PBCN-Ind reveals an interaction of HPBCD molecules with polymer chains of PBCA.

The available HPBCD hydroxyl groups could behave like an initiator in the anionic polymerization of n-BCA in aqueous medium resulting in covalently bonded to the polymer

Table 1. ^{1}H NMR chemical shifts (δ, ppm) of Ind in the presence and absence of HPBCD-PBCN

	H5	H7	H8	CCH_3	OCH_3	H3'-H7'	H1"
Ind	7.022	6.703	6.914	2.202	3.747	7.648	3.643
HPBCD-PBCN_Ind	7.024	6.705	6.915	2.207	3.751	7.651	3.647
HPBCD-PBCN+Ind	7.023	6.704	6.915	2.206	3.750	7.650	3.646

Table 2. Diffusion coefficients ($D \times 10^{10}$ (m^2s^{-1})) of Ind, HPBCD and HPBCD-PBCN in the samples studied.

Sample	Size, nm	Ind	HPBCD	HPBCD-PBCN
Ind		2.98		
HPBCD			1.38	
HPBCD-PBCN	209		1.01	1.22
HPBCD-PBCN-Ind	197	2.81	1.04	1.29
HPBCD-PBCN+Ind	209	2.92	1.02	1.21

chains HPBCD molecules. In the ^{1}H NMR spectrum of HPBCD-PBCN-Ind, resonances arising from Ind included in the polymer nanoparticles were clearly observed (Fig. 4). Relative to the sample of pure Ind, down field shifts of the resonance signals of Ind in ^{1}H NMR spectra of HPBCD-PBCN-Ind, more significant for the protons in the close proximity to the carboxyl group were registered (Table 1). These chemical shifts alterations were attributed to intermolecular interactions between Ind and HPBCD and/or polymer chains of PBCA. The NOE studies based on the analysis of the two-dimensional NOESY and ROESY spectra have shown no evidence of Ind inclusion into the cavity of HPBCD. Therefore, a presence of electrostatic or dipole-dipole interactions between the oxygen bearing functional groups of Ind, HPBCD and polymer molecules was assumed as a main contribution for the chemical shifts changes observed.

The drug content into the polymer matrix of HPBCD-PBCN was defined by quantitative NMR analysis, using the relative quantitative method according to Malz and Jancke [18]. The drug loaded HPBCD-PBCN in the scope of this investigation were considered as a two componentsystem composed by drug and polymer. The amount of Ind incorporated into HPBCD-PBCN was determined from the relative integral intensity of characteristic signals in ^{1}H NMR spectra of HPBCD-PBCN-Ind, considering the number of the contributing nuclei and molecular weights of Ind and monomer unit (n-BCA) in PBCN. The integral intensities of more than one resonance signal belonging to the individual compounds were measured. The Ind content (weight %) in HPBCD-PBCN-Ind was calculated using the following equation:

$$\text{Ind}\ (\%) = \frac{I_{Ind} \times E_{Ind}}{(I_{Ind} \times E_{Ind}) + (I_{BCA} \times E_{BCA})} \times 100 \quad (1)$$

where, **I** is the integral value for selected protons of Ind and monomer units (n-BCA), respectively; **E** is the molecular weight of the corresponding compound divided by the number of the absorbing protons. The Ind content (%) in the drug loaded HPBCD-PBCN (HPBCD-PBCN-Ind), was found to be 3.4 %.

Diffusion NMR spectroscopy (^{1}H DOSY) was further applied to confirm the Ind incorporation and location into HPBCD-PBCN. The diffusion coefficients (D) of Ind, HPBCD and poly(butylcyanoacrylate) in HPBCD-PBCN-Ind and the physical mixure HPBCD-PBCN+Ind were measured and compared with the corresponding values obtained for the free Ind, HPBCD and HPBCD-PBCN. The diffusion coefficients were obtained by measuring the signal intensity at more than one place in the spectra and all scaled to the D value obtained for residual water in DMSO-d_6. The results are presented in Table 2.

The diffusion coefficients measured for poly(butylcyanoacrylate) in the unloaded HPBCD-PBCN and the physical mixture of HPBCD-PBCN

with Ind were found to be similar but slightly lower than the corresponding value in the drug loaded HPBCD-PBCN (HPBCD-PBCN-Ind). The results are relevant to the smaller nanoparticales size determined for the drug loaded formulation (HPBCD-PBCN-Ind). The observed decrease of HPBCD diffusion in HPBCD-PBCN, HPBCD-PBCN-Ind and HPBCD-PBCN+Ind samples was attributed to the participation of molecules in the polymerization process of n-BCA most probably as an initiator and direct bonding of HPBCD molecules to the polymer chains of PBCA. The reduction of Ind diffusion in the polymer matrix of HPBCD-PBCN was found to be more significant when the drug was present in the polymerization medium through the process of polymer nanoparticles formation (HPBCD-PBCN-Ind). These results reveal the existence of association processes or/and intermolecular interactions between drug molecules and polymer matrix of HPBCD-PBCN. The diffusion behavior of Ind could be interpreted as a fast exchange between two sites, i.e. bound to the polymer and free (physically entrapped) in the polymer matrix of HPBCD-PBCN drug molecules [21,22]. In this case, the observed diffusion coefficients (D) are weighted-average values between the free and bound drug species and if we consider fast exchange between these two states, the mole fractions of the free or physically entrapped and bound drug molecules could be calculated using the following equation:

$$D = f_{free}D_{free} + f_{bound}D_{bound} \quad (2)$$

where **f** and **D** denote the molecular fractions and diffusion coefficients of the free and bound drug molecule and $f_{free} + f_{bound} = 1$. The fractions of the bound Ind in HPBCD-PBCN-Ind and HPBCD-PBCN+Ind were estimated using the diffusion coefficient of the free Ind (D_{free}) measured separately and assuming the diffusion coefficient of the bound drug molecules (D_{bound}) to be equal to that of the HPBCD-PBCN in the sample. The fraction of the bound Ind was found to be 10 and 3% from the total found (presenting) drug in the systems for HPBCD-PBCN-Ind and the physical mixture HPBCD-PBCN+Ind, respectively. The results suggest an inclusion of Ind in the polymer matrix of HPBCD-PBCN-Ind and existence of strong drug-polymer interactions. The low fraction of bound Ind in HPBCD-PBCN+Ind indicates weak drug-polymer interactions and drug molecules predominantly adsorbed on the surface of these NP was assumed.

4. CONCLUSIONS

The results of NMR analyses suggest an inclusion of Ind in the polymer matrix of HPBCD-PBCN-Ind and existence of strong drug-polymer interactions but no inclusion in the hydrophobic cavity of HPBCD. But the Ind content (%) in the drug loaded nanoparticles was found to be low (3.4 %). The presence of Ind molecules decreases the surface negativity (ζ-potential) of the formed drug-loaded nanoparticles supporting the contribution of Ind in the composition of nanoparticles. The FTIR study also evidenced some interactions of Ind molecules with the polymer matrix of nanoparticles.

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REFERENCES

1. N. Chieng, J. Aaltonen, D. Saville, T. Rades, *Eur. J. Pharm. Biopharm.*, **71**, 47 (2009).
2. A. K. Jain, *Eur. J. Pharm. Biopharm.*, **68**, 701 (2008).
3. T. S. Anirudhan, D. Dilu, S. Sandeep, *J. Magn. Magn. Mater*., **343**, 149 (2013).
4. K. Bury, F. D. Prez, D. Neugebauer, *Macromol. Biosci.*, **13**, 1520 (2013).
5. K. Tomoda, H. Terashima, K. Suzuki, T. Inagi, H. Terada, K. Makino, *Colloid. Surf. B Biointerfaces*, **88**, 706 (2011).
6. L. Upadhyaya, J. Singh, V. Agarwal, R. P. Tewari, *Carbohyd. Polym.*, **91**, 452 (2013).
7. A. T. S. Miyazaki, K. Wataru, *J. Pharm. Pharmaceut. Sci.*, **6,** 238 (2003).
8. S. Jambhekar, R. Casella, T. Maher, *Int. J. Pharm.*, **270**, 149 (2004).
9. P. J. Salústio, G. Feio, J. L. Figueirinhas, J. F. Pinto, H. M. C. Marques, *Eur. J. Pharm. Biopharm.*, **71**, 377 (2009).
10. D. Duchêne, G. Ponchel, *J. Incl. Phenom. Macro.*, **44**, 15 (2002).
11. X. Zhao, W. Li, Q. Luo, X. Zhang, *Eur. J. Drug Metab. Pharmacokinet.*, **39**, 61 (2014).
12. G. Bodenhausen, D. J. Ruben, *Chem. Phys. Lett.*, **69**, 185 (1980).
13. A. G. Palmer III, J. Cavanagh, P. E. Wright, M. Rance, *J. Magn. Reson.*, **93**, 151 (1991).

14. L. E. Kay, P. Keifer, T. Saarinen, *J. Am. Chem. Soc.*, **114**, 10663 (1992).

16. A. Jerschow, N. Mueller, *J. Magn. Reson. A,* **123**, 222 (1996).
17. A. Jerschow, N. Mueller, *J. Magn. Reson. A,* **125**, 372 (1997).
18. F. Malz, H. Jancke, *J. Pharm. Biomed. Anal.*, **38**, 813 (2005).
19. R. S. R. Murthy, L. H. Reddy, in: Nanotechnology for cancer therapy, M. A. Mansoor (ed), Taylor & Francis Group, LLC, New York, 2006, p. 251.
15. J. Schleucher, M. Schwendinger, M. Sattler, P. Schmidt, O. Schedletzky, S.J. Glaser, O. W. Sorensen, C. Griesinger, *J. Biomol. NMR*, **4**, 301 (1994).
20. M. Simeonova, G. Ivanova, V. Enchev, N. Markova, M. Kamburov, Ch. Petkov, A. Devery, R. O'Connor, D. Brougham, *Acta Biomaterialia* **5**, 2109 (2009).
21. K. Momot, P. Kuchel, *Concepts. Magn. Reson. A,* **19**, 51 (2003).
22. Y. Cohen, L. Avram, L. Frish, *Angew. Chem. Int. Ed.*, **44**, 520 (2005).

ПОВЪРХНОСТНО МОДИФИЦИРАНИ ПОЛИБУТИЛЦИАНАКРИЛАТНИ НАНОЧАСТИЦИ, НАТОВАРЕНИ С ИНДОМЕТАЦИН: ПОЛУЧАВАНЕ И ФИЗИКОХИМИЧНО ОХАРАКТЕРИЗИРАНЕ

В. Станева[1], Г. Иванова[2], М. Симеонова[1*]

[1]Химикотехнологичен и металургичен университет, Катедра Полимерно инженерство, 1756 София, България;
[2]Мрежа за химия и технология-асоциран научен център, Департамент по химия и биохимия, Факултет на науките, Университет на Порто, 4169-007 Порто, Португалия

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(Резюме)

Полибутилцианакрилатните наночастици (ПБЦН) като биоразградими и биосъвместими средства привличат интерес като колоидни системи за доставяне на лекарства. Основното им технологично предимство е възможността за получаване чрез анионна полимеризаци във водна среда без добавне на инициатор, който би могъл да има старнични нежелани влияния. За съжаление, при такива условия възниква проблем с енкапсулирането на слабо разтворими във вода лекарства.

С цел преодоляване на този проблем, беше изследвана модифициращата способност на хидроксипропил-β-циклодекстрин (ХПВЦД) при получаването на ПБЦН, натоварени с индометацин. Повърхностно модифицирани ХПВЦД-ПБЦН бяха получени чрез анионна полимеризация на мономера в присъствието на ХПВЦД. Натоварването на индометацина беше извършено едновременно с формирането на наночастиците.

Физикохимичното охарактеризиране на натоварените с индометацин ХПВЦД-ПВЦН е извършено чрез динамично разсейване на светлината (фотонна корелационна спектроскопия), лазер Доплерова електрофореза, инфра червена и ЯМР спектроскопия. Всички потвърждават присъствието на лекарство в полимерната матрица на наночастиците.