International Journal of Pharmaceutics 416 (2011) 160–163

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effect of storage on microstructural changes of Carbopol polymers tracked by the combination of positron annihilation lifetime spectroscopy and FT-IR spectroscopy

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ARTICLE INFO

Article history:
Received 29 May 2011
Received in revised form 15 June 2011
Accepted 17 June 2011
Available online 24 June 2011

Keywords:
Carbopol 71G
Carbopol Ultrez 10NF
Positron annihilation lifetime spectroscopy (PALS)
Fourier transformation infrared spectroscopy (FT-IR)
Water uptake

ABSTRACT

Different types of Carbopols are frequently applied excipients of various dosage forms. Depending on the supramolecular structure, their water sorption behaviour could significantly differ. The purpose of the present study was to track the supramolecular changes of two types of Carbopol polymers (Carbopol 71G and Ultrez 10NF) alone and in their physical mixture with a water-soluble drug, vitamin B_{12}, as a function of storage time. The combination of FT-IR spectroscopy, positron annihilation lifetime spectroscopy (PALS) and Doppler-broadening spectroscopy was applied to follow the effect of water uptake on the structural changes. Our results indicate that water-induced interactions between polymeric chains can be sensitively detected. This enables the prediction of stability of dosage forms in the course of storage.

1. Introduction

In the recent decades, there has been considerable interest in using Carbopol as an excipient in a diverse range of pharmaceutical applications. Carbopols are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. Depending upon the degree of cross-linking and manufacturing conditions, various grades of Carbopol are available. Each grade is having its significance for its usefulness in pharmaceutical dosage forms (Carnali and Naser, 1992; Perez-Marcos et al., 1991a,b; Guo, 1994; Berney and Deasy, 1979). Carbopol Ultrez 10NF is an interpolymer of carbomer homopolymer or copolymer that contains a block copolymer of polyethylene glycol and a long chain alkyl acid ester. The obtained polymer allows quick wetting and slow hydrating. This property helps minimize lumping, that can be problematic when turbulent mixing is not available during dispersion. Compared with traditional Carbopol polymers, Carbopol Ultrez 10NF polymer provides dispersions in water that are much lower in viscosity prior to neutralization. Carbopol 71G is a homopolymer, i.e., it is a polymer of acrylic acid cross-linked with allyl penta erythritol and polymerized in ethyl acetate. Carbopol 71G is the granular form which is available for direct compression of controlled release formulations. In the dry state, the drug is trapped in a glassy core. As the external surface of the tablet is hydrated, it also forms a gelatinous layer upon hydration; however, this gel layer is significantly different structurally from the traditional matrix tablet. The hydrogels are not entangled chains of polymer but discrete microgels made of many polymer particles, in which the drug is dispersed. The crosslink network enables the entrapment of drugs in the hydrogel domains. Because of this structure, drug dissolution rates are affected by subtle differences in rates of hydration and swelling of the individual polymer hydrogels. Dissolution rates are dependent on the molecular structure of the polymers, including crosslink density, chain entanglement, and crystallinity of the polymer matrix. The channels which form between the polymer hydrogels are influenced by the concentration of the polymer, as well as by the degree of swelling. Since Carbopol polymers are useful and versatile controlled-release additives for tablet formulations in direct compression, their structural stability is of impact from the point of the drug release stability of tablets (García-González et al., 1994). The supramolecular structure of both examined types of Carbopols is disturbed by swelling due

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doi:10.1016/j.ijpharm.2011.06.028

to hydration in the course of application and storage, consequently their free volume react very sensitively to changes. The purpose of the present study was to demonstrate the free volume changes of Carbopol polymers based on swelling alone and in their physical mixture with a water-soluble drug, vitamin B_{12}, as a function of storage time by the combination of FT-IR spectroscopy and positron annihilation lifetime spectroscopy.

2. Materials and methods

2.1. Materials

Carbopol 71G (Noveon, batch number: TW56GAJ066) Carbopol Ultrez 10NF (Lubrizol, batch number: 0100648897), B_{12} (Ph.Eur.) received from the Gedeon Richter PLC.

2.2. Storage conditions

Samples of the pure substances and their 1:1 physical mixtures were stored in closed containers at $40 \pm 2\,^{\circ}C$ and $75 \pm 5\%$ relative humidity (achieved by oversaturated NaCl solution) for 4 weeks.

2.3. Positron annihilation lifetime spectroscopy (PALS)

For positron lifetime measurements, a positron source made of carrier-free $^{22}NaCl$ was used. Its activity was around 10^5 Bq and the active material was sealed between two very thin Ti foils. Lifetime spectra were measured with a fast-fast coincidence system (MacKenzie, 1983) based on BaF_2/XP2020Q detectors and Ortec electronics. Every spectrum was recorded in 4096 channels of an analyser card and each contained 10^7 coincidence events. Several parallel spectra were measured at each concentration to increase reliability. All the lifetime spectra were evaluated individually by the RESOLUTION computer code (Kirkegaard et al., 1981); the indicated errors are the standard deviations of the lifetime parameters obtained. Three lifetime components were found in the Carbopols but only two in B_{12}, i.e., no positronium formation was observed in the drug. As our goal was to study the interactions of the drug and the carrier during storage, we needed a linear parameter to indicate any interaction. Since positronium is not formed in B_{12}, the only possibility left is the use of the average lifetime.

The average lifetime (τ_{av}) is a characteristic parameter indicating the presence of interactions between the components of the physical mixtures.

$$\tau_{av} = \sum I_i \cdot \tau_i \quad (i = 1\text{–}3) \tag{1}$$

where I_i is the intensity belonging to τ_i. If the tablet is a simple physical mixture, the average lifetime stands between the values of the constituents and indicates the exact composition of the tablet. Note that the average atomic numbers of the constituents are similar. Therefore, no significant backscatter effects are expected at grain boundaries. After that a variation of the MELT code (Shukla et al., 1993) was used to extract lifetime distributions from the spectra. These latter evaluations were used to characterize the size distribution of free volume holes in the samples through *ortho*-positronium (*o*-Ps) lifetime.

In several cases, the lifetime measurements were accompanied by Doppler-broadening measurements. For this purpose, a high-purity germanium detector (Detector Systems GmbH) was used with Tennelec electronics. The annihilation photo peak contained about 10^6 counts in each case. The energy resolution of the system was around 1.1 keV at 511 keV. The Doppler-spectra were characterized by means of the conventional *S* and *W* parameters (Süvegh et al., 1999). Roughly speaking, *S* is proportional to the number of low-momentum annihilations, and *W* to the number of high-momentum positron-electron pairs.

2.4. FT-IR spectroscopy

The ATR-FTIR spectra of the unstored and stored Carbopol powder samples were scanned over wavenumber range of 4000–300 cm^{-1} using Able Jasco FT-IR 4200 type A spectrometer with ATR Pro470H single reflection ATR accessory. 100 scans were performed at a resolution of 4 cm^{-1}.

3. Results and discussions

Fig. 1 illustrates the FT-IR spectra of Carbopol 71G as a function of storage time. Characteristic peaks could be observed in each Carbopol polymer at near to 3500 cm^{-1} which could be attributed to the presence of water in the hydrophilic polymers (Figs. 1 and 2). Characteristic peaks of Carbopol at 1710, 1171 and 1114 cm^{-1} wavenumbers were found to refer to the carbonyl group. The two

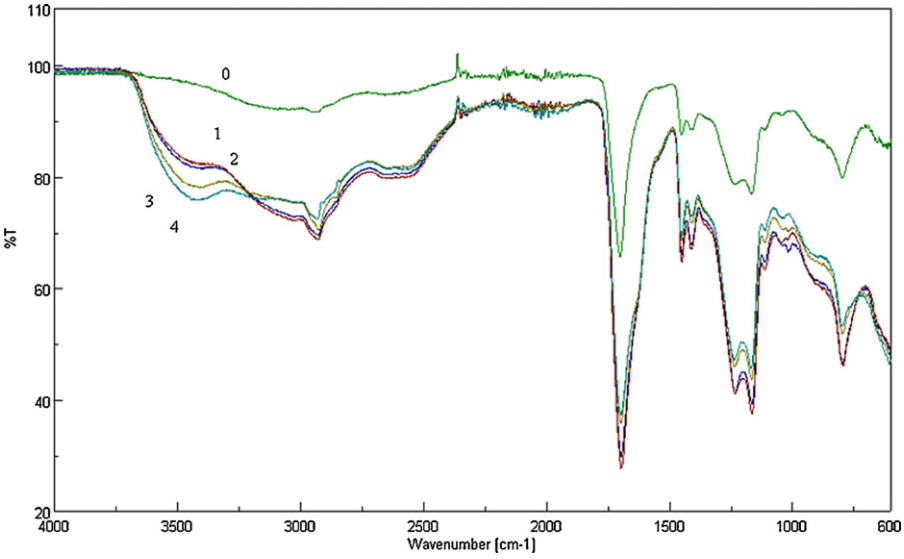

Fig. 1. FT-IR spectra of Carbopol 71G polymer after 0, 1, 2, 3, 4 weeks of storage.

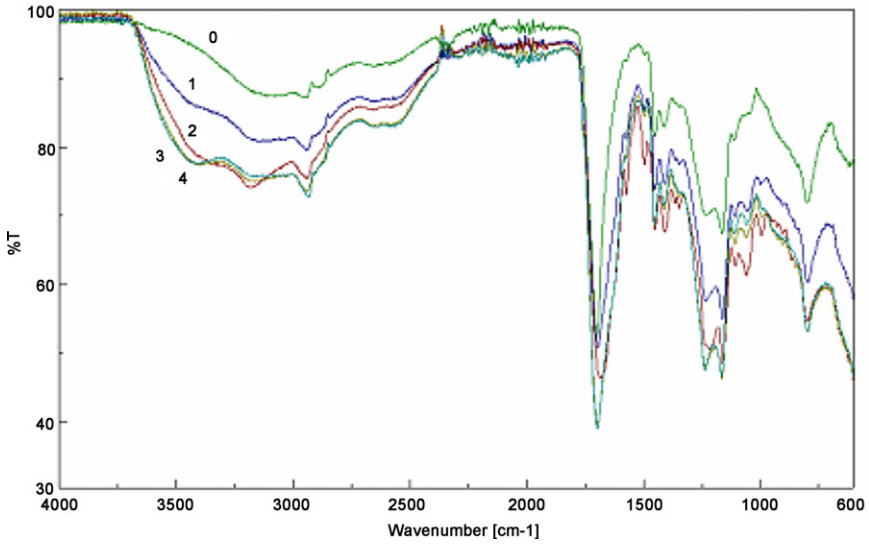

Fig. 2. FT-IR spectra of Carbopol Ultrez 10NF polymer after 0, 1, 2, 3, 4 weeks of storage.

types of Carbopols show different water absorption tendencies. Carbopol 71G readily absorbed water, get hydrated and swelled. Rapid water uptake can be observed within one week of storage and the water content increased slowly along with further storage. Fig. 2 represents that the water absorption of Carbopol Ultrez 10NF is slower compared to Carbopol 71G. Similar amount of water was absorbed within the first two weeks and then further water uptake leveled out to constant value. The explanation of this phenomena is the initial slow water sorption on the polymeric surface followed by hydration and swelling. Fig. 3 shows the *o*-Ps lifetime distribution in Carbopol Ultrez 10NF polymer as a function of storage. The shifting of peaks details what has happened with the free volumes during the water uptake indicated by FT-IR spectra (Zelkó et al., 2006; Papp et al., 2010). In the beginning, water molecules destroyed the original polymeric structure and formed larger free volumes. However, later on, a new structure was formed, involving hydrogen bonds between water molecules and polymeric chains. During storage, the peak at 1.4 ns, indicative of *o*-Ps atoms situated in holes between polymeric chains, shifted towards longer lifetimes, demonstrating the relaxation of the structure and the increase of free volume holes in size. This was most probably due to the plasticizing effect of water molecules absorbed from air.

Note that, between one and two weeks of storage, there is a little discrepancy in the continuous shifting of the peak towards longer lifetimes. On the other hand, the narrowing of peaks is continuous and the "big jump" in the structure appears at the first week of storage, just as it was indicated by FT-IR spectra.

Although the free volume changes in the formulas are best reflected by positron lifetime distributions, they do not detail all the aspects of the drug–carrier interaction.

Fig. 4 indicates the changes of the *S* parameter of Doppler-broadening as a function of storage of Carbopol 71G. Note that this parameter reflects the changes in local electron density. The significant decrease of the *S* value after a week of storage refers to the wetting of the polymer. Water molecules destroy the original structure and positrons have a higher chance to meet with energetic electrons. After the initial wetting, a continuous swelling starts. As the new structure forms, the electrons of high momentum become unavailable for positrons again and the *S* parameter increases.

Figs. 5 and 6 illustrate the average lifetimes of positrons and *o*-Ps atoms in pure substances and their 1:1 physical mixtures as a function of storage time. In the initial stage, Carbopol 71G and B_{12} represents a completely interaction-less mixture. Its average lifetime is exactly in the middle between those of the constituents. However, the storage develops an interaction between the ingredients in both mixtures. The presence of a certain amount of

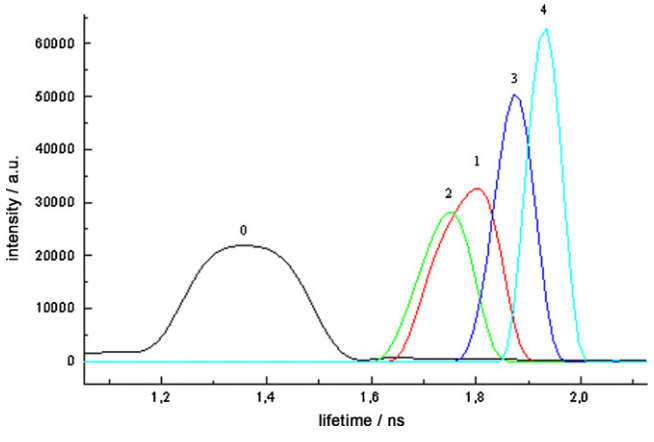

Fig. 3. *o*-Ps lifetime distribution in Carbopol Ultrez 10NF polymer after 0, 1, 2, 3 and 4 weeks of storage.

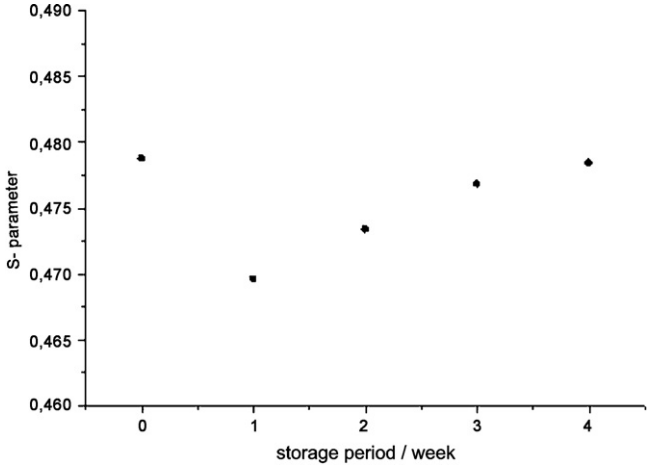

Fig. 4. S-parameters of Carbopol 71G polymer during the storage period.

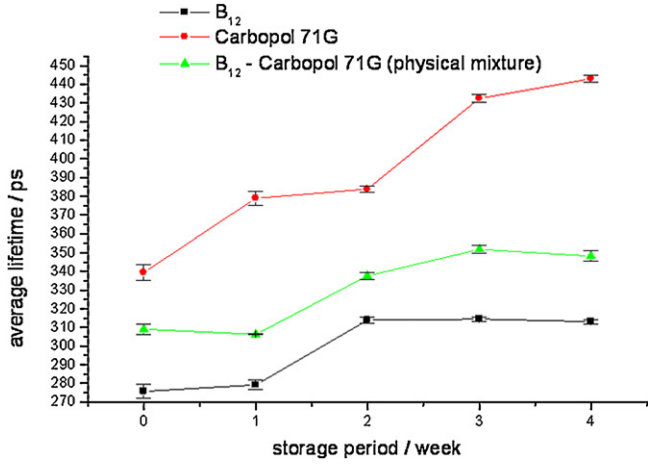

Fig. 5. *o*-Ps lifetimes of B_{12} and Carbopol 71G substances and of their 1:1 physical mixtures as a function of storage time.

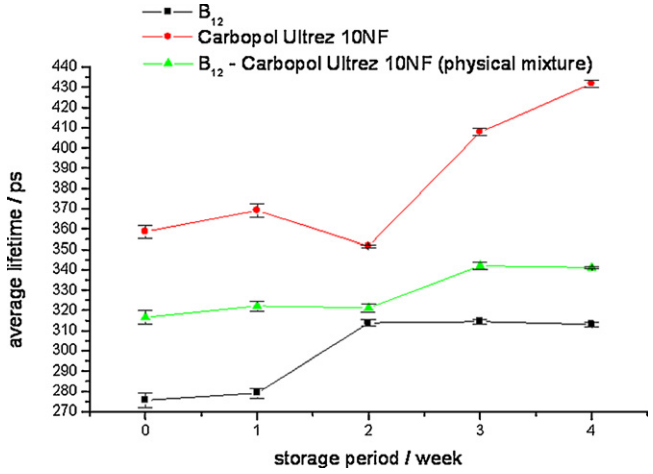

Fig. 6. *o*-Ps lifetimes of B_{12} and Carbopol Ultrez 10NF substances and of their 1:1 physical mixtures as a function of storage time.

water assures the local surrounding for the interaction between the polymer and the water-soluble active ingredient, in this case the vitamin B_{12}. The necessary time for developing this interaction was altered depending on the types of Carbopol due to the different kinetics of water uptake. Interaction could be observed even after 1 week of storage (Fig. 5), due to the rapid wetting in the case of Carbopol 71G, while it could be detected after 2-week storage (Fig. 6) in the case of Carbopol Ultrez 10NF. The latter could be derived from the deviation of the average lifetime values of the physical mixtures compared to the mean of average lifetime values of individual compounds. A longer storage means a higher deviation, i.e., a stronger interaction in both cases.

4. Conclusions

The combination of non-invasive spectroscopic methods, FT-IR spectroscopy and PALS enable sensitive means for the detection and the prediction of possible interactions initiated by the presence of water in the course of storage. The latter could be of impact from the point of the physical stability of dosage forms.

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