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Metolose–PEG interaction as seen by positron annihilation spectroscopy

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Abstract

The plasticizing effects of poly(ethylene glycol) (PEG 400) on methylcellulose (Metolose) cast films were studied by conventional physico-chemical methods and positron annihilation spectroscopy. The PEG concentrations relative to the total polymer content were varied within the range 0–75% (w/w). At low concentrations (below 33.3%, w/w), the plasticizer was found to build in into the methylcellulose structure. On the other hand, at higher concentrations (above 50%, w/w), it formed small separate phases in the films.

Positron annihilation spectroscopy (PALS) was applied to track the Metolose–PEG interaction. Controlled ageing of Metolose–PEG films at room temperature and at 75% RH revealed a significant difference between the ageing processes of the monophase and those of the separate phase films. The ageing involves two steps in both cases: a fast and a slow one. The PALS measurements demonstrated that the slow process is hindered in the phase-separated samples.

Keywords: Deformation process; Thermal behaviour; Positron annihilation spectroscopy

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1. Introduction

Different polymers are frequently used in the course of the formulation of various dosage forms in the pharmaceutical and food industries. Most of these applications require long-term stability. Amorphous polymers, such as methylcellulose, are not in equilibrium below their glass transition temperature (T_g), and these polymers therefore usually undergo spontaneous, though slow, transformations towards low-energy equilibrium states (Guo, 1994). This physical ageing is usually manifested in the relaxation phenomena (volume and enthalpy) (Chapman et al., 2001; Cowie and Ferguson, 1993; Gomez Ribelles et al., 1990), indicating considerable structural changes in the material. The plasticization effects of residual solvents, absorbed water, plasticizers and other additives can affect the long-term performance and stability of amorphous polymers in pharmaceutical dosage forms (Hodge et al., 1996; Hancock and Zografi, 1993, 1994, 1997; Hancock et al., 1995; Oksanen and Zografi, 1990; Süvegh and Zelkó, 2002; Süvegh et al., 1998). The plasticizer applied can modify the structure of a polymer film, causing significant changes in the mechanical properties of a polymeric binder or a coating. Even the viscoelastic state of a polymer is sometimes changed by the long-term physical ageing (Sakellariou et al., 1986).

The viscoelastic properties of amorphous solids differ significantly below and above glass transition temperature. Thus, the apparent state of the applied polymer might affect the activity of the drug present in the dosage form. As a result of these changes the stability of the final dosage form (the hardness of the tablets, the disintegration time and the drug release characteristics) can be seriously modified (Zelkó et al., 2000; Zelkó and Süvegh, 2004).

Sakellariou et al. (1986) studied the interactions between ethylcellulose and hydroxypropyl methylcellulose, hydrox-

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ypropyl cellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and poly(ethylene glycol) 6000 (PEG 6000) by a dynamic mechanical testing method, and the results were related to the transport mechanisms in the controlled release dosage forms. They established the limit of PEG 6000 in hydroxypropyl methylcellusose (HPMC). The objective of the present work was to study the influence of a poly(ethylene glycol), applied as plasticizer, on the deformation and thermal behaviour of free films of methylcellulose, and the related structural changes. The effects of the plasticizer on the structure and the viscoelastic properties of the polymer were studied by conventional physicochemical methods and positron annihilation spectroscopy. This latter method provides information on the size of free volume holes in an amorphous material, and thus on the plasticizer-induced structural changes of the polymers.

2. Experimental

2.1. Materials

Metolose is a non-ionic, water-soluble cellulose ether which is prepared from cellulose. The cellulose is processed with caustic soda and then treated with an etherification reagent such as methyl chloride, propylene oxide or ethylene oxide. Metolose is classified into three types, i.e. SM, SH and SE, according to the kind of etherification reagent used.

Plasticizers have the capacity to alter the physical properties of a polymer film. PEGs belong in the group of polyols. The PEG grades 200–6000 are generally used as plasticizers. In this work, Metolose SM-4 (Methylcellulose, Lot No. 406555, ShinEtsu Chemical Co. Ltd., Tokyo, Japan) was used as film-forming polymer and PEG 400 (Ph. Eur.) was used as plasticizer.Characteristic data of Metolose SM-4 are the followings:

viscosity: 3.0–5.6 mPa s (2%, w/w, aqueous solution);
methoxyl content: 27.5–31.5%;
degree of substitution: 1.8.

It can be used as gastrosoluble coating material or binder in wet granulation.

2.2. Compositions

The film-forming liquid contained Metolose SM-4 in a concentration of 2% (w/w) and also the plasticizer (PEG 400) in 0, 0.25, 0.5, 1, 2, 3, 4, 5 and 8% (w/w) concentrations. The PEG concentrations related to the total polymer content were 0, 11.6, 20, 33.3, 50, 60, 66.6, 71.4 and 75% (w/w), respectively. This latter concentration scale is used below because it reflects the construction of the studied films. The solvent applied for the preparation of the film-forming liquid was distilled water (Ph. Eur.). The free films were prepared by pouring approximately 20 g solution onto a Petri dish 7 cm in diameter. The solution was dried at room temperature (22 ± 1 °C) for 72 h. The deformation behaviour of the cast films was tested 1 day after preparation. Two to 5 mg samples of the cast films obtained were used for DSC analysis.

2.3. Deformation process and moisture content

A modified breaking hardness tester (Chinoin Chemical and Pharmaceutical Works Ltd., Budapest, Hungary) was used. The apparatus was connected to a computer, and software developed at the Department of Pharmaceutical Technology (University of Szeged) was utilized to evaluate the deformation (breaking) process of the free films. The tests were carried out under ambient circumstances (22 ± 1 °C/65% RH).

The moisture content of the free films was determined with a moisture analyzer (HR73 Halogen Moisture Analyzer, Mettler-Toledo GmbH, Greifensee, Switzerland). The standard drying program was used and the drying temperature was 105 °C. This program is set in the factory and is suitable for most samples. The sample is heated to the drying temperature and held constant at this temperature.

2.4. Differential scanning calorimetry (DSC)

The DSC examinations of the free films were made with a Mettler-Toledo DSC 821^e instrument. The start temperature was −40 °C, the end temperature was 200 °C and the heating rate was 5 °C min^{-1}. An argon atmosphere and aluminium pans were used.

To the calibration indium and zinc were used. To check the temperature and heat flow accuracy of a DSC modules indium (for the low temperature) and zinc (for the high temperature) were selected. Checks were within the defined limits:

Indium:
  onset temperature: 156.6 ± 0.3 °C;
  heat flow: 28.45 ± 0.6 J/g.
Zinc:
  onset temperature: 419.6 ± 0.7 °C;
  heat flow: 107.5 ± 3.2 J/g.

2.5. Positron annihilation spectroscopy

2.5.1. Principle of positron annihilation spectroscopy

Positrons are the antiparticles of electrons. When a positron meets with an electron, they undergo mutual annihilation and provide information on the surroundings of the annihilating pair. As the probability of such a meeting depends on the electron density in materials, positrons are exceptionally sensitive to free volumes, i.e. to the electron density. In polymers, a large proportion of the injected positrons form a bound state with electrons before their annihilation (Süvegh et al., 1999). One of the bound states, the *ortho*-positronium atom or *o*-Ps, has a “long” lifetime: in polymers it lives for 1–10 ns. This lifetime is long enough for positronium atoms to scan their surroundings and, fortunately, it is long enough to be observed easily. Moreover, according to a simple model, the lifetime of an *o*-Ps atom depends on the size of the free volume in which it is located (Deng and Jean, 1993):

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \quad (1)$$

Here, τ is the lifetime of the *o*-Ps, R the radius of the (expectedly) spherical free volume holes and ΔR is a constant. The equation indicates that the lifetime of *o*-Ps atoms increases with the size of the free volume holes.

The above equation provides the most important tool to with which gain information on a polymeric sample by positron lifetime spectroscopy. The *o*-Ps lifetime is directly correlated with the size of free volume holes in the material. Thus, any change in the free volume is reflected in the *o*-Ps lifetime. Although the chemical composition of a certain polymer affects the lifetime a little (Süvegh et al., 2000), *o*-Ps atoms provide the most direct information on the size of free volume holes for polymers.

Beside their electron density-dependent lifetime, positrons scan the momentum distribution of electrons in the material. The exact energy of annihilation photons depends on the momentum of the annihilating electron, and the corresponding gamma-line widens due to the electron momentum. This information can be gained with the aid of another form of annihilation spectroscopy, the Doppler-broadening method (Süvegh et al., 1999). The broadening of the annihilation photopeak reacts to very intricate changes in the electron structure. The above equation provides the most important tool to with which gain information on a polymeric sample by positron lifetime spectroscopy. The *o*-Ps lifetime is directly correlated with the size of free volume holes in the material. Thus, any change in the free volume is reflected in the *o*-Ps lifetime. Although the chemical composition of a certain polymer affects the lifetime a little (Süvegh et al., 2000), *o*-Ps atoms provide the most direct information on the size of free volume holes for polymers.

2.5.2. Positron lifetime measurements

The positron source applied for the measurements was made of carrier-free ^{22}NaCl. In this case, the radioactive nuclide ^{22}Na, sometimes used as positron source in positron emission tomography (PET), emits the positrons needed for the measurements. Although ^{22}Na is not the best choice for PET, it is widely used in annihilation spectroscopy. It has a suitably long lifetime and emits a prompt-gamma photon. This prompt-gamma marks the "date of birth" of the positron, making lifetime measurements possible.

The active NaCl was sealed between two very thin (5 μm) titanium foils, which ensured that 90–95% of the emitted positrons penetrated the studied polymer samples. The activity of the source was 4×10^5 Bq.

Positron lifetime spectra were recorded with a fast–fast coincidence system (MacKenzie, 1983). The system was constructed from standard ORTEC electronic units, and the detectors were made from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps.

The positron source applied for the measurements was made of carrier-free ^{22}NaCl with an activity of 4×10^5 Bq. The active NaCl was sealed between two very thin (5 μm) titanium foils.

The lifetime spectra were evaluated and lifetimes extracted from them by the RESOLUTION computer code (Kirkegaard et al., 1981). In every case, three lifetime components were obtained, the longest of them characterizing the *o*-Ps annihilation. As this is the most reliable parameter of lifetime spectra in the case of polymers, we use this parameter alone to characterize Metolose films.

Doppler-broadening spectra were measured with a high purity Germanium gamma-detector. The resolution of the spectrometer for the annihilation photopeak was 1.1 keV. The Doppler spectra were evaluated by the means of the *S*-parameter, which characterizes the width of the annihilation photopeak. Roughly speaking, the larger the *S*-parameter, the smaller the momentum of the annihilating electrons. The *S*-parameters given below are related to an appropriate standard, and any changes observed are therefore relative to this standard.

3. Results and discussion

The mechanical strength and the deformation of films can be described by deformation (breaking) curves. Fig. 1 depicts the breaking curve of the fresh Metolose film (1 day old) without addition of plasticizer. The moisture content of the films was about 6% (weight: 0.600–0.800 g, S.D.: 0.31%, $n = 3$).

The measurements indicated that the Metolose film exhibited "soft and viscous" behaviour (Bauer et al., 1988; Cole et al., 1995). The initial section is followed by an elastic deformation range, and the film then becomes viscoelastic because the strength of the force does not change. This section is followed by an elastic section again, at the end of which breaking occurs. The data can be obtained numerically with the aid of a movable measuring line. The films containing plasticizer exhibited similar characteristics.

Together with the increase of the plasticizer concentration, the strength of the films and consequently the work of breaking decreased (Table 1). This means that the resistance of the films is reduced. The strength of the film containing 75% PEG could not be measured because of its softness.

The thermograms of different cast films just after their preparation are presented in Fig. 2. All the films can be characterized as purely amorphous substances; thus, a prolonged endothermic peak can be observed between 30 and 100 °C. DSC curves of the free films of Metolose show the lack of crystalline peak thus referring to the amorphous characteristics of the film. The measured glass transition temperatures also represent the amorphous state. The appearance of the freezing endotherm indicates the presence of free plasticizer in the film above 50% (w/w) PEG contents.

Table 1
Deformation parameters of free films

Sample	Force (N)	Work (mJ)	Time (s)
MET-0	43.84 (8.76)	169.07 (59.02)	11.28 (2.04)
MET-11	24.59 (8.57)	51.97 (23.59)	6.16 (0.79)
MET-20	21.41 (8.22)	73.72 (35.03)	9.92 (1.52)
MET-33	6.49 (3.17)	14.25 (8.29)	4.97 (1.57)
MET-50	4.77 (0.89)	12.51 (4.15)	7.71 (1.20)
MET-60	3.46 (0.56)	5.86 (1.63)	5.02 (0.79)
MET-67	2.47 (0.49)	6.99 (2.26)	8.29 (1.47)
MET-71	1.89 (0.75)	4.46 (2.29)	6.84 (0.75)

Ten parallel measurements were carried out. Values in parentheses are S.D.

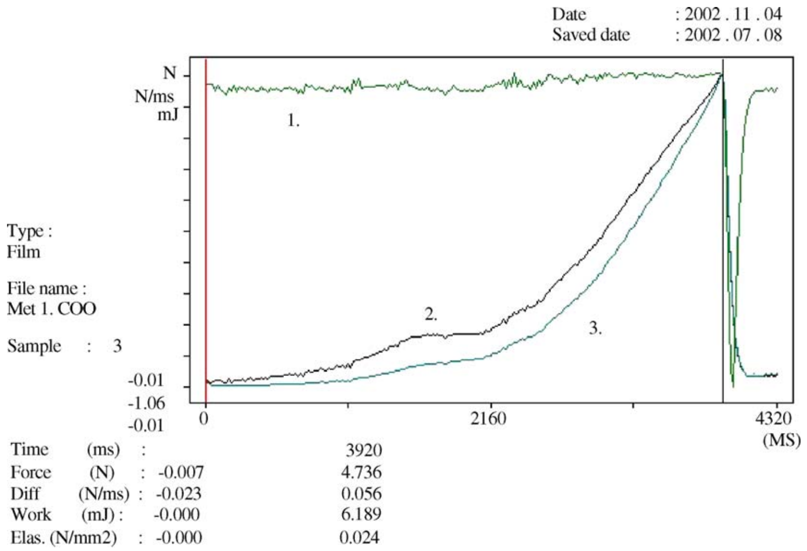

Fig. 1. Breaking process of Metolose film without plasticizer: (1) differential curve, (2) breaking curve and (3) integral curve.

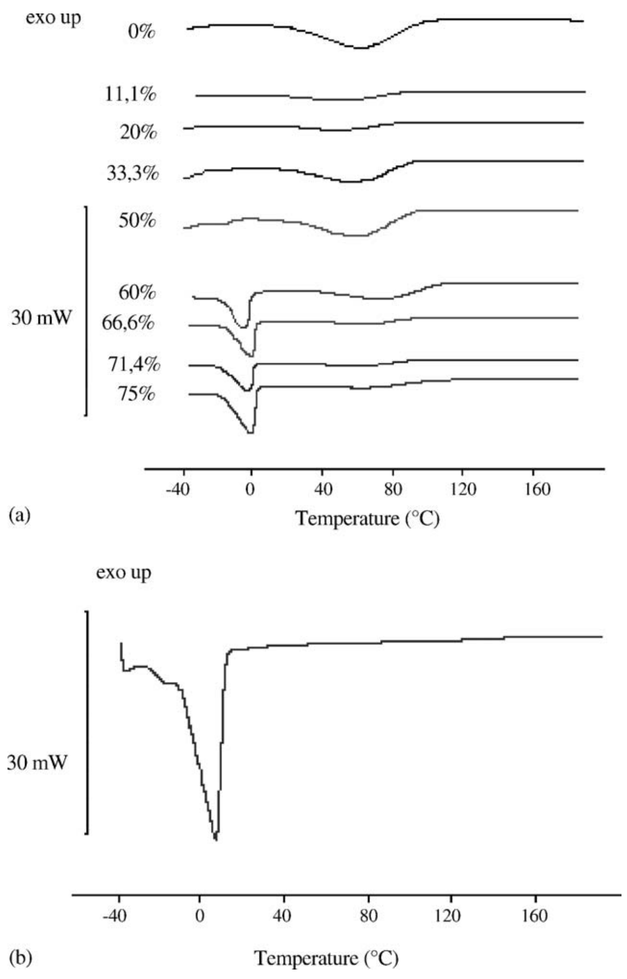

Fig. 2. DSC curves of: (a) Metolose films with PEG and (b) PEG.

For the pure Metolose film, produced without any plasticizer (Fig. 2a; 0%), only the prolonged endothermic peak at about 80 °C can be seen. This peak is caused by the evaporation of water from the film. The DSC curves of the films containing 11, 20 and 33.3% of PEG 400 exhibited similar profiles. In contrast, the DSC curve of the film containing 50% of the plasticizer revealed a small peak at about −5 °C. The enthalpy change accompanying this endothermic peak was small (2.05 J/g). As the PEG concentration was increased, the enthalpy change too increased and the endothermic peak shifted to higher temperatures. On the basis of these data and Fig. 2b, we can identify these peaks with the freezing point of PEG 400.

Comparison of all the curves demonstrates a breakpoint between 20 and 33.3% (w/w) PEG (Fig. 3). Eq. (2) describes the effect of the PEG 400 concentration on the strength of free films of Metolose containing PEG 400 as plasticizer. The correlation between the data and Eq. (2) is quite good (correlation coefficient = 0.9912).

$$F = a + b\left\{1 - \exp\left[-c\frac{C_{\mathrm{PEG\,400}}}{C_{\mathrm{PEG\,400}} + C_{\mathrm{Metolose}}}\right]\right\} \tag{2}$$

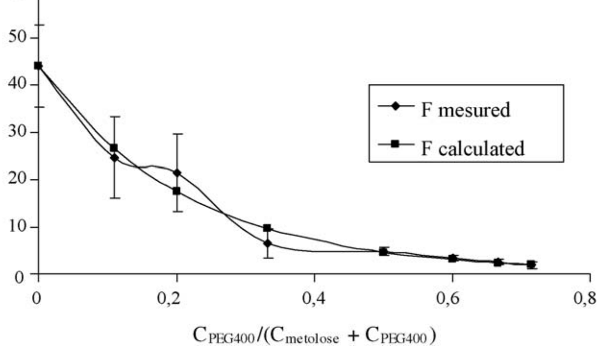

Fig. 3. Relationship between the PEG concentration and the strength of the films (±S.D., $n = 10$).

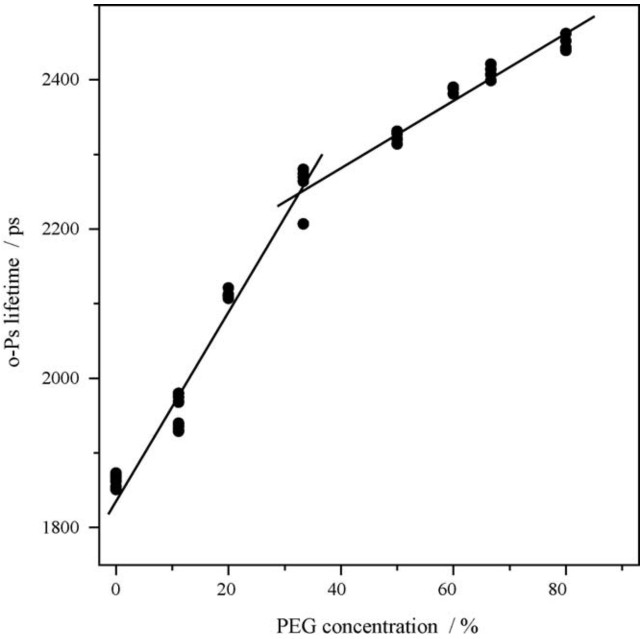

Fig. 4. The *o*-Ps lifetime as the function of the PEG concentration in Metolose SM-4 films. The lines are given only to guide the eye.

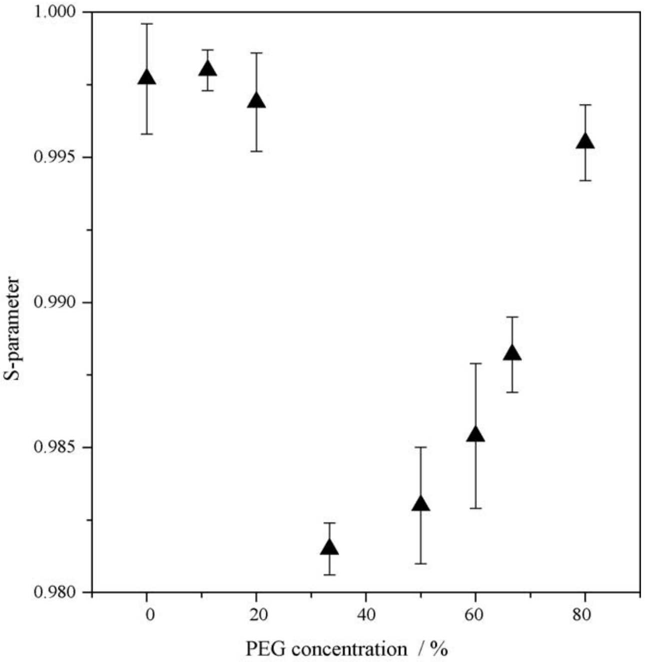

Fig. 5. The relative *S*-parameter of Doppler-broadening spectra in Metolose SM-4 films.

where $C_{\mathrm{PEG\,400}}$ is the PEG 400 concentration (%, w/w) in the film-forming solution, C_{Metolose} the Metolose concentration in the film forming solution (2%, w/w), and a, b and c are constants.

The observed breakpoint is well expressed in the positron annihilation results, too. As shown in Fig. 4, the lifetime of the *o*-Ps atoms increases as the PEG content of the films rises. The increase is monotonous; however, the breakpoint of the curve is clearly visible between 20 and 33.3% (w/w). The increase in the lifetime indicates that the size of the free volume holes in the films increases accordingly (Eq. (1)). This increase might well explain the plasticizing effects of PEG 400. Its addition increases the space between the chains of Metolose, and therefore weakens the interactions between them. The effect is major at low concentrations, but fades above 33.3%.

The breakpoint is even more expressed by the *S*-parameter of Doppler-broadening spectra (Fig. 5). At low PEG concentrations the average electron momentum in the films is constant, indicating that a sharp drop occurs in the *S*-parameter curve between 20 and 33.3% (w/w) PEG. Above the breakpoint, the *S*-parameter increases monotonously with increasing PEG concentration. The Doppler spectra reveal that a fundamental structural change in the films occurs at the breakpoint.

Comparison of the positron annihilation results with those of physicochemical measurements allows the conclusion that the breakpoint observed in all of the curves is due to the formation of small separate PEG phases in the previously homogeneous Metolose/PEG films. The first occurrence of these phases was observed between 20 and 33% (w/w) PEG. The overall amount of these small "droplets" of PEG increases on further plasticizer addition, and they ruin the film totally at very high PEG concentrations.

The positron annihilation data indicate that PEG and Metolose molecules do not interact strongly. At low PEG concentrations, while the individual PEG molecules are incorporated between the methylcellulose chains, the size of the free volume holes increases because the plasticizer molecules forces the chains farther apart from each other. However, the average electron momentum does not change, suggesting that the electron structure of the Metolose chains remains unaffected by the PEG molecules. A higher concentrations, however, the occurrence of PEG "droplets" does not change the free volume size dramatically. The seemingly serious change in the average electron momentum is simply due to the increase in the amount of PEG phases. As the PEG concentration increases, more and more positrons undergo annihilation in the PEG and not in the Metolose.

4. Conclusions

These results indicate that there might be a concentration range of PEG 400 (below 33.3%, w/w) at which the plasticizer can build into the polymeric film structure as "bonded" plasticizer, and thereby increase the elasticity of the film. In the presence of excess PEG 400 (above 50%, w/w), the plasticizer cannot build into the Metolose structure. It remains in its "free" form as small "droplets" in the films. With increase of the amount of "free" plasticizer, the elasticity of the film increases, in spite of the decrease in the breaking value. This is an unfavourable property of the obtained film from the aspect of pharmaceutical applications. Positron annihilation spectroscopic measurements permitted the tracking of the structural changes caused in Metolose films caused by the addition of PEG in different concentrations.

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