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The effect of storage and active ingredient properties on the drug release profile of poly(ethylene oxide) matrix tablets

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ABSTRACT

Different molecular weight forms of poly(ethylene oxide) can be used successfully in controlled release drug delivery due to their excellent matrix forming properties. Drug release of these materials follows nearly zero order kinetics, and is mainly governed by polymer swelling and erosion and diffusion of drug molecules. Because of its partly amorphous structure, poly(ethylene oxide) undergoes structural changes caused by elevated temperature and relative humidity of the storage medium resulting in an increased drug release. This physical process can be highly influenced by the structure of different drug molecules, such as polymer-binding ability and hydration tendency. These properties of two basic drugs embedded into poly(ethylene oxide) matrices were characterized by molecular modelling and an attempt was made to reveal their effect on the change of drug release stability, a prerequisite of the marketing authorization of dosage forms. The findings suggest that both the hydration properties of the active ingredient and the molecular weight of the polymer influence the effect of physical ageing of poly(ethylene oxide) on the drug release properties of the matrix.

1. Introduction

Among a variety of hydrophilic polymers, poly(ethylene oxide) (PEO) is one of the most important materials used in pharmaceutical formulation, mainly because of its non-toxicity, high water-solubility and swellability, insensitivity to the pH of the biological medium and ease of production (Kim, 1995; Picker-Freyer, 2006). High molecular weight PEOs have been successfully applied in controlled release dosage forms, because the rate of swelling and erosion of the polymer allows the sustained release of active ingredients. As swelling, thus matrix forming capacity depends on the molecular weight, modification of the release kinetics is possible via choosing the appropriate type of PEO (Maggi, Segale, Torre, Machiste, & Conte, 2002).

Drug release characteristics of the aforementioned polymers have been studied recently in the literature (Borgquist, Körner, Piculell, Larsson, & Axelsson, 2006; Kim, 1995; Maggi et al., 2002; Wu, Wang, Tan, Moochhala, & Yang, 2005). The process involves two mechanisms, diffusion through the swollen polymer and release via polymer dissolution. It has also been discussed, that both swelling and dissolution are faster in the case of the lower molecular weight forms, which results in higher release rates. On the other hand, the extent of swelling is higher for higher molecular weights and this is the dominant factor in drug release. In the case of lower molecular weight PEOs, both swelling and dissolution are important, and the synchronization of the two processes can be observed.

The main drug release determining factors of a hydrophilic polymer-based dosage form are the swellability and erosibility of the polymer matrix, as well as the diffusibility of drug molecules. Besides the concentration gradient between the dosage form and the release medium, this latter property highly depends on the size, molecular weight and solubility of the molecule, and the extent and nature of the drug–polymer interaction. On the other hand, swellability and the erosibility of the matrix also depend on the molecular weight and hydration tendency of the polymer, as well as on the interaction between polymer molecules. In the case of amorphous or partly amorphous polymers, this latter property can strongly be influenced by a phenomenon known as physical ageing. As such polymers are not in equilibrium below their glass transition temperature, they usually undergo spontaneous, although slow transformations towards low-energy equilibrium states. This process is usually manifested in volume and enthalpy relaxation indicating serious structural changes in the material. Sometimes common gases (as CO_2) or the natural humidity of air initiate these processes and the plasticization effects of these everyday materials are enough to change the crystallinity or the glass transition temperature of the polymer significantly (Süvegh & Zelkó, 2002). In an earlier study, physical ageing of two types

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of poly(ethylene oxide) could be tracked by the combination of differential scanning calorimetry, positron annihilation lifetime spectroscopy and scanning electron microscopy. Structural changes, i.e. an increase in the degree of crystallinity and volume relaxation could be observed even after a short storage time (4 weeks), which highlights the importance of the effects of physical ageing on the properties of dosage forms containing PEO (Kiss et al., 2006).

The effect of physical ageing on the drug release behaviour of several polymers and lipids was studied and can be found in the literature (Lovrecich, Nobile, Rubessa, & Zingone, 1996; Nafee, Ismail, Boraie, & Mortada, 2003; Vincente, Hernández, Gascón, Calvo, & Pedraz, 2000; Zelkó & Süvegh, 2005) but not for PEO. Here we report the possible changes in the drug release behaviour of this polymer caused by storage, and the effects of two basic drugs of similar molecular weight and water solubility but with different polymer-binding ability and hydration tendency.

For this purpose, matrix tablets were formulated using two different molecular weight forms of PEO, and dissolution tests were carried out before and after storing the dosage forms under stress conditions for different time intervals. Polymer–drug, polymer–water and drug–water interactions possibly taking place along with storage were modelled by means of computer simulation.

2. Materials and methods

2.1. Materials

Polyethylene oxide (Polyox® WSR N-12K – $M_w = 1 \times 10^6$ and Polyox® WSR 303 – $M_w = 7 \times 10^6$; PEO N-12K and PEO 303, respectively) (The Dow Chemical Company, New Milford, U.S.A.), metronidazole (Unichem Laboratories Ltd., Maharashtra, India) or anhydrous theophylline (Hungaropharma Ltd., Budapest, Hungary), and magnesium stearate (Hungaropharma Ltd., Budapest, Hungary) were used for the formulation of the matrix tablets.

2.2. Tablet preparation

Four kinds of tablets were prepared, each containing 250 mg metronidazole or 150 mg theophylline, 250 mg PEO N-12K or PEO 303 and 0.5 or 0.4 mg magnesium stearate as a lubricant. After weighing and homogenizing the components thoroughly in a mortar, tablets of 12 mm in diameter were directly compressed with a Diaf type (Denmark) single punch press at constant compression force.

2.3. Storage conditions

Samples of the four kinds of tablets were stored at 40 ± 2 °C and at 75 ± 5% relative humidity for 4 weeks.

2.4. Dissolution tests

Dissolution tests were carried out before and right after storage, in an ERWEKA DT6RE type dissolution tester at 37 ± 1 °C and 50 rpm, using rotating baskets. The dissolution medium was 500 ml of 0.1 N HCl with 2 g/l of sodium chloride. Samples were taken after 15, 30, 45, 60, 90 and 120 min and after that every 60 min up to 8 h. The sample volume was 10 ml, which was replaced each time with the equivalent of dissolution medium. The dilution caused by this addition was corrected when the amount of drug released was calculated. After dilution and filtration through a membrane filter (Sartorius) of 200 nm pore size, the active content of the samples was determined with a JASCO V-550 UV/VIS spectrophotometer at 280 nm (metronidazole) or 270 nm (theophylline) on the basis of calibration curves recorded earlier.

2.5. Comparison of the dissolution curves

Mathematical comparison of drug release profiles before and after storage was carried out by calculating the difference (f_1) and similarity (f_2) factors according to Eqs. (1) and (2) proposed by Moore and Flanner (1996) and implemented by FDA CDER.

$$f_1 = \frac{\sum_{t=1}^{n'} \|R_t - T_t\|}{\sum_{t=1}^{n'}} \times 100 \quad (1)$$

$$f_2 = 50 \times \log \sqrt{\left(1 + \frac{\sum_{t=1}^{n'} (R_t - T_t)^2}{n'}\right)} \times 100 \quad (2)$$

where n is the number of time points, R is the dissolution value of the reference sample (here the sample before storage) at time t, and T is the dissolution value of the test sample (here the sample stored for 4 weeks) at time t. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference samples.

2.6. Computer simulation

For the ab initio calculations the GAUSSIAN computer code (Frisch et al., 1998) was used. For the simulation of PEO chains, we have used a short sequence of the molecule. Even so, the simplified molecule was very large and we used a relatively small basis set, namely, HF/3-21G*. Consequently, the determined optimum geometries and energies are not the most exact ones but, anyhow, give some practical hints on the structure of hydrogen bound complexes forming between PEO, drugs and water.

2.7. Particle size measurement

For the determination and comparison of the particle size distribution of actives and PEOs of different molecular weights laser diffraction particle size analysis (Sympatec, Germany) was carried out. Table 1 summarizes the particle size data of actives and of the matrix forming polymers.

3. Results and discussion

Fig. 1 shows the drug release profiles of the two different molecular weight PEO matrices containing metronidazole before and after 4 weeks of storage. In the case of the lower molecular weight polymer, a significant increase in drug release ($f_2 < 50$) could be observed after storing the samples under stress conditions. The reason behind this phenomenon could be that the above mentioned structural changes of poly(ethylene oxide) lead to stronger polymer–polymer interaction, which could result in the decrease of the strength of the secondary bonds formed between the polymer chains and the active ingredient molecules. On the other hand, no such changes could be seen in the case of the higher molecular weight form, although earlier studies confirmed structural alterations similar to those of the low molecular weight polymer. This suggests that not only the modified physical properties of

Table 1
Particle size data of actives and of the matrix forming polymers

Material	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
Metronidazole	25.0	126.1	300.3
Theophylline	24.3	124.0	305.2
Polyox WSR 303®	37.7	145.1	347.4
Polyox WSR N-12K®	26.3	142.5	360.0

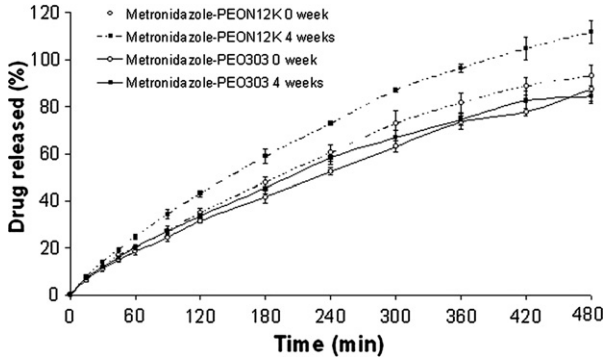

Fig. 1. Drug release profiles of PEO matrices containing metronidazole.

the polymer matrix determine the behaviour of the dosage form in the course of storage but also the characteristics of the molecules. This assumption could be affirmed by the finding that, in the case of theophylline, drug release of high molecular weight matrices increased to an even greater extent (Fig. 2).

The above figures also indicate that metronidazole release is higher than that of theophylline, which can partly be attributed to the greater density of metronidazole molecules in the polymer matrix (5840 vs. 3330 drug molecules per polymer molecule in the case of PEO N-12K and 40,880 vs. 23,310 drug molecules per polymer molecule for PEO 303). This could lead to the higher concentration gradient of metronidazole, resulting in the faster diffusion of this drug. Another contributing factor can be that the interaction between theophylline and poly(ethylene oxide) is stronger, as according to the ab initio calculations, the energy gain of the H-bond between these two molecules is greater than in the case of metronidazole (Fig. 3).

According to the results of the computational simulations, the formation of the theophylline–water complex also leads to higher energy gain than in the case of metronidazole (Figs. 4 and 5).

The formation of drug–water complexes alone would not be enough to break the PEO-drug H-bonds, but the hydration of PEO molecules (Fig. 6) also contributes to this process.

The difference in the changes of drug release of the higher molecular weight matrices could be explained with the different hydration tendency of the drug molecules. As it can be seen, the overall formation of theophylline–water complexes leads to higher energy gain, than that of metronidazole–water complexes. Thus, theophylline is released easier from the polymer matrix, because its interaction with water molecules during storage possibly leads to the weakening of the theophylline–polymer interaction. This phenomenon is less remarkable in the case of metronidazole, where drug–water interaction is weaker. The two different molecular weight forms of the polymer act differently from this aspect, as PEO N-12K matrices present equally increased drug release of both kinds of molecules. The reason behind this could be that because of its lower molecular weight, PEO N-12K has seven times more –OH end-groups capable of H-bond formation with water molecules. Thus, the lower molecular weight form hydrates faster and water molecules can penetrate easier into the matrix, being able to compete with PEO-molecules in H-bridges with the drug molecules. On the other hand, PEO 303 forms a much thicker matrix, leaving less opportunity for water molecules to get imbibed and interact with drug molecules. Thus, water–drug interaction

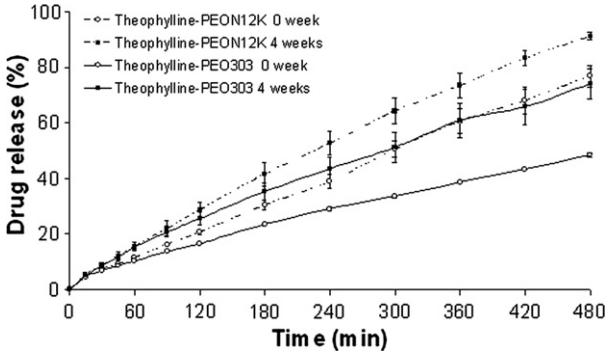

Fig. 2. Drug release profiles of PEO matrices containing theophylline.

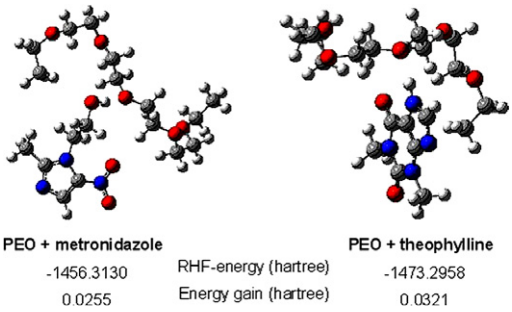

Fig. 3. Optimized geometry of PEO-complexes of the two examined drug molecules and the corresponding energy values.

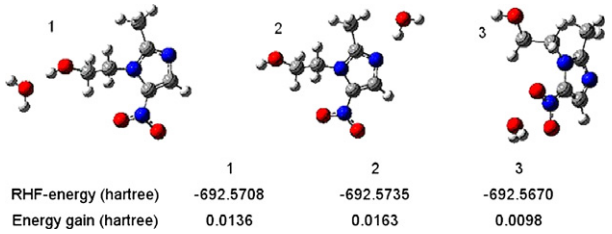

Fig. 4. Optimized geometry of metronidazole–water complexes and the corresponding energy values.

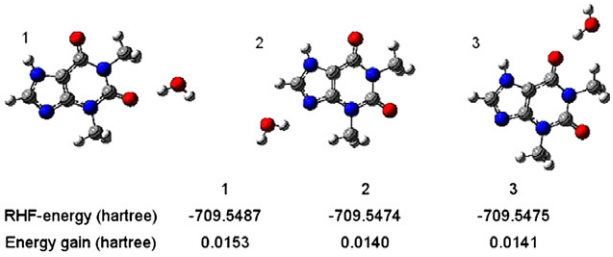

Fig. 5. Optimized geometry of theophylline–water complexes and the corresponding energy values.

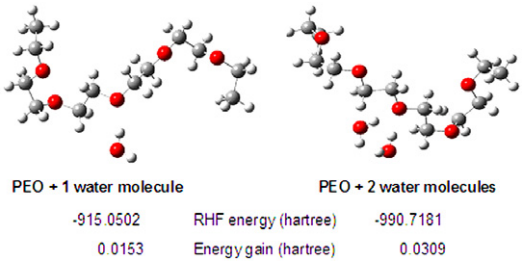

Fig. 6. Optimized geometry of PEO–water complexes and the corresponding energy values.

could gain greater significance in the case of theophylline, where complex formation is energetically more favourable.

4. Conclusions

The above drug-release measurements and ab initio calculations suggest that both the hydration properties of the active ingredient and the molecular weight of the polymer influence the effect of physical ageing of poly(ethyle oxide) on the drug release of matrix tablets.

References

Borgquist, P., Körner, A., Piculell, L., Larsson, A., & Axelsson, A. (2006). A model for the drug release from a polymer matrix tablet – Effects of swelling and dissolution. *Journal of Controlled Release, 113*, 216–225.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., et al. (1998) *Gaussian 98, Revision A.7. Pittsburgh: Gaussian Inc.*

Kim, C. J. (1995). Drug release from compressed hydrophilic Polyox®-WSR tablets. *Journal of Pharmaceutical Sciences, 84*, 303–306.

Kiss, D., Süvegh, K., Marek, T., Dévényi, L., Novák, Cs., & Zelkó, R. (2006). Tracking the physical aging of poly(ethylene oxide): A technical note. *AAPS PharmSciTech, 7* (4), article 95. doi: 10.1208/pt070495.

Lovrecich, M., Nobile, F., Rubessa, F., & Zingone, G. (1996). Effect of ageing on the release of indomethacin from solid dispersions with Eudragits. *International Journal of Pharmaceutics, 131*, 247–255.

Maggi, L., Segale, L., Torre, M. L., Machiste, E. O., & Conte, U. (2002). Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study. *Biomaterials, 23*, 1113–1119.

Moore, J. W., & Flanner, H. H. (1996). Mathematical comparison of dissolution profiles. *Pharmaceutical Technology, 20*, 64–74.

Nafee, N. A., Ismail, F. A., Boraie, N. A., & Mortada, L. M. (2003). Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. *International Journal of Pharmaceutics, 264*, 1–14.

Picker-Freyer, K. M. (2006). Polyethylene oxides. Analysis of tablet formation and properties of the resulting tablets. *Journal of Thermal Analysis and Calorimetry, 85*, 495–504.

Süvegh, K., & Zelkó, R. (2002). Physical ageing of polyvinylpyrrolidone under different humidity conditions. *Macromolecules, 35*, 795–800.

Vincente, A. S., Hernández, R. M., Gascón, A. R., Calvo, M. B., & Pedraz, J. L. (2000). Effect of aging on the release of salbutamol sulphate from lipid matrices. *International Journal of Pharmaceutics, 208*, 13–21.

Wu, N., Wang, L.-S., Tan, D. C.-W., Moochhala, S. M., & Yang, Y.-Y. (2005). Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. *Journal of Controlled Release, 102*, 569–581.

Zelkó, R., & Süvegh, K. (2005). Correlation between the release characteristics of theophylline and the free volume of polyvinylpyrrolidone. *European Journal of Pharmaceutical Sciences, 24*, 351–354.