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Antibiotics 2019: Effect of drug solubility and accelerated ageing on drug release from polyethylene oxide matrices - Saeed Shojaee - Azad Damgan University

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Introduction:

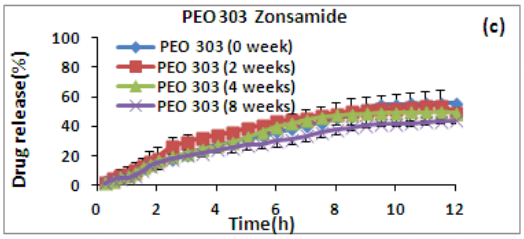
Hydrophilic matrices are extensively accepted and widely used for oral controlled release (CR) drug delivery systems. Recently, in addition to HPMC, polyethylene oxide (PEO) has been used in the pharmaceutical industry because of its availability in a range of molecular weights, wide regulatory acceptance, and high water-swellability and erosion characteristics (1). As PEO is sensitive to thermal oxidation, it might also be susceptible to free radical oxidative attack. It has been shown that the properties of PEO were subjected to changes because of degradation. The mode, extent and mechanism of degradation are strongly dependent on the intensity and duration of the physical and chemical stresses, to which the polymer is exposed (2). Drug solubility is one of the primary parameters that dictate drug release and dissolution from solid dosage forms. An increase in drug solubility enhanced the diffusion of the drug out of the matrix along with elevated matrix hydration. Moreover, low solubility drugs caused depletion in polymer erosion rates, thus limiting drug release. This is due to insoluble drug particles residing in the gel layer and decreasing the level of swelling and bond formation strength of the polymer chains (3, 4). The aim of this study was to investigate the effect of drug solubility and accelerated ageing (40 °C) on drug release from aged high molecular weight PEO 303 matrices.

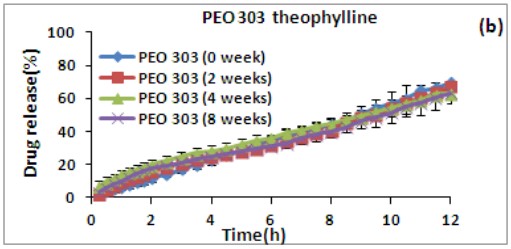
Methods:

The model drugs (Propranolol HCl, Theophylline and Zonisamide) and PEO 303 were mixed with a 1:1 ratio. Matrix tablets of 240 mg were prepared by the direct compression of the mixture at 1500 psi. The tablets were stored in an oven at 40 °C and at different time intervals (0, 2, 4 and 8 weeks) and the release rate of the tablets were determined using dissolution tester, USP II paddle apparatus. Distilled water at 37 °C was used as a dissolution medium. The drug concentration in the samples was determined by UV spectroscopy at 290, 270 and 271 nm for propranolol, theophylline and zonisamide respectively. A differential scanning calorimetry (DSC) was used to evaluate thermal properties of the polymer.

Results and discussion:

The results showed that PEO 303 matrices containing a highly soluble drug (propranolol HCl, 61 mg/ml), had an increased release rate when stored at 40 °C for different period of times (8 > 4 >2 > 0 weeks) (Figure 1a) suggesting that thermo oxidation leads to chain destruction which increased the release rate (2). In case of semi water-soluble drug (theophylline (8 mg/ml)), storage time had no effect on drug release from PEO 303 matrices (Figure 1b). This could be due to solubility of the theophylline which is less than propranolol. Finally, zonisamide was selected as a poorly water soluble drug (0.8 mg/ml) in the present study to cover all the range of solubility.





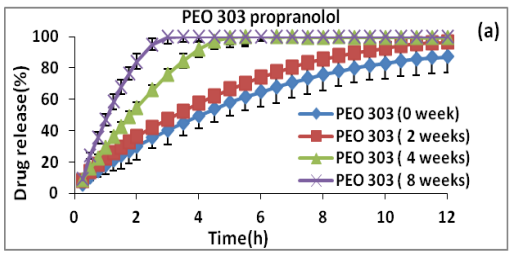


Figure 1. Effect of drug solubility. Panel a) propranolol, panel b) theophylline , panel c) zonisamide on drug release from PEO matrices after different storage times.

Drug releases from PEO 303 and poorly soluble drug zonisamide from and stored samples for the first 4 weeks were similar however; it decreased significantly after 8 weeks (Figure 1c). The dissolution test for the soluble drug (propranolol HCL) showed almost 100% drug release within 2 h after 8 weeks storage times, whereas for semi-soluble drug (theophylline) it was around 60%, but for poorly water-soluble drug (zonisamide) it was less than 40%. Even after 12 h, 100% drug release is not obtained and the graph continues to increase (Figure 1c). Comparing all dissolution profiles for all drugs used in this study clearly showed that the drug release is faster when highly water-soluble drug was used compared to poorly water-soluble drug incorporated in polyox matrices. This indicated that one of the parameters controlling the drug release from polyox matrices is the solubility of the drug in the dissolution medium used. This was in good agreement with the data reported by Chakraborty et al., (2009) where they showed that the drug release from HPMC matrices is faster when verapamil HCL (a highly water soluble drug) is compared to matrices containing aceclofenac (a poorly water soluble drug). They showed that drug solubility has a significant effect on the release kinetics and mechanism of drug release (5). They also demonstrated that water soluble drug required a larger amount of HPMC K4M to sustain the drug release in comparison with HPMC matrices containing an insoluble drug and the mechanism of drug release followed anomalous non-Fickian diffusion transport (for water soluble drug) and zero-order (for insoluble drug).

To elucidate the dissolution results further, the thermal behaviour of the fresh and aged tablet matrices were studied by DSC thermograms and their DSC data are shown in Figure 2.

Figure 2. Melting point of fresh and aged (8 weeks) PEO 303 tablet matrices containing various drugs stored at 40 ˚C.

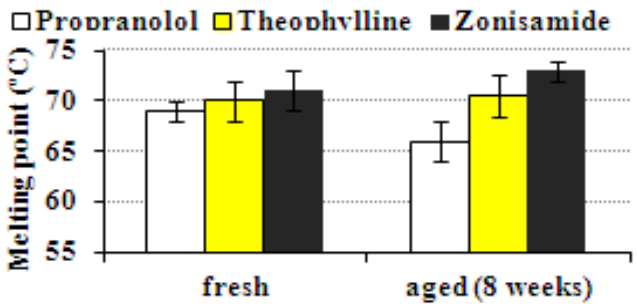
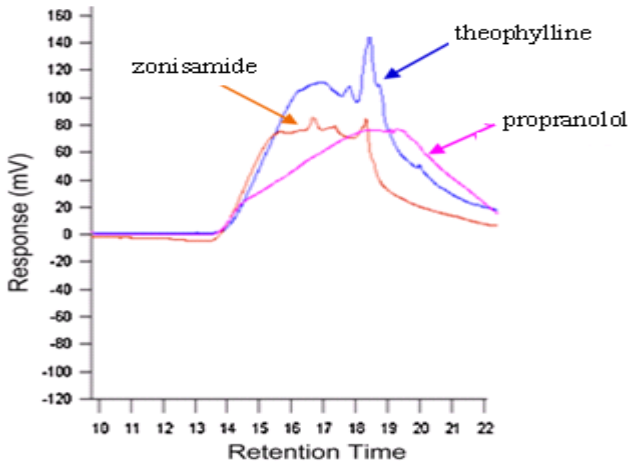


Figure 2. Melting point of fresh and aged (8 weeks) PEO 303 tablet matrices containing various drugs stored at 40 ˚C.

The prominent trend exhibited by DSC traces demonstrated that there was a significant reduction in peak melting temperatures upon storage for propranolol, whereby melting transitions have significant shifted to lower temperatures in the endothermic direction. While, DSC data also clearly demonstrated that the extensive changes were not visible in semi and poorly water-soluble drugs, which were theophylline and Zonisamide. This suggests that there was no noteworthy shortening in polymer chain length of these drugs through aerobic auto-oxidation, although it seen for propranolol. The reduction in melting peak could be an indication of a reduction in the molecular weight of the aged sample containing Propranolol HCL.

We employed GPC to verify the underlying causes of these dramatic shifts that occurred in dissolution profiles upon storage (Figure 3). The propranolol sample stored at 40 °C for eight weeks was more diffuse and showed a significant move to longer retention times indicating a significant reduction in the molecular weight of the aged sample (Fig. 3). Similar data was not obtained for the other two drugs which this indicated with increases in retention time corresponding to decreases in molecular weight occurring following storage at 2, 4 and 8 weeks.



Conclusion:

The solubility of drug had a big impact on stability of drug release from aged polyox matrices. Aged matrices containing highly soluble drug (propranolol HCl) showed a higher sensitivity of drug release against storage time leading to fast drug release. On the other hand, semi and poorly water-soluble drugs showed a stable release rate and drug release controlled at longer storage time. This may suggested preparation sustained release tablets with these types of drugs would be ideal.

References:

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