Investigation into the sorption of nitroglycerin into PVC tubes and alternative tube materials during application

Anna Treleano[1], Gerd Wolz[1], Rainer Brandsch[2], Frank Welle[1]

[1]Fraunhofer Institute for Process Engineering and Packaging (IVV), Giggenhauser Straße 35, 85354 Freising, Germany,
email: welle@ivv.fraunhofer.de, phone: ++49 8161 491 724
[2]Macrodynamic Chemical Technologies Limited (MDCTec Ltd.), Untere Läng 8c, 82205 Gilching, Germany

Introduction

Plastic bags and tubes are increasingly used for the storage and application of pharmaceutical formulations. The most common polymer material for such applications is plasticized poly(vinylchloride) (PVC). Whereas the discussion of leaching of plasticizers is focused on the toxicological properties of a drug/packaging system, the sorption/permeation of drug formulation compounds has an influence on the dosage of the active pharmaceutical ingredient resulting in a reduced drug delivery to the patient. Therefore sorption has an influence on the effectiveness of the therapy. In order to evaluate this effect, quantitative information on the sorption/permeation of drugs into polymers like PVC as well as suitable alternatives are necessary.
Aim of the study was a survey of the concentration curves of two drug examples (nitroglycerin, diazepam) applied by a dynamic system applied through infusion administration sets. From the experimental data the diffusion behavior was mathematically modeled. The mathematical modeling of the real sorption behavior is one of the crucial steps in the application of a constant drug concentration in a solution applied to the patient by PVC tubes.

Materials

For the PVC tubes, the following plasticizers were used: Di-(2-ethylhexyl) phthalate (DEHP), tri-(2-ethylhexyl)trimellitate (TEHTM), di-(isononyl)-cyclohexan-1,2-dicarboxylate (DINCH, isomeric mixture of isononyl moeties), di-(2-ethylhexyl) adipate (DEHA), poly adipate and di-(2-ethylhexyl)terephthalate (DEHT). The non-PVC tubes were used without plasticizers. All investigated tubes had a length of 155 cm and an inner diameter of 3 mm. The wall thickness of the tubes was 0.5 mm. The effective inner contact surface area of the investigated tubes was calculated to 143.5 cm^2. The concentration of nitroglycerin and diazepam were determined automatically by HPLC (UV) every 3.8 min after passing the polymer tubes of infusion administration sets with a constant flow rate of 1 ml min^{-1}.

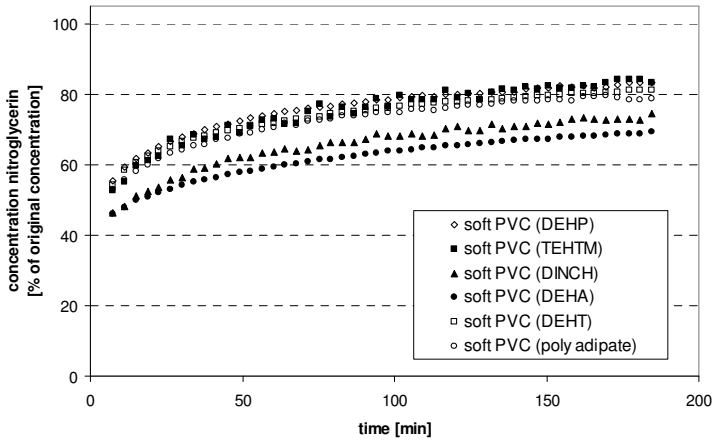

Figure 1: Sorption of nitroglycerin into PVC tubes with different plasticizers at the same shore hardness of 80

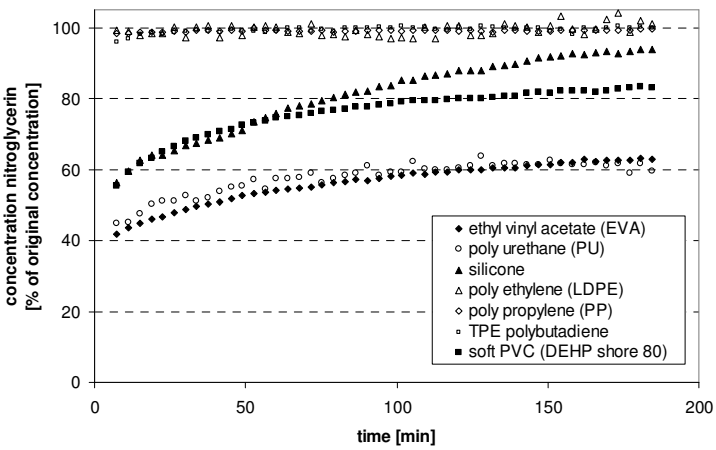

Figure 2: Sorption of nitroglycerin into alternative tube materials and PVC (DEHP shore 80) as reference

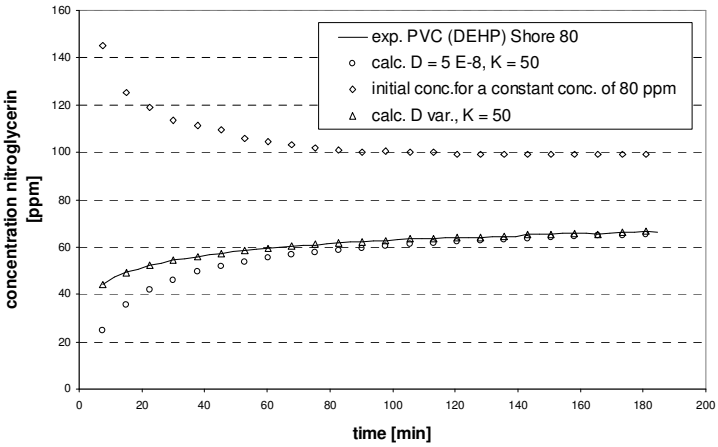

Figure 3: Calculated concentration of nitroglycerin in the drug solution pumped through PVC tubes (shore 80) in comparison to the experimental results and calculated concentration of nitroglycerin in the initial solution resulting in a constant concentration of 80 ppm in the applied solution

Results and Conclusions

The experimental concentration curves (Figure 1) show, that in the first minutes of the application of the drug solution the sorption of the active compound is at its maximum, resulting in the lowest concentration in the applied pharmaceutical solution. For a PVC tube with DEHP as plasticizer and a shore hardness of 80 only about 57% of the initial nitroglycerin concentration in the solution is applied to the patient in the first minutes of the application. Subsequently the concentration of the active pharmaceutical compound in the solution increases. The sorption behavior of the PVC tubes makes the application of a constant concentration of a certain active ingredient to the patient very difficult. On the other hand, the alternative tube materials like PE or PP show a significantly lower sorption compared to PVC plasticizer systems (Figure 2).
For the PVC(DEHP) tube the experimental data were simulated using mathematical diffusion models. The concentration profiles during application could be well simulated using the partition coefficient K = 50 (nitroglycerin, Figure 3) and K = 300 (diazepam, not shown), respectively. However, the diffusion coefficients of the drugs increase during sorption. The simulated partition and diffusion coefficients for given PVC(DEHP) pairs were used to simulate the initial concentration profiles of the drug solution to assure a constant concentration flow profile after passing the administration set (Figure 3). From the results a non-constant initial concentration profile for the active ingredient in a pharmaceutical drug solution can be established in order to compensate the loss of the pharmaceutical compound by sorption during infusion.

Reference

A. Treleano, G. Wolz, R. Brandsch, F. Welle, Investigation into the sorption of nitroglycerin and diazepam into PVC tubes and alternative tube materials during application, *International Journal of Pharmaceutics*, 2009, in press.

Acknowledgements

All tube materials were manufactured by and purchased from Raumedic GmbH, Erlangen, Germany. Special thanks are due to Prof. Dr. Viviana Schulz (University of Applied Science Nuremberg) and Georg Kühlein (Raumedic GmbH) for fruitful discussions.

Fraunhofer Institut Verfahrenstechnik und Verpackung

November 2008