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

Anna Treleano[a], Gerd Wolz[a], Rainer Brandsch[b], Frank Welle[a,*]

[a] Fraunhofer Institute for Process Engineering and Packaging (IVV), Giggenhauser Straße 35, 85354 Freising, Germany
[b] MDCTec Ltd., Untere Laeng 8c, 82205 Gilching, Germany

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ABSTRACT

Plastic bags and tubes are increasingly used for the storage and application of pharmaceutical formulations. The most common polymer material for drug application sets is plasticized poly(vinylchloride) (PVC). During application of pharmaceutical drug solution through PVC tubes, the polymer and the contact media interact which leads to leaching out of polymer additives or sorption of ingredients of the drug solution. Whereas the discussion of leaching of plasticizers is focussed on the toxicological properties of a drug packaging system, the sorption 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 and success of the therapy. Within the study, the concentration profiles of nitroglycerin and diazepam solutions were determined after pumping the solutions through infusion administration sets. The study includes plasticized PVC tubes with different plasticizers (DEHP, DEHA, DEHT, TEHTM, DINCH, poly adipate), PVC (DEHP) tubes with different shore hardness as well as alternative polymer materials like EVA, TPE, PUR, silicone, LDPE and PP. From the experimental concentration curves it could be shown, 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. For PVC tube (DEHP, shore 80) 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) and $K = 300$ (diazepam), respectively. However, the experimental results indicate, that the sorption of nitroglycerin into the PVC tube alters the diffusion behaviour of the polymer over flow time, which results in an increase of the diffusion coefficient during application. On the other hand, the other investigated alternative tube materials like PE or PP show a significantly lower sorption compared to PVC plasticizer systems. Due to the fact that the amount of sorption is varying over time, the concentration of the active pharmaceutical compound in the solution after passing the infusion administration set is not constant which makes the application of a constant concentration of a certain active ingredient to the patient very difficult. The simulated partition and diffusion coefficients for given PVC(DEHP) tubes were therefore used to simulate the initial concentrations profile of the feeding drug solution to assure a constant concentration flow profile after passing the administration set. The proposed methodology of this study represents a straight forward approach for the assessment of the drug sorption in dynamic flow systems based on experimental data as well as mathematical diffusion modelling. 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.

1. Introduction

Plastic bags and tubes are increasingly used for the storage and application of pharmaceutical formulations. For example infusion bags and the application sets are manufactured from poly(vinylchloride) (PVC). Due to the fact that PVC is a rigid polymer, PVC has to be plasticized for plastic bag or tube applications. Typically chemical compounds like phthalic acid esters are added up to a concentration of about 40% to the PVC polymer in order to establish the desired mechanical properties of the materials. One of the most applied plasticizer used for pharmaceutical applications is di(ethylhexyl phthalate) (DEHP). On the other hand, the

* Corresponding author.
E-mail address: welle@ivv.fraunhofer.de (F. Welle).

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applied compounds are relatively small molecules which are not chemically bound to the polymer backbone. Therefore, the chemical substances are able to migrate from the polymer into contact media and might lead to an unwanted exposure of the patient with such plasticizers. Several studies have been published on the leaching of PVC plasticizers such as DEHP (Kambia et al., 2005; Takehisa et al., 2005; Jenke, 2002; Loff et al., 2002; Tickner et al., 2001; Hanawa et al., 2000; Allwood and Martin, 1996; Faouzi et al., 1995). Therefore alternatives have been developed which show a lower amount of migration or have a better toxicological profile than DEHP. Examples for such alternative plasticizer are tri-(2-ethylhexyl)trimellitate (TEHTM), di-(2-ethylhexyl)adipate (DEHA), poly adipate and di-(2-ethylhexyl)terephthalate (DEHT). The latest development was di-(isononyl)-cyclohexan-1,2-dicarboxylate (DINCH), which shows a lower migration of DINCH into enteral feeding solutions compared to DEPH plasticized PVC (Welle et al., 2005).

It is well known, that PVC softened with plasticizers shows high interactions with contact media whereas more inert polymers like polyethylene terephthalate (PET) or polyamide (PA) result in a lower interaction (Stoffers et al., 2004, 2005). On the other hand, not every polymer is suitable for packaging of pharmaceuticals. Due to its rigid mechanical properties, PET for example can hardly be used for flexible tubes or bags. So alternatives for plasticized PVC as packaging and application of active pharmaceutical compounds are restricted by the performance, the polymer and manufacturing costs as well as by the general suitability and handling in the day-by-day business in the hospitals.

Driving force of the leaching process of compounds, i.e. diffusion of organic compounds in polymer materials in general is the concentration gradient of the migrating compound between the polymer material and the contact media. At the starting point of the migration process the concentration of the migrant in the polymer (or in the contact medium) is at the maximum level and the concentration in the contact media (or the polymer) is nearly zero. The system polymer/contact medium is trying to equilibrate the concentration (more precisely the chemical potential) of compounds between both media. However, the concentration profile of a compound in the system is defined by its diffusion and partition coefficient. The diffusion coefficient of the substance in the polymer is a kinetical parameter defining the time scale of the leaching process and the partition coefficient as the thermodynamic parameter is defining the concentration levels in the contact medium and the polymer at the equilibrium state, which might be toxicologically relevant. Due to the fact that the diffusion process of compounds in polymers is a reversible process, also the reverse process – the sorption of pharmaceutical ingredients into the polymer from the contact medium can be taken into account. Compounds from the pharmaceutical solution, e.g. the active pharmaceutical ingredient, which are stored in plastic bags or pumped through plasticized PVC tubes, might be absorbed into the polymer matrix. Sorption describes the loss of drugs to the plastic material and includes adsorption to the surface as well as the absorption into the polymer. In addition, permeation through the polymer might occur, which leads to the loss of the migrant into the environment. Whereas the discussion on plasticizer leaching from polymers is focussed on the toxicological properties of the plasticizer, the sorption/permeation of drug formulation compounds into the polymer 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 and success of the therapy. In order to evaluate this effect, quantitative information on the sorption/permeation of drugs into polymers like plasticized PVC as well as suitable alternatives is necessary. Current information suggests that the following drugs may exhibit significant sorption into plastics: insulin, nitroglycerin, diazepam, medazepam, oxaepam, nitrazepam, phenoxyethanol, lignocaine, chlormethiazole, vitamine A acetate, isosorbite dinitrate and a miscellaneous group of drugs like phenothiazines, warfarin sodium, hydralazine hydrochloride, thiopental sodium and fluorouracil (Salomies et al., 1994; Yahya et al., 1988; Illum and Bundgaard, 1982; Yliruusi et al., 1982; Kowaluk et al., 1981). On the other hand, drugs are chemical components and their sorption/leaching behaviour follows Fick's law of diffusion. Therefore it is expected that every drug formulation interacts with the polymer matrix of the packaging material. The extent of this interaction depends, however, on the diffusion rate of the compound into the polymer matrix and the partition coefficient of a chemical compound between the polymer and the drug formulation. Therefore the amount of the sorption is related to the physicochemical properties of the polymer, the drug compound as well as the contact media, in which the drug is dissolved. Regarding a drug pumped through an infusion administration set, the amount of sorption is difficult to estimate because in the dynamic system the concentration of the drug changes over time. In the case of plasticized PVC, the migration of the plasticizer into the contact medium alters the diffusion properties of the PVC polymer. In addition, sorption of chemical compounds from the contact medium might swell the PVC polymer. In conclusion, sorption of components from the contact medium and leaching of components from the polymeric matrix may change the diffusion coefficients of the active component in the polymer leading to a non-constant sorption rate of the active ingredient over time resulting in a non-constant dose of the active component applied to the patient. Such a behaviour might have serious consequences for the reliable application an active pharmaceutical compound with a certain (required) concentration to a patient in medical applications.

Aim of the study was a survey of the concentration curves over the administration time for two drug examples (nitroglycerin, diazepam) applied by a dynamic system through infusion administration sets. From the experimental data, the concentration curves over time were modelled mathematically based on a diffusion model. From the partition and diffusion coefficient pairs derived by simulating of the experimentally determined sorption behaviour, concentration profiles should be available for the application of a certain target concentration of the active compound of a drug solution to the patient.

2. Materials and methods

2.1. Infusion administration sets, tube materials and plasticizers

All tube materials were manufactured and supplied by Raumedic GmbH, Helmbrechts, Germany. The material information and the material short cuts used in this study are given in Table 1. For the polyvinylchloride tubes, the following plasticizers were used: Di-(2-ethylhexyl)phthalate (DEHP), tri-(2-ethylhexyl)trimellitate (TEHTM), di-(isononyl)-cyclohexane-1,2-dicarboxylate (DINCH, isomeric mixture of isononyl moeties), di-(2-ethylhexyl)adipate (DEHA), poly adipate and di-(2-ethylhexyl)terephthalate (DEHT). 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.

2.2. Drug formulations and chemicals

Nitroglycerin (Nitrolingual® infuse) was purchased from G. Pohl-Boskamp GmbH & Co. KG, Hohenlockstedt, Germany. A standard solution of nitroglycerin at a concentration of 1.0 mg ml^{-1}

Table 1
Investigated tube materials, plasticizer concentrations and shore hardness.

Tube polymer	Plasticizer	Short cut	Shore hardness	Plasticizer concentration spiked to the polymer (%)
Poly vinyl chloride	Di-(2-ethylhexyl)phthalate	PVC DEHP 60	60	46.7
Poly vinyl chloride	Di-(2-ethylhexyl)phthalate	PVC DEHP 70	70	39.6
Poly vinyl chloride	Di-(2-ethylhexyl)phthalate	PVC DEHP 80	80	35.9
Poly vinyl chloride	Di-(2-ethylhexyl)phthalate	PVC DEHP 90	90	29.8
Poly vinyl chloride	Tri-(2-ethylhexyl)trimellitate	PVC TEHTM 80	80	36.3
Poly vinyl chloride	Di-(isononyl)-cyclohexan-1,2-dicarboxylat	PVC DINCH 80	80	28.7
Poly vinyl chloride	Di-(2-ethylhexyl)adipate	PVC DEHA 80	80	23.4
Poly vinyl chloride	Poly adipate	PVC poly adipate 80	80	29.3
Poly vinyl chloride	Di-(2-ethylhexyl)terephthalat	PVC DEHT 80	80	28.7
Ethylene vinyl acetate		EVA 80	80	
Thermoplastic elastomer (polybutadien)		TPE 80	80	
Poly urethane		PUR 80	80	
Silicone		silicone 80	80	
Low density poly ethylene		LDPE 80	80	
Poly propylene		PP 80	80	

in acetonitril was purchased from Cambridge Isotope Laboratories Inc., Andover, USA. Diazepam (Diazepam-ratiopharm®) was supplied by Ratiopharm GmbH, Ulm, Germany. A standard solution of diazepam at a concentration of 1.0 mg ml^{-1} in methanol was purchased from LGC Promochem GmbH, Wesel, Germany. Isotonic sodium chloride solution (0.9% NaCl in water) was purchased from Fresenius Kabi GmbH, Bad Homburg.

2.3. Sorption kinetics for nitroglycerin and diazepam

The sorption kinetics for nitroglycerin and diazepam into the investigated tube materials was determined in triplicate for each polymer tube. The nitroglycerin (80 ppm) and the diazepam solution (20 pm) were prepared in 0.9% sodium chloride infusion solutions and stored in a glass vial before use. Both drug solutions were pumped through the investigated tubes at a flow rate of 1.0 ml min^{-1}. The solutions, which have passed the polymer tubes, were directly analysed for their concentrations of the active ingredient without further sample preparation. For that purpose, every 227 s a sample of the passed solution was analysed by high performance liquid chromatography (HPLC) via loop injection. The initial concentrations were determined by pumping the solution through a steal tube and analysing the nitroglycerin and diazepam concentration according to the same procedure. The concentrations of nitroglycerin and diazepam were analysed in the fractions using HPLC with ultraviolet (UV) detection.

2.4. Quantitative determination of nitroglycerin concentration

The concentration of nitroglycerin was determined by HPLC with an UV detector. The mobile phase was 80% methanol, 10% distilled water and 10% ammonium acetate buffer at a concentration of 0.05 M. The detector was set at 220 nm. Column: Phenomenex ULTRACARB^{TM} 5 μ ODS (30). Retention time nitroglycerin: 2.5 min. Quantification was achieved by external calibration using standard solutions of nitroglycerin according to the standard addition method.

2.5. Determination of diazepam concentration

The concentration of diazepam was determined by HPLC with an UV detector. The mobile phase was 80% acetonitril and 20% distilled water. The detector was set at 235 nm. Column: Phenomenex Luna® 5 μ phenyl–hexyl. Retention time diazepam: 2.8 min. Quantification was achieved by external calibration using standard solutions (concentrations) of diazepam according to the standard addition method.

2.6. Mathematical modelling of the sorption of nitroglycerin into PVC

The mathematical diffusion modelling was performed using the AKTS SML software version 4.1 (AKTS AG, 3960 Siders, Switzerland). The continuous sorption behaviour of the plasticized PVC tubings was simulated by a system with intermittent flow. A stagnation time of 7.5 min for each cycle was applied, resulting from the volume of the tubing and the flow rate of the drug solution. During the stagnation period the concentration of the active component decreases in the solution and increases in the polymer. After every cycle step the concentration of the active compound in the solution was set to the initial concentration. Using this model the sorption behaviour of the PVC tubes could be simulated and the diffusion coefficient as well as the partition coefficient of the drug/polymer set could be derived. The partition coefficients are defined as the ration of the equilibrium drug concentration in the polymer and in the aqueous solution.

3. Results and discussion

3.1. Experimental determination of the concentrations of nitroglycerin and diazepam

Within the study a method for the fast and semi-continuous quantitative determination of active pharmaceuticals (nitroglycerin, diazepam) in aqueous drug solutions was developed. With this method the concentration of nitroglycerin and diazepam were determined automatically every 3.8 min after passing the polymer tubes of infusion administration sets with a constant flow rate of 1 ml min^{-1}. The experimental design of this study was using glass vials (not plastic bags!) as reservoir for the drug solution in order to exclude the sorption of the drugs into the plastic bags. Therefore the measured concentrations of nitroglycerin and diazepam are only related to the time which the solutions pumped through the PVC tube. The solutions were pumped through the administration sets in order to establish a constant flow rate of 1 ml min^{-1}.

Fig. 1 shows the nitroglycerin concentration after passing a PVC tube with DEHP as plasticizer. The concentration of the plasticizer DEHP in the PVC tubes was varied which results in different shore hardness of the tube. As expected, the PVC (DEHP) tube with the highest shore hardness of 90 shows the lowest sorption of nitroglycerin. On the other hand the tube with a shore hardness of 60

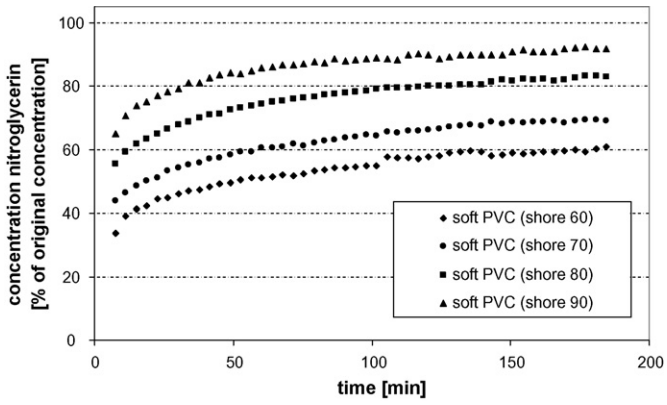

Fig. 1. Concentration of nitroglycerin after passing PVC tubes (plasticizer DEHP) with different shore hardness.

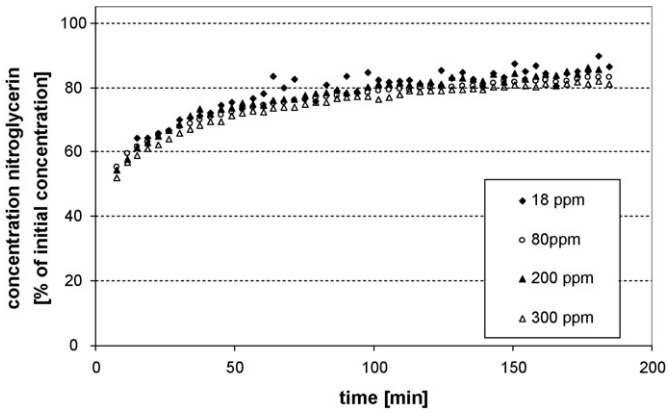

Fig. 3. Concentration of nitroglycerin after passing PVC tubes (DEHP, shore 80) at different initial concentrations.

results in the highest loss of nitroglycerin during application of the drug solutions. These results are in compliance with migration theory, where more rigid polymers show a lower diffusivity than plasticized polymers. From the concentration curves given in Fig. 1 it could be shown that in the first minutes of the application of the nitroglycerin solution the sorption of the active compound is at its maximum, resulting in the lowest concentration of nitroglycerin in the applied pharmaceutical solution. For a PVC tube with DEHP as plasticizer and a shore hardness of 80, which is typically used in hospital applications, only about 57% of the initial nitroglycerin concentration in the solution is applied to the patient in the first minutes of the application. For longer application times, the sorption amount per time decreases which leads to an increase of the nitroglycerin concentration in the solution applied to the patient. At the end of the application time, however, the concentration of the pharmaceutical compound is still significantly lower than the concentration in the reservoir before passing the PVC tube. Only about 82% of the initial concentration was determined in the solution pumped through the PVC tube with a shore hardness of 80. This can be explained by the sill ongoing sorption into the PVC tube as well as by the loss of nitroglycerin to the outside of the tube by permeation through the polymer material.

A similar behaviour as for nitroglycerin was found for diazepam (Fig. 2). Using the same type of PVC tube samples, the tube with the highest shore hardness shows the lowest sorption. Going into higher concentrations of the plasticizer and therefore lower shore hardness results in a significant higher sorption of diazepam during application. As a result, for a typical PVC tube used in hospital applications (shore hardness of 80) the concentration of diazepam in the first drops of the applied diazepam solution was only about 57% of the initial concentration of diazepam. Going to higher application times, the concentration increases for this tube up to about 70% of the initial concentration after an application time of 180 min.

The initial concentrations of nitroglycerin and diazepam in the solution do not affect the relative concentration for the active compound in the solutions after passing the PVC tubes. For nitroglycerin the initial concentration was varied from 18 ppm up to 300 ppm without a significant influence on the relative concentration in the drug solution after passing the PVC tube (Fig. 3). In the case of diazepam the concentrations were 5 ppm and 20 ppm, respectively, resulting in similar concentration curves given in per cent of the initial concentration for the active compound (Fig. 4). Long term application trials up to 20 h are shown in Fig. 5 for nitroglycerin and diazepam, respectively, using the standard PVC(DEHP) tube at a shore hardness of 80 typically applied in hospital applications. It could be shown that the initial concentration of the active pharmaceutical compound was not reached for both compounds. For nitroglycerin a constant level of about 90% of the initial concentration was found. In the case of diazepam the equilibrium is not reached. After 20 h about 82% of the initial concentration was determined in the solution after passing the PVC tube.

Figs. 6 and 7 show the sorption behaviour of nitroglycerin and diazepam of PVC tubes with different plasticizers at a shore hardness of 80. As a result different plasticizers influence the sorption behaviour of the PVC tubes. The sorption of nitroglycerin in PVC tubes with DINCH and DEHA as plasticizer is significantly higher

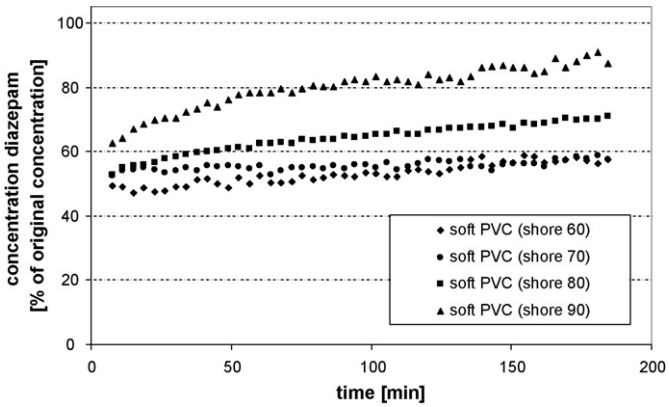

Fig. 2. Concentration of diazepam after passing PVC tubes (plasticizer DEHP) with at different shore hardness.

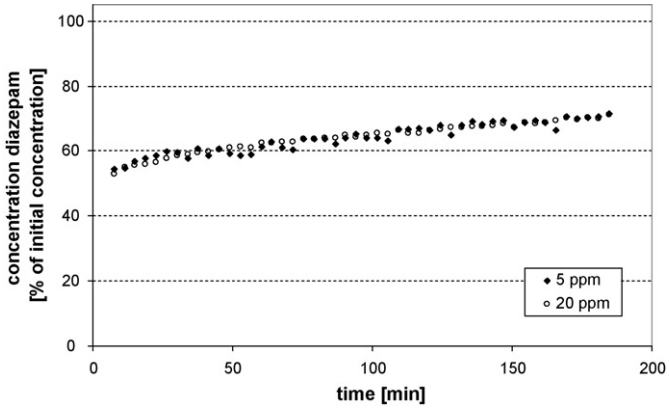

Fig. 4. Concentration of diazepam after passing PVC tubes (DEHP, shore 80) at different initial concentrations.

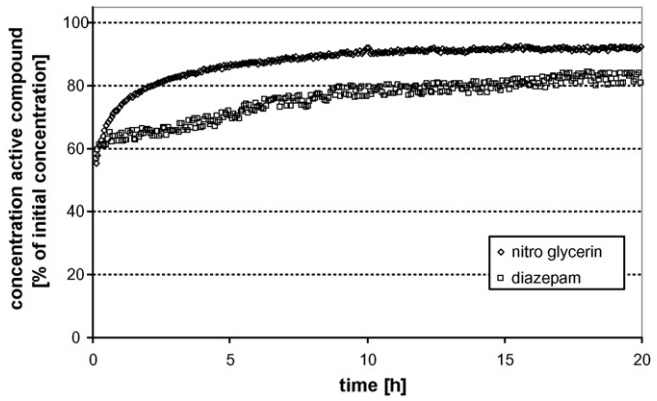

Fig. 5. Long-term sorption kinetics of nitroglycerin and diazepam into PVC tubes (DEHP, shore 80).

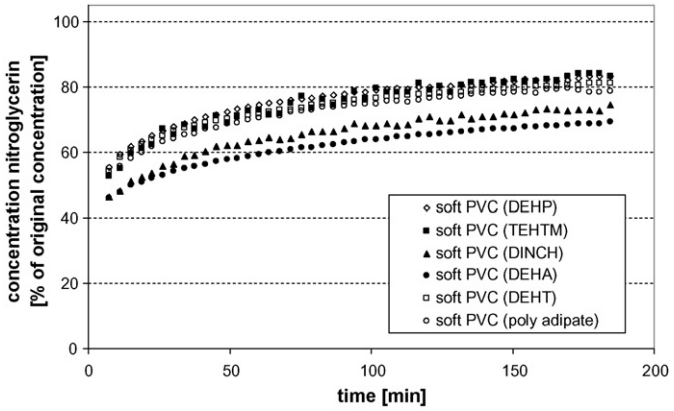

Fig. 6. Concentration of nitroglycerin after passing PVC tubes with different plasticizers at the same shore hardness of 80.

than for PVC tubes with plasticizers like DEHP, TEHTM, DEHT or poly adipate (Fig. 6). In the first minutes of the drug application, for the PVC(DINCH) and PVC(DEHA) tube only about 46% of the initial concentration nitroglycerin was found in the solution after passing the tube. The final concentration after an application time of 180 min was about 74% and 69% for these tubes, respectively. For diazepam a similar behaviour was found (Fig. 7). The concentrations after passing the PVC(DINCH) and PVC(DEHA) tubes start at about 51% of the initial concentration. Both concentrations rose up to 65% and 60% after 180 min, respectively. PVC with poly adipate

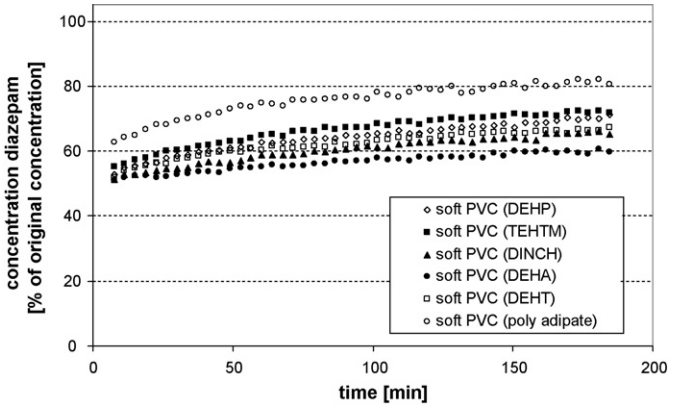

Fig. 7. Concentration of diazepam after passing PVC tubs with different plasticizers at the same shore hardness of 80.

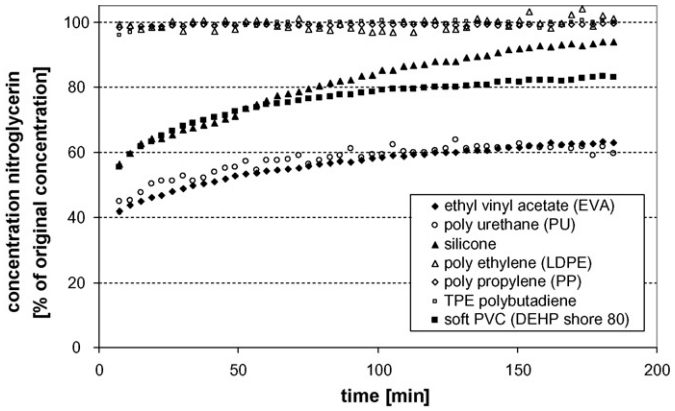

Fig. 8. Concentration of nitroglycerin after passing alternative tube materials and PVC (shore 80) as reference.

as plasticizer shows the lowest sorption of diazepam at concentrations of about 62% at the beginning of the application and about 82% after 180 min.

In Figs. 8 and 9 the sorption behaviour into non-PVC polymer materials is shown. In the graphs the standard PVC tube at a shore hardness of 80 with DEHP as plasticizer used in hospital applications was used as reference. Non-PVC materials like EVA or PU show a higher sorption of nitroglycerin into the tube material during application than for the standard PVC(DEHP) tube. For EVA and PU the starting concentrations of nitroglycerin were 42% and 45% of the initial concentrations, respectively. The investigated silicone tube shows a similar initial concentration like the standard PVC(DEHP) tube, but results in a higher final concentration after 180 min (94%). On the other hand, the alternative tube materials PE and PP show a significantly lower sorption than the standard PVC tube. For diazepam, the lowest concentrations after passing the tubes were found for silicone and PU starting from 48% and 52%, respectively. Similar as for nitroglycerin, for PE and PP a nearly constant concentration of diazepam was found during the application time of 180 min. For both drugs, in the first few minutes the concentration of nitroglycerin and diazepam in the applied solutions drops for about 2% in the case of nitroglycerin and about 8% for diazepam.

3.2. Mathematical modelling of the sorption behaviour

Several approaches have been published in the literature to predict the sorption behaviour of drugs into polymeric contact

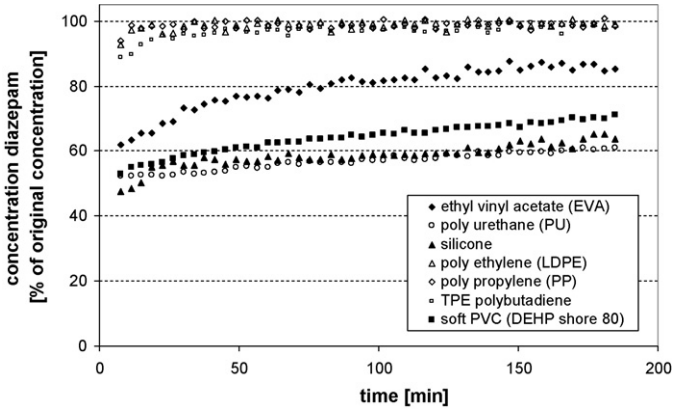

Fig. 9. Concentration of diazepam after passing alternative tube materials and PVC (shore 80) as reference.

media (Piringer and Baner, 2008; Jenke, 1993; Atkinson and Duffull, 1991; Roberts et al., 1980). For static applications, e.g. packaging of pharmaceutical drugs, the sorption/leaching behaviour can be easily predicted using mathematical diffusion models (Piringer and Baner, 2008). On the other hand dynamic systems, which were investigated in this study, are much more difficult to simulate because some of the typical boundary conditions of the mathematical models might need to be modified. For example the concentration of the migrant is not constant during sorption. In the case of the pumped liquids, the compound will be absorbed continuously, which results in a concentration gradient of the drug solution from the beginning of the tube to the end.

The continuous sorption behaviour of the plasticized PVC tubes was simulated by a system with intermittent flow. In detail the intermittent diffusion model works as follows. It is assumed that a polymeric tubing is brought in repeated contact with a drug solution. For each cycle the tubing is filled instantaneously with the drug solution and kept in contact for 7.5 min. The contact time is calculated from the ratio of the volume of the tubing [in ml] over the flow rate of the solution [in ml min^{-1}]. After the stagnation period of each cycle, the solution with decreased drug concentration is replaced instantaneously with drug solution exhibiting the initial concentration. The concentration profile of the active component in the polymeric tubing from the previous cycle is changed during the next cycle due to sorption of the drug. Using this procedure the concentration of the drug in the tubing increases stepwise after each cycle, instead of a continuous increase when in contact with a continuously flowing solution. The procedure is repeated 24 times in order to simulate the total flow time of 180 min of the drug solution used in the experimental study. The diffusion equation (Fick's second law – one dimensional) is solved numerically by the applied software (Roduit et al., 2005). The software calculates the concentration profile of the active component in the polymer and in the contacting solution for each cycle based on the following inputs: (i) initial concentration of the active component in the solution and in the polymer for the first cycle, (ii) the concentration profile of the active component in the polymer from the previous cycle (for the further cycles), (iii) the volume, thickness and density of the polymer, (iv) the contact area and volume of the drug solution, (v) time and temperature of contact and (vi) diffusion and partition coefficient of the active component. Based on the procedure described above the diffusion and partition coefficients characterising a given polymeric tubing in contact with a given drug solution were derived through comparison of modelled solution concentration profiles over flow time against experimental values.

Fig. 10 shows the calculated concentration profile of the nitroglycerin solution pumped through a plasticized PVC tube (shore 80) in comparison to the experimental results. Due to the fact that the partition coefficient as well as the diffusion coefficient for nitroglycerin in the investigated PVC(DEHP) tube was only roughly known, the first simulation was established using a constant diffusion coefficient for nitroglycerin in PVC. With the partition coefficient $K = 50$ and a constant diffusion coefficient $D = 8 \times 10^{-8}$ cm^2 s^{-1} the concentration profile of nitroglycerin during the application could be well simulated for long flow times. In the second step the partition coefficient was kept constant and the diffusion coefficient was varied in order to simulate the concentrations found in the nitroglycerin solutions short time after passing the administration set. A simulation of the experimental concentrations failed for short flow times if a constant diffusion coefficient was applied. The change of the diffusion coefficients for nitroglycerin in plasticized PVC at room temperature is shown in Fig. 11. These results clearly indicate, that the sorption of nitroglycerin into the PVC tube alters the diffusion behaviour of the polymer over flow time, which results in an increase of the diffusion coefficient of nitroglycerin over time.

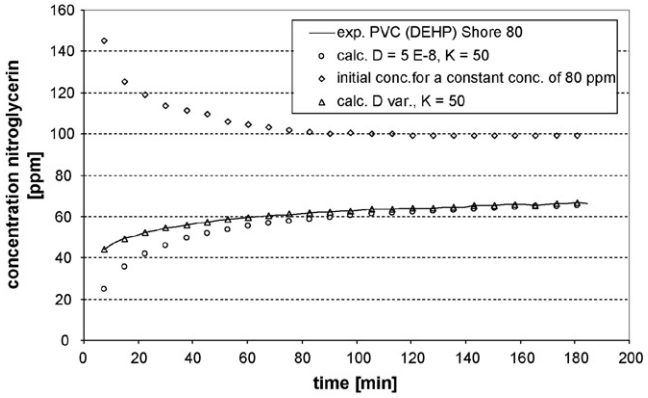

Fig. 10. Calculated concentration of nitroglycerin in the drug solution pumped through PVC tubes (shore 80) in comparison to the experimental results and calculated concentration of nitroglycerin in the initial solution resulting in a constant concentration of 80 ppm in the applied solution.

After 180 min flow time the diffusion coefficient was not constant over time, which indicates that the equilibrium was not reached. At the end of the flow experiment the concentration of nitroglycerin was constant at about 82% of the initial concentration.

Based on the diffusion and partition coefficients determined by diffusion modelling from the flow experiments performed the concentration profile of the feeding drug solution with constant flow could be simulated which results in an output solution from the polymeric tubing with a well defined and constant active component concentration.

In Fig. 12 the calculated concentration flow profile for diazepam is shown. The simulation fitted best to the long-term flow experimental data with a partition coefficient $K = 300$. In comparison to nitroglycerin, the partition coefficient of diazepam is significantly higher, which will lead to higher concentrations of diazepam in the plasticized PVC tube at equilibrium. On the other hand, the diffusion coefficient of diazepam for short flow times (2.7×10^{-10} cm^2 s^{-1}) is one order of magnitude lower than for nitroglycerin (8.0×10^{-9} cm^2 s^{-1}). Similar to the nitroglycerin kinetics, the experimentally determined concentration flow profile could be simulated only when the diffusion coefficient of diazepam was altered. Therefore the sorption of diazepam also swells the PVC polymer which leads to increasing diffusion coefficients over time (Fig. 13). The simulated partition and diffusion coefficients for given PVC(DEHP) pairs were used in a second calculation to simulate the initial concentrations profile of the feeding drug solution

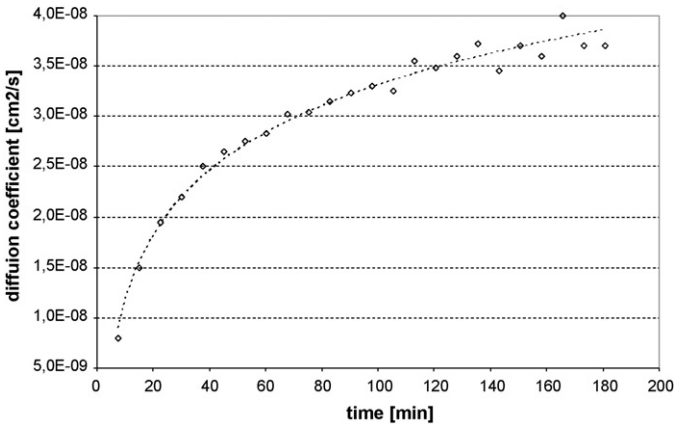

Fig. 11. Alteration of the diffusion coefficients of nitroglycerin in PVC (shore 80) derived from the simulation of the sorption of nitroglycerin in to the PVC tube.

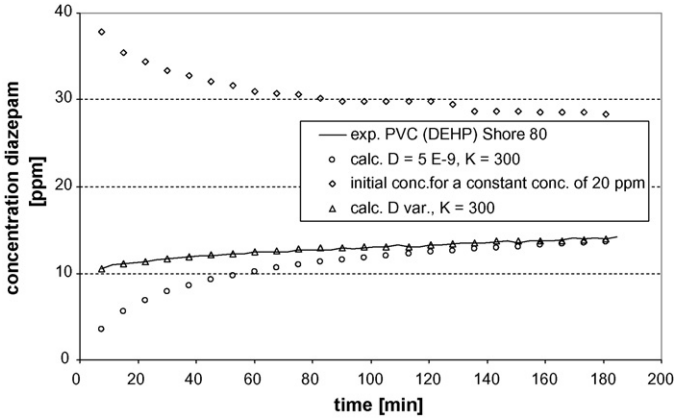

Fig. 12. Calculated concentration of diazepam in the drug solution pumped through PVC tubes (shore 80) in comparison to the experimental results and calculated concentration of nitroglycerin in the initial solution resulting in a constant concentration of 20 ppm in the applied solution.

to assure a constant concentration flow profile after passing the administration set. Figs. 10 and 12 show these initial concentration flow profiles for nitroglycerin and diazepam, which must be established in order to assure a constant concentration for nitroglycerin (80 ppm) and diazepam (20 ppm) after pumping through the administration sets. For nitroglycerin a starting initial concentration of 145 ppm has to be established. During infusion the concentration of the feeding solution needs to be reduced down to a steady state concentration of about 99 ppm. Due to the fact that the PVC tube is not completely saturated as well as the permeation of nitroglycerin to the environment should be taken into account, the steady state concentration of 99 ppm is significantly higher than the target concentration for nitroglycerin of 80 ppm used in this study. In the case of diazepam a starting initial concentration of about 38 ppm is required to establishing a target concentration of 20 ppm at the beginning of the application. The concentration flow profile should be reduced during infusion to 28.3 ppm after 180 min. For diazepam, the steady state concentration is not reached after 180 min, which can be explained by the lower diffusion coefficient of diazepam in PVC in comparison to nitroglycerin. It should be noted here, that the concentration of the drug solutions does not influence the sorption behaviour of the drugs into the PVC(DEHP) tubes (Figs. 3 and 4). Therefore the applied modelling approach can be used for the calculation of other concentration profiles, which might be applied to the patient. Instead of a feeding drug solution

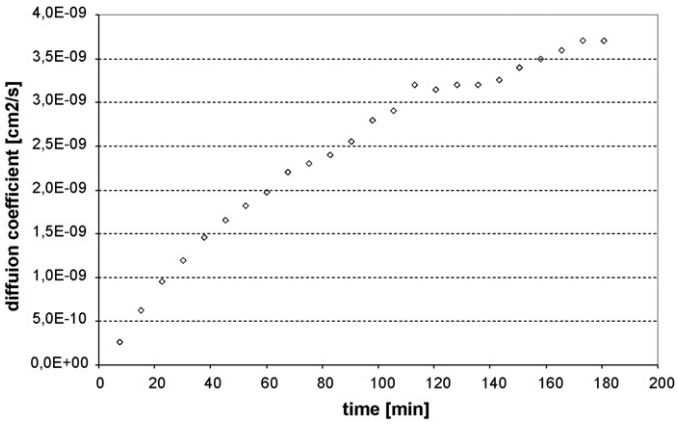

Fig. 13. Alteration of the diffusion coefficients of diazepam in PVC (shore 80) derived from the simulation of the sorption of diazepam into the PVC tube.

with an initial concentration profile but constant flow a feeding solution with constant concentration but decreasing flow might be simulated (figure not shown). Accordingly changes in the flow rate can be considered in the simulation with changing contact times for the cycles.

Another possibility to stabilize the concentration of the drugs in the pumped solutions is the pre-equilibration or pre-conditioning of the administration set with the applied drug solution. Regarding nitroglycerin with a partition coefficient of 50 and a target concentration of 80 ppm in the applied drug solution, a concentration of 4000 ppm in the PVC tube has to be established in order to tie up the sorption of nitroglycerin into PVC. For diazepam (K = 300, c = 20 ppm) 6000 ppm has to be established in the PVC tube before administration of the drug solution. Using this approach, for each drug solution and target concentration an individual tube system has to be established, which is hardly to realize in the day-by-day business of hospitals.

Octanol/water coefficients were suggested for the prediction of the sorption into PVC infusions bags (Illum and Bundgaard, 1982; Illum et al., 1983; Atkinson and Duffull, 1991; Jenke, 1993). Roberts et al. (1983) found an octanol/water coefficient of 41.8 and a PVC/water coefficient of 115.2 for nitroglycerin. Illum and Bundgaard (1982) reported an octanol/water coefficient of 159 and a PVC/water coefficient of 39.8 for nitroglycerin. For diazepam an octanol/water coefficient of 501 (Illum and Bundgaard, 1982; Biagi et al., 1980) and 456 (Kowaluk et al., 1981) was reported. The PVC/water coefficient for diazepam was found to be 79.4 (Illum and Bundgaard, 1982). It is interesting to note that the octanol/water coefficients for nitroglycerin and diazepam have huge deviations. However, as a result, the octanol/water partition coefficients found in the above mentioned literature are in agreement with the partition coefficients of 50 for nitroglycerin and 300 for diazepam, respectively, assumed for the mathematical modelling within this study.

4. Conclusions

The results of this study show that the tube material as well as the amount of plasticizer is influencing the concentration of active pharmaceutical compounds in solutions pumped through tubes during infusion. Even if the contact time of the solution is low, the tube materials show a significant sorption of the active ingredients into the tube materials. The shore hardness of the PVC tube as well as the type of plasticizer used in the PVC tube influences the sorption behaviour. Both have an influence on the diffusion coefficient as well as on the partition coefficient of a given active compound. The plasticizer might change the polarity of the plasticized PVC which might lead to an alteration of the partition coefficient, whereas the hardness of the PVC directly influences the diffusion coefficient of the active compound in the polymer. Due to the fact that the amount of sorption is varying over time, the concentration of the active pharmaceutical compound in the solution after passing the infusion administration set is not constant. This makes the application of a constant concentration of a certain active ingredient to the patient very difficult. On the other hand, the other investigated alternative tube materials like PE or PP show a significantly lower sorption compared to PVC plasticizer systems.

Nitroglycerin and diazepam have been used within this study as model compounds for the sorption. It is most likely that other active ingredients of pharmaceutical solutions are absorbed in a similar manner. However, the amount of sorption depends on the polymer/drug solution systems. Polar to medium polar polymers with high diffusivity like plasticized PVC in combination with small molecules (e.g. nitroglycerin) can be considered as the worst case for sorption. Partition coefficient of active components between the

polymer and its solutions as well as the diffusion coefficient of the molecule in the polymer matrix are the main factors, which determine the sorption behaviour of a drug during infusion through an administration set. The data of this study show also, that swelling of the polymer matrix influences the diffusion behaviour of the compound in the polymer. Swelling agents are not necessarily the active compound itself. In general every compound of the drug formulation can act as a swelling agent, which might increase the sorption of the active ingredient into the administration set. Therefore different drug formulations with the same active ingredient might behave different in view of its sorption behaviour. It is therefore necessary to get a deeper insight into the interaction of different drug solutions/application set combinations in order to evaluate the concentration over flow time of the active pharmaceutical ingredient over administration time to the patient. Based on the results of the sorption simulation, initial concentration flow profiles for nitroglycerin and diazepam could be established, which result in a defined and constant active component concentration after passing the infusion administrations sets.

The proposed methodology of this study represents a straight forward approach for the assessment of the drug sorption in dynamic flow systems based on experimental data as well as mathematical diffusion modelling. 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.

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