Substantial drop of plasticizer migration from polyvinyl chloride catheters using co-extruded thermoplastic polyurethane layers

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ABSTRACT

The flexibility and required softness of polyvinyl chloride (PVC) -one of the most widely used polymeric materials for medical device production- is achieved by the addition of an appropriate amount of plasticizer (up to 40 %) into the polymer matrix. As plasticizers are not chemically bound to PVC they can easily migrate to surrounding media such as saliva, blood, plasma or serum resulting in undesirable toxic effects. Migrations of plasticizers from PVC can be significantly suppressed by embedding plasticized PVC into another -'less harmful'-polymer, thus preventing its direct contact with the surrounding media. Co-extruded TPU/PVC/TPU catheters were prepared with various thicknesses of thermoplastic polyurethane (TPU) layers to evaluate the retarding effect of the protective TPU layer on releasing bis(2-ethylhexyl) terephthalate plasticizer (the only one approved by European Pharmacopoeia). A substantial difference was found in the migration of plasticizer from non-coated and coated (three-layer) catheters into a saline solution and acetonitrile which was dependent on the time exposed to the concentration of released plasticizer determined simultaneously by reverse-phase liquid chromatographic technique and weight loss analysis. The results proved that the TPU inner and outer layers represent an efficient protective barrier and significantly reduce amounts of released plasticizer.

Keywords: Co-extrusion Polyvinyl chloride Bis(2-ethylhexyl) terephthalate Plasticizer leaching High performance liquid chromatography

1. Introduction

Plastic materials play a crucial role in many branches of application owing to their cost-effectiveness and numerus positive attributes, for instance workability. Polyvinyl chloride (PVC) along with polyethylene and polypropylene rank as the most widely used polymeric materials **[1].** The dominant position in medicine is held by PVC **[2]** also due to the flexibility of its final products. This property is achieved by the high presence of added plasticizers achieving up to 40 % **[3]** while PVC itself contributes by approximately 55 %, the remainder is formed of various additives. The advantage of

such prepared compounds -its flexibility-over other candidates in the production of e.g. catheters is apparent and provides certain comfort in their application from the patients' viewpoint. However, an application of common plasticized polyvinyl chloride (pPVC) is accompanied by an adverse phenomenon, specifically by the non-negligible and potentially harmful migration of plasticizers into the surrounding media as they are not covalently bound to PVC.

Plasticizers -in general- are high boiling point organic liquids consisting of polar groups and linear parts added to polymers to improve their processability, flexibility and distensibility even at low temperatures **[4].** During plasticisation polar groups of plasticizers interact with polar groups of polymer substituting in this way the polymer-polymer interactions with the polymer-plasticizer ones. The linear parts act as spacers between PVC polymer chains increasing their mutual distance. This process weakens the binding between adjacent polymer chains, imparting much higher flexibility and other desirable physico-mechanical properties of the polymeric materials **[5-7].** Generally, the presence of plasticisers reflects in the reduction of glass transition temperature and tensile strength and is simultaneously accompanied by an increase in elongation. Since plasticizers in PVC are not chemically bound to polymer backbone, they can leach out when a pPVC containing medical device comes into contact with body fluids such as blood, serum, saliva and intravenous infusion liquids **[8,9].**

Leaching of plasticizers from pPVC becomes a serious problem because of the two following aspects. Firstly, the mechanical properties, transparency and physical characteristics of pPVC are considerably changed **[10,11].** Among other things a decrease in plasticisation results in stiffer and more brittle pPVC products. This can result in an uncomfortable experience for patients when catheters are applied. Secondly, extracted plasticizers may represent a relevant risk, especially for patients undergoing transfusions, dialysis, or aphaeresis, since there is a great concern about toxicity of plasticizers and its metabolites **[8,12]**.

The measures taken for reducing plasticizer migration should suppress at least one out of three migration paths: diffusion towards the pPVC surface, passage through the surface, and penetration to the neighbouring medium. In principle, there are five possibilities to reduce the dangerous impact of migrated plasticizers on human health:

1) curing of pPVC,
2) replacing unsuitable plasticizers in pPVC compounds,
3) replacing pPVC with another materials,
4) making a blend of pPVC with other materials,
5) surface modification of catheters.

1.1. Curing of pPVC

It was shown **[13,14]** that increasing the dose of irradiation results in a continuous decrease of plasticizer leakage caused by crosslinking and grafting reactions. Oxygen and argon plasma treatments **[15,16]** contributes to a more even distribution of plasticizer within the pPVC material as normally plasticizers exhibit a tendency to cumulate closer to the surface, even for lower proportional participation. Physical and chemical modifications of PVC materials to prevent plasticizer migration are presented in Ma et al. **[2]**, internal plasticization (a plasticizer is covalently bound to the PVC backbone) is comprehensively reviewed in Skelly et al. **[17].**

1.2. Replacing unsuitable plasticizers in pPVC compounds

In this context as emphasized by Bernard et al. **[18]** it is necessary to carry out sufficiently reliable experimental methods to determine plasticizer leakage. Various methods are presented in Al Salloum et al. **[19**] and Bernard et al. **[20].** Various plasticizers and a comparison of their migration is analysed in Bernard et al. **[21]** and Haned et al. **[22].** Leaching rates can be reduced by using branched and hyper-branched plasticizers **[23-26]**. Generally, usage of plasticizers with large molecular mass or high degree of branching significantly contributes to plasticizer immobility. Other approaches are presented in **[27-32].** Bodaghi **[33]** presents an overview of reactive plasticizers (covalently linked to the polymer chains) for two groups: a) binding to the polymer (PVC) via the nucleophilic substitution reaction, b) plasticizers having an alkyne group binding to the polymer by the click reaction. However, a substantial factor influencing migration rate is the flow rate of the transported liquid **[34].** Nevertheless, it is necessary to point out that at present bis(2-ethylhexyl) terephthalate (DEHTP) is the only plasticizer approved in European Pharmacopoeia for use in flexible pPVC medical devices **[8].**

1.3. Replacing pPVC with another materials

Biocompatible and biodegradable thermoplastic polyurethane TPU and polyolefins, as low density polyethylene (LDPE) or polypropylene (PP), are the two most employed types of thermoplastic candidates to replace pPVC. PP was studied by Grenadyorov et al. **[35],** biocompatible and biodegradable TPU by Gharibi and Agarwal [36] and Liu et al**. [37].** Beside these most commonly examined substitutions, utilisation of catheters involving ethylene vinyl acetate (EVA), low density polyethylene (LDPE), thermoplastic olefin elastomers (TPO), isobutyl, eth-ylenepropylene (EPDM) and silicon rubbers as well as compounds based on these materials could be found in research practice **[38]**

1.4. Making a blend of pPVC with other materials

Huang and Chen [39] consecutively tested four different polymeric materials and obtained a best result blend of pPVC with TPU. Ajili et al. **[40]** introduced blends of TPU with PP with the best ratio 4/1, while modification via ethylene-vinyl acetate to this blend with an optimal ratio 16/4/1 was defined additionally **[41].** Adding nanoparticles seems to be another way to restrict plasticizer migration **[42].** Nanoparticles easily adsorb other substances on the surface due to a large portion of unsaturated bonds on their surface. Consequently, the restricted mobility of nanoparticles substantially reduces movement of plasticizers.

1.5. Surface modification of catheters

Surface modification can be carried out either by physical or chemical methods. The goal of both methods is to initiate massive crosslinking of the molecular chains at pPVC surface aiming to create a threedimensional network structure. This structure should protect plasticizers from passage through the pPVC surface. Reddy et al. **[43]** treated pPVC with poly(azido acrylate)s then followed by irradiation under UV light to prevent plasticizer migration. Bernard et al. **[44]** applied a sol gel hybrid coating to suppress DEHTP migration from PVC matrix. Munch et al. **[45]** investigated the potential effects of phospholipid-lining as anti-coagulation coating. Surface modification of TPU material was studied by Gharibi and Agarwal **[36]** and Liu et al. **[37].** Apart from plasticizer migration the surfaces of an indwelling catheter offers sites for the adherence of bacteria to form biofilms, this can lead to various infections **[46].** Bacterial exposure of pPVC significantly intensifies migration **[47].** This stimulates a development of antibacterial and antifouling surface treatment of indwelling catheters **[37,48,49]** or

direct modification of polymeric compound **[37,46,49,50].** Tokhadze et al. **[6]** described effect of various materials (TPU, SEBS, PU, TPO, and PE) coextruded together with PVC in order to retard plasticiser release and decrease drugs (Diazepam and insulin) sorption, however in this study the effect of coextruded layer thickness is neglected, moreover the thickness of coextruded layers are not defined at all.

As efficiency of the hitherto applied alternatives has its pros and cons there is still a lot of open questions and no trend from the above mentioned alternatives is unequivocal. The aim of this contribution is to propose a co-extrudated pPVC catheter (as plasticizer used officially approved DEHTP) covered from inside and outside by a TPU layer. Catheters with TPU layers of various thicknesses were prepared and investigated in order to evaluate the influence of TPU layer thickness on DEHTP migration with regard to find compromise between catheter cost and its efficacy to hinder plasticizer leaching. It will be shown that in this case of multilayer TPU-PVC-TPU catheters migration of DEHTP is dramatically dropped.

2. Materials and methods

2.1. Materials

Medical grades of plasticized polyvinyl chloride (RB 3, produced by ModenPlast Medical, S.r.l, Ubersetto di Fiorano, Italy) and thermoplastic polyurethane Tecoflex 93A (supplied by VELOX GmbH, Hamburg, Germany) with a density of 1.23 and 1.08 g/cm^3, respectively, were used for catheters extrusion and co-extrusion.

Acetonitrile (ACN) of HPLC grade (supplied by VWR Internal, Stribrna Skalice, Czech Republic) and ultrapure Milli-Q water were employed for high performance liquid chromatography (HPLC) analysis. Standard of bis(2-ethylhexyl) terephthalate was supplied by Sigma-Aldrich (Prague, Czech Republic).

The material properties are summarized in the Supplement, Table S1.

2.2. Catheters fabrication

Pure pPVC tubes with outer/inner diameters of 5.4/3.8 mm, respectively, marked as PVC sample in the text below, were produced using an extrusion line equipped with a twin-screw extruder (Lab-Compounder KETSE 20/40, Brabender GmbH & Co. KG, Duisburg, Germany). Consequently, this extrusion line was supplemented by a laboratory extruder (BOCOMATIC EB25, Boco Pardubice Machines s.r. o., Pardubice, Czech Republic) and a Tomas Bata University designed coextrusion die (see Fig. 1) supplied by Compuplast s.r.o. (Zlin, Czech Republic) to prepare three-layer TPU/PVC/TPU tubes.

The constant outer diameter 5.4 mm of co-extruded catheters was kept through speed control of haul-off unit and precisely inspected using a 2-axis laser device (AccuScan 5040, BETA LaserMike Inc., Dayton, OH, United States). The size of 3.8 mm for an inner diameter was controlled through co-extruded tubes inner air pressure and checked via calibrated cone gauge. Various thicknesses of TPU layers were prepared varying a co-extruder screw speed.

To evaluate the actual TPU layer thicknesses, transverse sections of catheters were examined employing a transmitted light optical microscope (Carl Zeiss NU, Jena, Germany) supplemented with a digital camera (Sony DSC F717, Sony Corporation, Tokyo, Japan).

2.3. Leaching tests

In order to compare the amount of DEHTP released from extruded mono-layer and co-extruded three-layer tubes, two different leaching tests were performed. In the first test, isotonic saline solution (0.9 %, w/ v of NaCl in distilled water) was used as an extraction medium simulating human body conditions. The samples of the investigated tubes with two different TPU layer thicknesses were cut to a defined length, bent in a midway to form U-shaped specimens, placed in a sealed volumetric flask (capacity volume of 250 mL) filled with leaching saline medium and extracted for 6, 12, and 24 h, 7 and 30 days in a shaking incubator Orbital SI500 (Stuart, Stone, U. K.) at the temperature of 37 °C and circulation motion speed of 80 rpm.

To assure a contact solely with TPU layer and avoid direct contact with PVC core, level of leaching medium during extraction was below the catheters ends, hence only an outer surface of catheter was in the contact with the leaching medium. For analogous results comparison, reference extraction of bare PVC catheters of corresponding diameters was performed under identical conditions.

The second test was conducted with the aim to evaluate TPU barrier properties at stressed conditions.

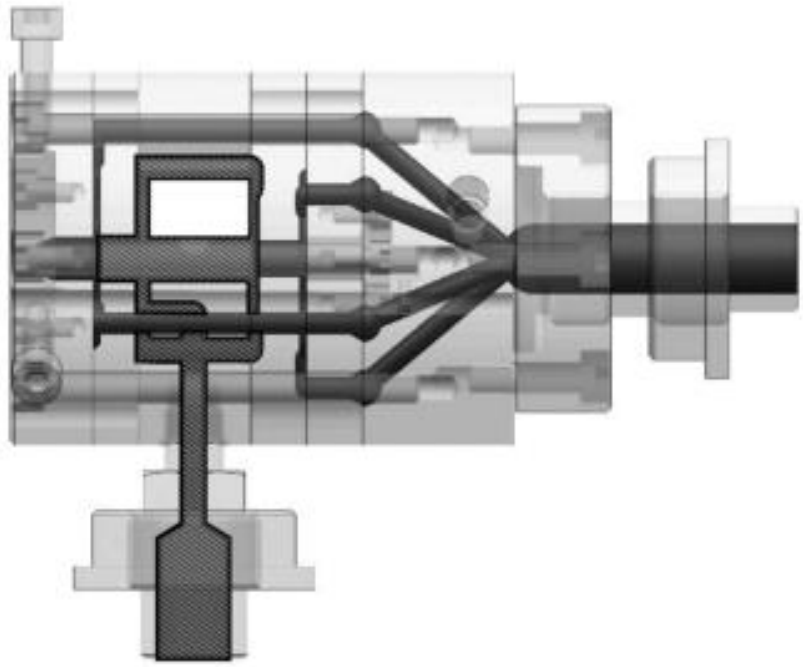

Fig. 1. Scheme of the used co-extrusion die.

The second test was conducted with the aim to evaluate TPU barrier properties at stressed conditions. In this case the U-shape specimens of the investigated tubes with a length of approximately 4 cm were placed in a vial with 2 mL ACN and extracted without shaking for 2, 4, 8, 12, and 24 h at the temperature of 37 °C. Prior to extraction all samples were accurately weighed. After expiring chosen time intervals, the specimens were removed from ACN and dried in the oven at the temperature of 37 °C up to achieving a constant weight. The amount of migrated plasticizer was then calculated from the

specimens' percentage weight loss. Also in this case, the extract of bare PVC catheters was used as a reference.

As the standard solvent extraction procedures are time-consuming and cause solvent waste problems, solid phase extraction was employed. DEHTP for HPLC analysis was isolated from saline solution using the Oasis® HLB solid phase extraction cartridges (Waters Corporation, Milford, MA, U.S.A.). The cartridges are composed of hydrophilic-lipophilic-balanced sorbent and were employed according to manufacturer recommendation. Prior to sample load, cartridges were equilibrated with methanol and washed with water. After the leachates passed through, they were washed with water/methanol mixture (1/9, v/v) to remove impurities. Consequently, DEHTP was eluted out of cartridges with acetonitrile and injected directly into a HPLC system.

High performance liquid chromatography analysis was carried out employing a Breeze HPLC system (Waters Corporation, Milford, MA, U. S.A.) equipped with a dual solvent delivery system, autosampler and column heater. Chromatographic separation was performed on a Symmetry C18 reverse phase column (Waters Corporation, Milford, MA, U.S. A.) at room temperature using ACN in isocratic elution. Mobile phase flow rate of 1 mL/min and injection volume of 70 µL were employed. The eluent was monitored at 196 nm with a Waters 2487 dual λ UV detector (Waters Corporation, Milford, MA, U.S.A.). Data processing was performed with Breeze HPLC software. Quantification of DEHTP leached into saline solution was achieved by external calibration using standard solutions of DEHTP.

3. Results and discussion

Dependence between co-extruder screw speed, v, in revolutions per minute (rpm), and TPU layer thickness, δ, is depicted in Fig. 2. As the correlation coefficient between these two quantities attains the value of 0.998 it is possible to propose as a first approximation a linear relationship between these two variables.

$$\delta = 52 + 6{\cdot}1\ v \qquad (1)$$

More detailed specification of the samples used for extraction studies is listed in the Supplement (Table S1).

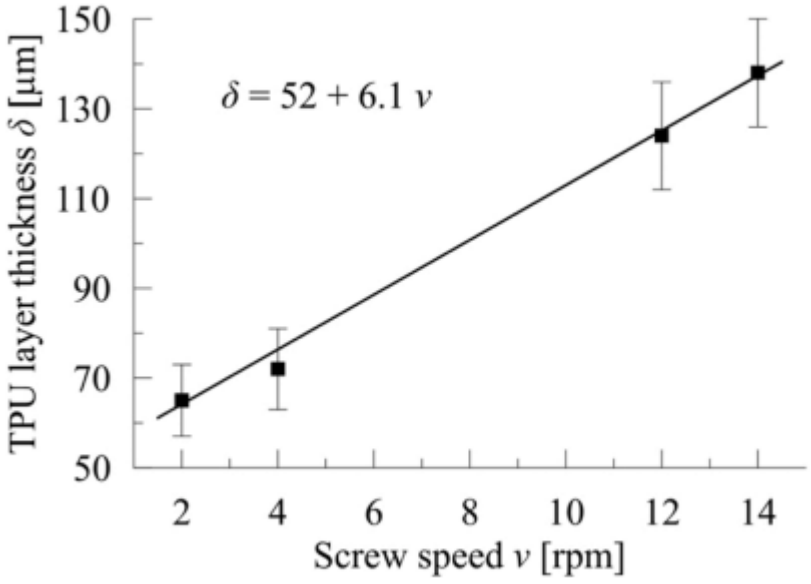

Fig. 2. Thickness of co-extruded TPU layer, S, as a function of co-extrusion screw speed, v.

The chosen examples of microscope images of co-extruded tubing are shown in Fig. 3. From each tube, two sections were inspected and measured. In each section the outer layer thickness was measured at 10 different locations around the circumference. The averages are summarized in the Supplement (Table S2).

Concentrations of plasticizer leached from the immersed surface of bare PVC and co-extruded TPU/PVC/TPU catheters into saline solution after selected time periods (6, 12, 24, 168, and 720 h) are presented in Fig. 4. Values of DEHTP concentration are normalized with an area of the catheters being in contact with leaching medium. In all cases the DEHTP leaching rate gradually decreased with the prolonged extraction time as documented in Fig. 4 (the abscissa is in the logarithmic scale). This trend can be explained by gradual equilibrium establishment in investigated systems due to counter-going diffusion processes **[51].** In other words, as DEHTP molecules move out of PVC to leaching medium, arisen vacant places in PVC are slowly filled with the molecules of surrounding leaching medium. Therefore, in the initial stage of leaching DEHTP migration is faster and then gradually slows down till a temporary equilibrium of DEHTP concentration and leaching medium is established.

The results of HPLC analysis indicate notable differences between DEHTP migration from extruded and co-extruded catheters already after 6 h of leaching. The highest DEHTP concentration was, in accordance with presumptions, determined in bare PVC tubes extracts and its concentration decreased with increasing thickness of protective TPU layer. Using logarithmic fitting data interpolation it can be shown that amount of released DEHTP from PVC catheters after six hours complied with plasticizer amount released from co-extruded tubes with TPU layer thickness of 63 pm (PVC-TPU 2) after roughly 220 h. A positive role of TPU layers is even more progressive using catheters with 124 pm TPU layer (PVC-TPU 12). In this case DEHTP release did not reach even after 720 h extraction the level of DEHTP leached in 6 h from catheters with the TPU layer of half thickness. From the comparison of the two coextruded sample types it is evident that increase of a TPU layer thickness significantly reduces the content of released DEHTP.

The experimental data in Fig. 4 were approximated using a relation.

$$c_s = \mathrm{A} + \mathrm{B}\cdot\log(t), \qquad (2)$$

where the parameters for the individual co-extrusion screw speed are summarized in Table 1. As the slope is identical for all three co-extrusion screw speeds (B = 5) it implies that the normalized concentration of DEHTP is composed of two terms:

1) a value corresponding to the initial time interval (in this case 6 h) which strictly differentiate among the individual co-extrusion screw speeds,
2) an additive term common for all co-extrusion screw speeds.

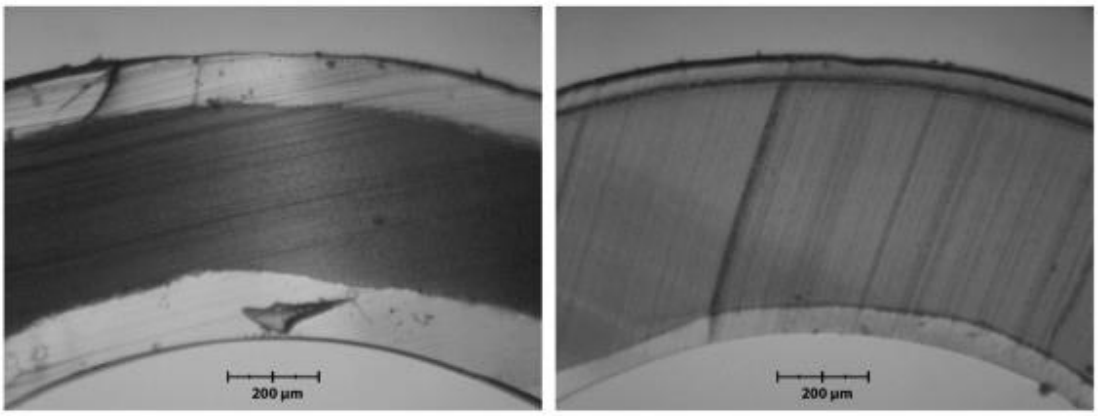

Fig. 3. Optical microscopes images of TPU/PVC/TPU catheters with two different thicknesses of TPU protective layer: (left) PVC-TPU 14; (right) PVC-TPU 4.

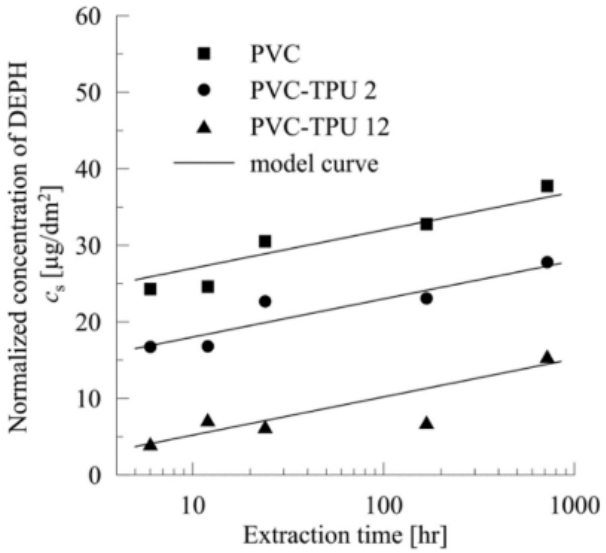

Fig. 4. Migration of DEHTP (per dm2) into saline solution at 37 °C from both the non-coated and TPU coated samples. PVC-TPU samples are labelled according to screw speed revolution. The solid lines represent logarithmic fitting of the experimental data using rel. (2). In all cases deviations of the repeated measurements do not exceed 0.5 % from the mean values (on average about 0.16 %).

Table 1 Parameters A, B, C, and D of logarithmic fittings of DEHTP releasing described through concentration change in time (cs = A + B-log(t), cv = C + D-log(t)).

Co-extrusion screw speed [rpm]	Parameters of fitting curves in Fig. 4		Parameters of fitting curves in Fig. 5	
	A	B	C	D
0	22	5	2.4	0.8
2	13	5	1.8	0.8
12	0.2	5	0.1	0.8

A drop of the fitting parameter A with increasing thickness of TPU layer, as documented in Table 1, proves that the velocity of DEHTP migration is apparently suppressed in the case of co-extruded tubes. The common value at time t of this velocity is given by a difference (A + 5-log (t)) - (A + 5-log(t_0)) = 5-log(t/t_0), where t0 represents a reference time (in this case t_0 = 6 h). In other words, if a value of the normalized concentration of DEHTP cs is known at the reference time t0 then we can evaluate cs at any time t by simply adding the term 5-log(t/t_0).

Knowledge of the only value then determines all the values along the whole curve. Nevertheless, observed behaviour could be caused by the following two factors: 1) reduction of releasing velocity is influenced by the presence of TPU layer performing here as a DEHTP diffusion barrier, or 2) reduced migration can correlate to a lower overall content of plasticizer in the tested systems "tube/saline" originating from a lower overall amount of PVC material in co-extruded samples where outer layers of the catheter are formed by TPU. From Table 1 (the values of the parameter A) it also follows that dramatic changes in migration of plasticizers are generated for lower screw speeds and the differences among higher speeds are not so progressive. However, following the proposed relation it is possible to find a sound balance between screw speeds and acceptable suppression of migration.

Fig. 5 clarifying the fundamental of plasticizer release retardation depicts concentration of DEHTP leached per total volume of PVC. The obtained data was fitted using the same functional logarithmic fitting as in the previous case where migration per immersed tube surface was evaluated.

$$c_v = \mathrm{C} + \mathrm{D}\cdot\log(t), \tag{3}$$

where C and D are the adjustable parameters. The invariability of parameter D in logarithmic data fittings shown in Fig. 5, and documented in Table 1 (D = 0.8), indicates that the rate of plasticizer migration is approximately constant. Hence, the analogous conclusions as in the preceding case concerning cs are also valid for cv. In this case an additive term attains a value of 0.8-log(t/t_0).

In order to estimate efficacy of TPU layer thickness for retardation of DEHTP migration from PVC catheters, a plot of retardation efficiency based on DEHTP concentration normalised with total volume of PVC determined after 720 h extraction (see Fig. 5) as a function of TPU layer thickness was constructed. To interpolate the retardation efficiency data -a typical representative of sigmoidal functions- the Boltzmann model was used **[52].**

$$y = \mathrm{P_2} + (\mathrm{P_1}\text{-}\mathrm{P_2})/(1 + \exp[(x - x_0)/\mathrm{s}] \tag{4}$$

In this model -describing a monotonous S-shaped course of the variable y in dependence on x- all parameters have a clear interpretation: P1 and P2 which represent an infimum (for x→-∞it holds y→P_1) and a supremum (for x→+∞ it holds y→P_2), respectively; a value x_0 determines a location where the function y attains its mean value (= (P_1 + P_2)/2), and the parameter s indicates a steepness of the slope of the function y in the vicinity of x = x_0.

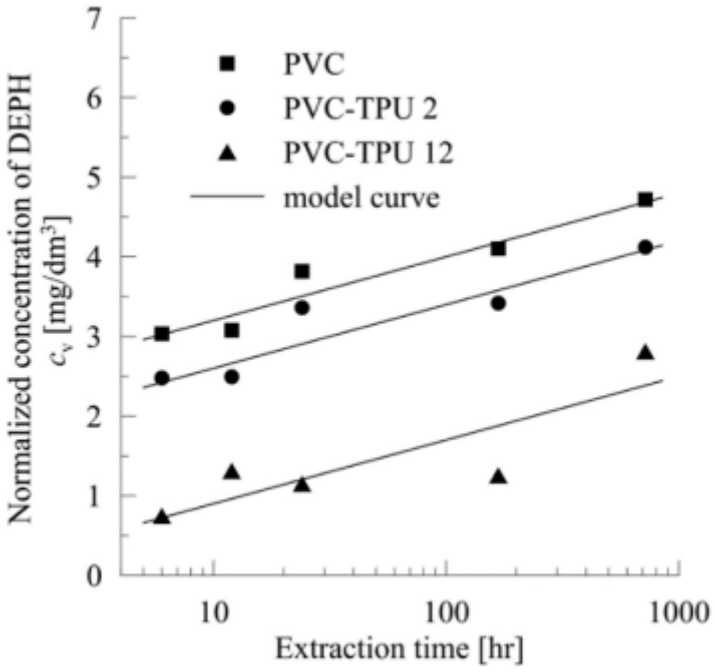

Fig. 5. Migration of DEHTP (per dm3) into saline solution at 37 0C from both the non-coated and TPU coated samples. PVC-TPU samples are labelled according to screw speed revolution. The solid lines represent logarithmic fitting of experimental data using rel. (3). In all cases deviations of the repeated measurements do not exceed 0.5 % from the mean values (on average about 0.20 %).

In this model -describing a monotonous S-shaped course of the variable y in dependence on x- all parameters have a clear interpretation: P_1 and P_2 which represent an infimum (for x→-∞it holds y→P_1) and a supremum (for x→+∞ it holds y→P_2), respectively; a value x0 determines a location where the function y attains its mean value (= (P1 + P_2)/2), and the parameter s indicates a steepness of the slope of the function y in the vicinity of x = x_0.

A notation suitable for the presented application with the efficacy r_E is rewritten in the following relation.

$$r_E = 100 + (P_1\text{-}100)/(1 + \exp[(\delta - \delta_0)/d\delta], \qquad (4a)$$

where the parameter P_2 attains a value of 100 % (TPU layer efficacy increases with its thickness), dS (=29.9) describes a slope round the inflexion point x_0 (lower values of dδ contributes to better efficacy) and δ is considered as a positive value (layer thickness), see Fig. 6. The optimized value for x_0 (=108) indicates a location from which the rate of efficacy starts its attenuation. Obviously, the model smoothly interlaces retardation efficiency of TPU coating and as such it could be utilised as a useful tool for easier description of various TPU layer thickness ability to act as a DEHTP diffusion barrier. From the graphical presentation of the Boltzmann fit in Fig. 6 it can be shown that there exists a

hypothetic effective thickness of TPU layer providing significant depression of plasticizer migration. Utilisation of the sigmoidal function for a description of efficiency is based on the assumption that a coating layer should have a specific thickness to reduce effectively leaching of plasticizer while an additional increase of layer thickness does not provide more practical protection against plasticizer migration.

Efficacy of TPU barrier properties under stressed conditions were challenged in an extraction test performed with acetonitrile as a leaching medium. Fig. 7 shows the comparison of DEHTP migration behaviour from the TPU coated and non-coated catheters determined from the weight loss analysis in ACN for various time periods. Comparing to saline solution, the DEHTP migration into ACN is apparently more intense, since ACN is one of the typical leaching solvents having good ability to dissolve terephthalates due to presence of polar bonds in the molecules. Due to this fact the extraction time was reduced to the range from 2 to 24 h.

From the weight loss analysis of the examined samples presented in Fig. 7 (left) it is obvious that a co-extruded TPU layer hinders DEHTP release as coated tubing exhibits generally lower DEHTP migration. In more detail, it was found that the sample with the 137 µm thickness of coated TPU layer showed after 24 h weight loss of approximately 10 % only, while the sample coated with 75 µm thick layer of TPU and non-coated one attained about 13 % and 17 %, respectively.

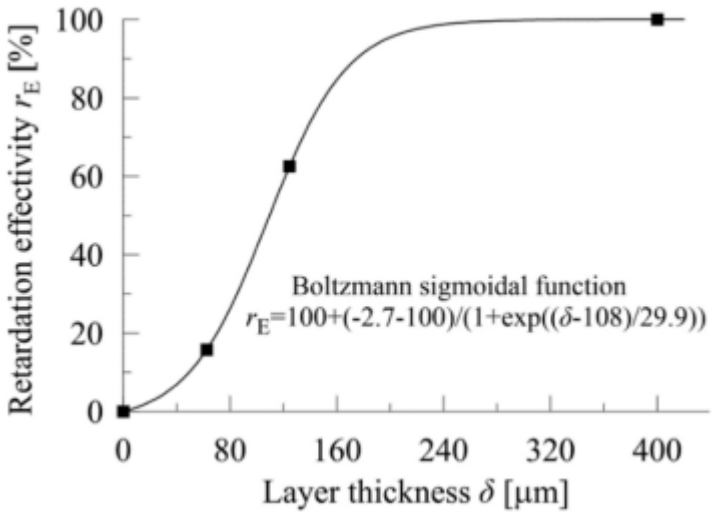

Fig. 6. Effectiveness of TPU layer thickness for retardation of DEHTP migration. The solid line represents data fitting through the sigmoidal Boltzmann function (4). Deviations of the repeated measurements from the mean values: for δ = 0 µm - 0 % (fixed value), for δ = 62.5 µm - lower than 2.5 %, for δ = 124.5 µm - lower than 8.5 %, for δ = 400 µm - 0 % (fixed value).

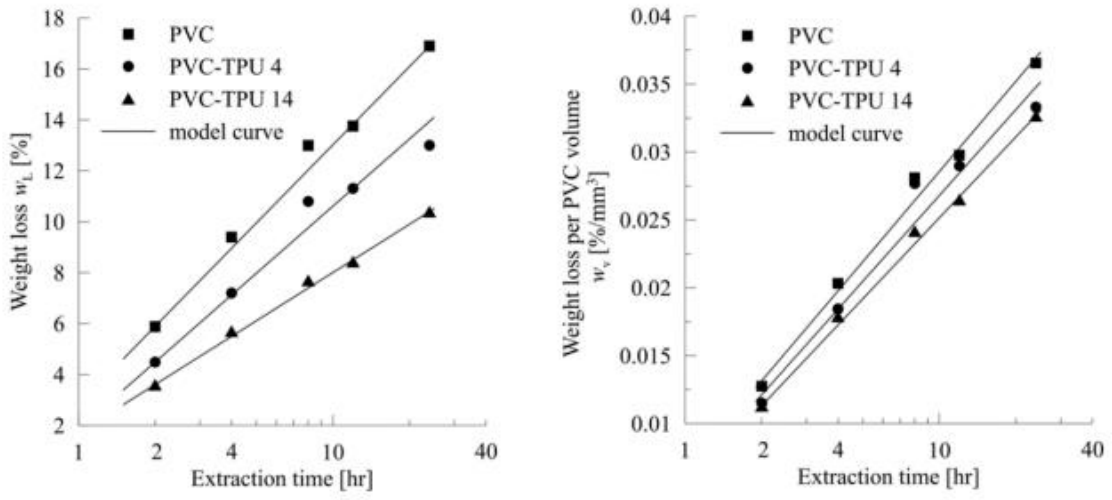

Fig. 7. Accelerated migration of DEHTP into ACN at 37 °C at selected extraction time intervals from both non-coated and coated samples, expressed as dependence of (left) weight loss of initial samples and (right) weight loss of initial samples normalised with the total amount of PVC in each tested sample. Deviations of the repeated measurements from the mean values: for PVC - 2 %, for PVC-TPU 4 - lower than 1 % (on average 0.6 5%), PVC-TPU 14 - lower than 1 % (on average 0.6 %).

The presented results indicate that the co-extruded catheters might withstand rather rough extraction conditions and still to some extent slow down DEHTP leaching. Nevertheless, as it is clear from the comparison of Fig. 7 (left) and 7 (right) described retardation of DEHTP migration is mainly associated with a decrease of absolute amount of PVC in the co-extruded catheters. Taking into account reduced volume of PVC in the coated samples it seems that the role of TPU coating is minor for suppression of DEHTP leaching into polar organic solvents. It is due to the fact that organic solvents can easily swell TPU layer enabling thus better access of solvents into PVC. This means that extent of DEHTP leaching is significantly affected not only by the thickness of a coating layer but also by the nature of surrounding media.

4. Conclusions

Release study of DEHTP from extruded PVC and co-extruded TPU/ PVC/TPU tubes was carried out with the aim to evaluate influence of TPU coating of PVC catheters on plasticizer leaching behaviour. Based on the experimental data it was found that coating of PVC catheters with TPU layers decreased the plasticizer release from tested tubings into acetonitrile -as expected- only slightly. Nevertheless, the migration test performed employing acetonitrile does not cover the real user situations where catheters are utilized for patients' treatments. Thus, more relevant complex study on leaching of DEHTP into physiologically relevant liquid, saline solution, was conducted. The results indicate that even if a TPU layer does not affect DEHTP migration velocity, it notably decreases overall leaching of plasticizer from coated tubes. Moreover it was shown that efficiency of TPU coating is strongly dependent on thickness of this co-extruded layer.

Hypothesis of existence of effective coating layer thickness however indicates the necessity of optimum co-extruded layer thickness determination for specific system (catheter/solution) in order to tune up the coating performance ratio (cost/efficiency). Hence TPU/PVC/TPU catheter features a reasonable compromise between price and user-friendliness of the product and significantly contributes to a reduction of health hazard and patients exposure related to toxic DEHTP.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mtcomm.2022.103895.

References

[1] Polyvinyl Chloride, sixth ed., Caresana, October 2021, 510.

[2] Y. Ma, S. Liao, Q. Li, Q. Guan, P. Jia, Y. Zhou, Physical and chemical modifications of poly(vinyl chloride) materials to prevent plasticizer migration - still on the run, React. Funct. Polym. 147 (2020), 104458.

[3] L. Di Landro, C. Capone, F. Inzoli, P. Malacari, P.V.C. Coextruded, tubes for biomedical application, J. Vinyl Addit. Technol. 3 (11) (2005) 111-118.

[4] C.E. Wilkes, J.W. Summers, C.A. Daniels. PVC Handbook, Hanser Publications, Munich; Cincinnati, 2005, p. 723.

[5] J.-C. Huang, R.D. Deanin, Concentration dependency of interaction parameter between PVC and plasticizers using inverse gas chromatography, Appl. Polym. Sci. 91 (1) (2004) 146-156.

[6] N. Tokhadze, P. Chennell, L. Bernard, C. Lambert, B. Pereira, B. Mailhot-Jensen, V. Sautou, Impact of alternative materials to plasticized PVC infusion tubings on drug sorption and plasticizer release, Sci. Rep. 9 (1) (2019) 18917.

[7] S. Patrick. Practical Guide to Polyvinyl Chloride, Rapra Technology Limited, Shrewsbury, Shropshire, UK, 2005, p. 162.

[8] European Pharmacopoeia, tenth ed.,Council of Europe, Strasbourg, 2020.

[9] F. Chiellini, M. Ferri, A. Morelli, L. Dipaola, G. Latini, Perspectives on alternatives to phthalate plasticized poly(vinyl chloride) in medical devices applications, Prog. Polym. Sci. 38 (7) (2013) 1067-1088.

[10] V.J.R.R. Pita, E.E.M. Sampaio, E.E.C. Monteiro, Material properties, Polym. Test. 21 (5) (2002) 545-550.

[11] X.-F. Wei, E. Linde, M.S. Hedenqvist, Plasticiser loss from plastic or rubber products through diffusion and evaporation, npj Mater. Degrad. 3 (1) (2019) 18.

[12] M.F. Aignasse, P. Prognon, M. Stachowicz, R. Gheyouche, D. Pradeau, A new simple and rapid HPLC method for determination of DEHP in PVC packaging and releasing studies, Int. J. Pharm. 113 (2) (1995) 241-246.

[13] J. Colombani, G. Herbette, C. Rossi, C. Joussot-Dubien, V. Labed, T. Gilardi, Leaching of plasticized PVC: effect of irradiation, J. Appl. Polym. Sci. 112 (3) (2009) 1372-1377.

[14] M. Ferri, F. Chiellini, G. Pili, L. Grimaldi, F.E. Tiziana, S. Pili, F. Cucci, G. Latini, Di-(2-ethylhexyl)-phthalate migration from irradiated poly(vinyl chloride) blood bags for graft-vs-host disease prevention, Int. J. Pharm. 430 (1) (2012) 86-88.

[15] X. Zhang, C. Zhang, J.M. Hankett, Z. Chen, Molecular surface structural changes of plasticized PVC materials after plasma treatment, Langmuir 29 (12) (2013) 4008-4018.

[16] X. Zhang, Y. Li, J.M. Hankett, Z. Chen, The molecular interfacial structure and plasticizer migration behavior of “green” plasticized poly(vinyl chloride), Phys. Chem. Chem. Phys. 17 (6) (2015) 4472-4482.

[17] Skelly, P.W., Li, L., Braslau, R., Internal plasticization of PVC, Polymer Reviews, Early View. (https://doi.org/10.1080/15583724.2021.1986066).

[18] L. Bernard, B. Décaudin, M. Lecoeur, D. Richard, D. Bourdeaux, R. Cueff, V. Sautou, Analytical methods for the determination of DEHP plasticizer alternatives present in medical devices: a review, Talanta 129 (2014) 39-54.

[19] H. Al Salloum, J. Saunier, A. Tfayli, N. Yagoubi, Studying DEHP migration in plasticized PVC used for blood bags by coupling Raman confocal microscopy to UV spectroscopy, Mater. Sci. Eng. C Mater. Biol. Appl. 61 (2016) 56-62.

[20] L. Bernard, D. Bourdeaux, B. Pereira, N. Azaroual, C. Barthelémy, C. Breysse, P. Chennell, R. Cueff, T. Dine, T. Eljezi, F. Feutry, S. Genay, N. Kambia, M. Lecoeur, M. Masse, P. Odou, T. Radaniel, N. Simon, C. Vaccher, C. Verlhac, M. Yessaad, B. Déecaudin, V. Sautou, Analysis of plasticizers in PVC medical devices: performance comparison of eight analytical methods, Talanta 162 (2017) 604-611.

[21] L. Bernard, R. Cueff, C. Breysse, B. Décaudin, V. Sautou, Migrability of PVC plasticizers from medical devices into a simulant of infused solutions, Int. J. Pharm. 485 (1) (2015) 341-347.

[22] Z. Haned, S. Moulay, S. Lacorte, Migration of plasticizers from poly(vinyl chloride) and multilayer infusion bags using selective extraction and GC-MS, J. Pharm. Biomed. Anal. 156 (2018) 80-87.

[23] W. Choi, J.W. Chung, S.Y. Kwak, Unentangled star-shape poly(e-caprolactone)s as phthalate-free PVC plasticizers designed for non-toxicity and improved migration resistance, ACS Appl. Mater. Interfaces 6 (14) (2014) 11118-11128.

[24] K.W. Lee, J.W. Chung, S.-Y. Kwak, Synthesis and characterization of bio-based alkyl terminal hyperbranched polyglycerols: a detailed study of their plasticization effect and migration resistance, Green Chem. 18 (4) (2016) 999-1009.

[25] Y. Feng, Z. Chu, L. Man, Y. Hu, C. Zhang, T. Yuan, Z. Yang, Fishbone-like polymer from green cationic polymerization of methyl eleostearate as biobased nontoxic PVC plasticizer, ACS Sustain. Chem. Eng. 7 (23) (2019) 18976-18984.

[26] M.W. Halloran, J.A. Nicell, R.L. Leask, M. Maric, Small molecule plasticizers for improved migration resistance: investigation of branching and leaching behaviour in PVC blends, Mater. Today Commun. 29 (2021), 102874.

[27] J. Simmchen, R. Ventura, J. Segura, Progress in the removal of Di-[2-Ethylhexyl]-phthalate as plasticizer in blood bags, Transfus. Med. Rev. 26 (1) (2012) 27-37.

[28] S.-T. Bee, W.-R. Mok, T.S. Lee, T.-T. Tee, G. Issabayeva, A.R. Rahmat, Evaluation performance of multiple plasticizer systems on the physicomechanical, crystallinity and thermogravimetry of polyvinyl chloride, J. Polym. Eng. 34 (6) (2014) 521-529.

[29] M. Bocque, C. Voirin, V. Lapinte, S. Caillol, J.-J. Robin, Petro-based and bio-based plasticizers: chemical structures to plasticizing properties, J. Polym. Sci. Part A Polym. Chem. 54 (1) (2016) 11-33.

[30] M. Matos, R.A. Cordeiro, H. Faneca, J.F.J. Coelho, A.J.D. Silvestre, A.F. Sousa, Replacing di(2-ethylhexyl) terephthalate by di(2-ethylhexyl) 2,5-furandicarboxy-late for PVC plasticization: synthesis, materials preparation and characterization, Materials 12 (14) (2019) 2336.

[31] A.K. Mazitova, G.K. Aminova, I.N. Vikhareva, Designing of green plasticizers and assessment of the effectiveness of their use, Polymers 13 (11) (2021) 1761.

[32] J. Czogala, E. Pankalla, R. Turczyn, Recent attempts in the design of efficient pvc plasticizers with reduced migration, Materials 14 (4) (2021) 844.

[33] A. Bodaghi, An overview on the recent developments in reactive plasticizers in polymers, Polym. Adv. Technol. 31 (2020) 355-367.

[34] L. Bernard, T. Eljezi, H. Clauson, C. Lambert, Y. Bouattour, P. Chennell, B. Pereira, V. Sautou, on behalf of the, A. S. G., Effects of flow rate on the migration of different plasticizers from PVC infusion medical devices, PLoS One 13 (2) (2018), e0192369.

[35] A.S. Grenadyorov, A.A. Solovyev, V.V. Malashchenko, I.A. Khlusov, Stability of a-C:H:SiOx coating on polypropylene to chemical sterilization, J. Appl. Polym. Sci. 137 (48) (2020), e49570.

[36] R. Gharibi, S. Agarwal, Favorable antibacterial, antibiofilm, antiadhesion to cells, and biocompatible polyurethane by facile surface functionalization, ACS Appl. Bio Mater. 4 (5) (2021) 4629-4640.

[37] F. Liu, W. Qu, J. Zhang, J. Liu, Q. Zhu, T. Yue, X. Xu, N. Ma, J. Ma, Y. Sun, Y. Tang, W. Zhang, P.K. Chu, Cationic alternating polypeptide fixed on polyurethane at multiple sites for excellent antibacterial and antifouling properties, Langmuir 37 (36) (2021) 10657-10667.

[38] Jacob, M., Carsten, L., Ulla, K.B., Jesper, K., Lise, M., Sonja, H.M., Identification and Assessment of Alternatives to Selected Phthalates, Danish Ministry of the Environment, 2010.

[39] C. Huang, J. Chen, Comparison of four polymeric PVC modifiers, Polym. Plast. Technol. Eng. 33 (5) (1994) 615-625.

[40] S.H. Ajili, Golshan Ebrahimi, N. Khorsasani, M.T. Studies, on TPU/PP blend and comparing it with PVC used as blood bag, Iran. Polym. J. 12 (3) (2003) 179-184.

[41] S.H. Ajili, N.G. Ebrahimi, M.T. Khorasani, Study on thermoplastic polyurethane/ polypropylene (TPU/PP) blend as a blood bag material, J. Appl. Polym. Sci. 89 (9) (2003) 2496-2501.

[42] J. Xu, X. Qiu, G. Chen, Research progress on inhibition of plasticizer migration in flexible PVC, Plastics 47 (5) (2018) 17-21.

[43] N.N. Reddy, Y.M. Mohan, K. Varaprasad, S. Ravindra, K. Vimala, K.M. Raju, Surface treatment of plasticized poly(vinyl chloride) to prevent plasticizer migration, J. Appl. Polym. Sci. 115 (3) (2010) 1589-1597.

[44] L. Bernard, R. Cueff, C. Massard, C. Blavignac, K.O. Awitor, J. Chopineau, V. Sautou, Hybrid sol gel coating: a solution to prevent interactions between plasticized poly(vinyl chloride) and injectable drugs? J. Appl. Polym. Sci. 131 (8) (2014), e40145.

[45] F. Munch, C. Hollerer, A. Klapproth, E. Eckert, A. Ruffer, R. Cesnjevar, T. Goen, Corrigendum to “Effect of phospholipid coating on the migration of plasticizers from PVC tubes” [Chemosphere 202 (July 2018) 742-749], Chemosphere 258 (2020), 127538.

[46] Y. Wang, S. Liu, K. Ding, Y. Zhang, X. Ding, J. Mi, Quaternary tannic acid with improved leachability and biocompatibility for antibacterial medical thermoplastic polyurethane catheters, J. Mater. Chem. B 9 (23) (2021) 4746-4762.

[47] A. Paluselli, V. Fauvelle, F. Galgani, R. Sempere, Phthalate release from plastic fragments and degradation in seawater, Environ. Sci. Technol. 53 (1) (2019) 166-175.

[48] M.M. Nasef, B. Gupta, K. Shameli, C. Verma, R.R. Ali, T.M. Ting, Engineered bioactive polymeric surfaces by radiation induced graft copolymerization: strategies and applications, Polymers 13 (18) (2021) 3102.

[49] B. De la Franier, D. Asker, D. van den Berg, B. Hatton, M. Thompson, Reduction of microbial adhesion on polyurethane by a sub-nanometer covalently-attached surface modifier, Colloids Surf. B Biointerfaces 200 (2021), 111579.

[50] R. Al Nakib, A. Toncheva, V. Fontaine, J. Vanheuverzwijn, J.M. Raquez, F. Meyer, Thermoplastic polyurethanes for biomedical application: a synthetic, mechanical, antibacterial, and cytotoxic study, J. Appl. Polym. Sci. 139 (4) (2022) 17.

[51] S. Lakshmi, A. Jayakrishnan, Synthesis, surface properties and performance of thiosulphate-substituted plasticized poly(vinyl chloride), Biomaterials 23 (24) (2002) 4855-4862.

[52] J. Reséndiz-Munoz, M.A. Corona-Rivera, J.L. Fernández-Munoz, M. Zapata-Torres, A. Márquez-Herrera, V.M. Ovando-Medina, Mathematical model of Boltzmann's sigmoidal equation applicable to the set-up of the RF-magnetron co-sputtering in thin films deposition of BaxSr! xTiO3, Bull. Mater. Sci. 40 (5) (2017) 1043-1047.