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Proffesional paper

Parametars for the evaluation of the quality of PVC containers for pharmaceutical preparations

Aneta Dimitrovska[1]*, Liljana Ugrinova[1], Suzana Trajkovic-Jolevska[1], Slavica Tanceva[2]

[1]*Institute of Drug Quality Control, Faculty of Pharmacy, Sts. Cyril and Methodius University, Vodnjanska 17, 1000 Skopje, Macedonia,* [2]*OHIS A.D., 1000 Skopje, Macedonia*

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Abstract

An overview of the parameters for the evaluation of the quality of poly(vinyl chloride) (PVC) containers for pharmaceutical preparations is made. The requirements for the quality of PVC containers regulated by Ph. Eur., DIN and ISO standards differ in the prescribed parameters for physical, chemical and biological examination. Different ranges of tolerance for certain parameters also exist. The comparison of the parameters prescribed for these types of containers in Ph. Eur., DIN and ISO standards is made for a more detailed evaluation of PVC container quality.

Key words: poly(vinyl chloride) containers, pharmaceutical preparations, evaluation of the quality

Introduction

The primary containers used for packing of pharmaceutical preparations should provide a physically, chemically and microbiologically stable, therapeutically effective and non-toxic product within the date of expiry.

The material used for the production of containers for pharmaceutical preparations should comprise one or more polymers, including some additives (lubricants, stabilizators, plastificators, anti-oxidants, colors and pigments, anti-static agents, etc.)

The most widely used polymers include: polyethylene (low and high density), polypropylene, poly(vinyl chloride), poly(ethylene tereftalate) and ethyl-vinyl acetate copolymer (1). The polymer of choice used for the packaging of water solutions for intravenous infusion and packaging for blood and blood elements of human origin, is plastificated poly(vinyl chloride).

Physico-chemical methods and separative techniques are widely used for the evaluation of the quality of pharmaceutical containers (2). Among the spectroscopic methods, infrared spectroscopy is the method of choice for the identification of the components that comprise the contents of the containers in question; ultraviolet spectroscopy for the identification and the quantitative determination of extractive additives that contain conjugated double bonds and aromatic rings; and atomic absorption spectroscopy for the determination of trace metals. Among the separative techniques, thin-layer chromatography is most often used for identification; high-pressure liquid chromatography for the separation of the main polymer of the additives, their identification and determination, and gas chromatography for the determination of some monomers as impurities, for example vinyl chloride (2).

The aim of this study is to determine the quality of PVC containers for pharmaceutical preparations using selected parameters, grouped as physical, chemical and biological tests. An overview and comparison of the parameters prescribed for this type of containers in Ph. Eur., DIN and DIN ISO standards will be carried out for a more detailed assessment of the quality of PVC containers.

* e-mail:aneta.dimitrovska@baba.ff.ukim.edu
tel: 126 024 Fax: 123 054

Experimental

Materials

Poly(vinyl chloride) bags for aqueous solutions for intravenous infusion (500 ml), (sample 1) and sterile containers of plasticised poly(vinyl chloride) for human blood containing an anticoagulative solution (450 ml) (sample 2).

Methods

For the evaluation of the quality of the material in question, physical, chemical and biological studies were conducted according to the steps outlined in:

- Ph. Eur.
- DIN 53 363-15 - Infusion bags and bottles made of plastic (sample 1)
- DIN ISO 3826 - Plastics collapsible containers for humanblood and blood components (sample 2)
- Internal procedures for the determination of the content of a PVC polymer; plastificator and liquid stabilizators, fillers and solid stabilizators and vinyl chloride content.

Preparation of the test solution and blank for the chemical and biological tests was done according to the steps outlined in Ph. Eur. (by autoclavation at 110 ^{0}C for 30 minutes with distilled water and sterile apirogen 0.9 % solution of NaCl for chemical and biological test, respectively).

Results and discussion

Physical tests

The physical tests of the PVC containers include examination of appearance, dimensions, thickness of the walls, resistance to temperature, pressure and sealing, resistance to centrifugation and leakage, stretching, with the goal of evaluating the physical characteristics of the packaging.

The thickness of the wall of the plastic containers should provide the packaging to be non-permeable to gases, moisture and microorganisms, thus ensuring the quality of the pharmaceutical preparation until the expiry date. Permeability for gases, moisture and microorganisms decreases with increased thickness of the wall of the containers. The thinnest plastic packaging should be 0.1 mm. Double this thickness (0.2 mm) decreases the permeability for gasses by 70 %. The manufacturers of different plastic containers for pharmaceutical preparations suggest that the thinnest wall should be 0.3 mm, which would ensure the quality of the plastic containers regarding permeability. However, the walls of the plastic containers should not be abnormally thick because the plastic packaging should posses a certain flexibility that allows easy and complete filling and emptying, ensuring a correct way of administering the medication.

Table 1. Physical tests on PVC containers for aqueous solutions for intravenous infusion

Parameters	Results	Standards and Limits	
	Sample 1	Ph. Eur.	DIN 58 363 - 15
Resistance to temperature, pressure and sealing	complies^{DIN}	/*	- 25 ^{0}C to 50 ^{0}C for 24 hours internal pressure: 20 kPa for 10 min.
Resistance to fall	complies^{DIN}	/*	Fall from 2 m on hard base
Vapor permeability	complies^{DIN}	/*	T = 20 ± 5 ^{0}CRH ≤ 60 % for 21 days Loss in mass is not greater than 5 % for the shelf life of a plastic container
Transparency	complies$^{Ph\ Eur}$	Primary opalescent suspension diluted 1 in 400	Primary opalescent suspension (1 : 100)
Attaching to plastic bag	complies^{DIN}	/*	Part intended for attachment required to stand force from 25 N for 60 min.
Permanence of labeling	complies^{DIN}	/*	The printing on the label remains legible and the label shall not separate from the container after removal from water if plastic container is submerged in water at a temperature 20 ± 1 ^{0}C for 24 hours
Appearance	complies	Internal specification	
Dimensions	complies	Internal specification	
Thickness of wall (mm)	0.35	Internal specification	

n = 6; /* parameter is not prescribed for examination

Table 2. Physical tests on sterile containers of plasticised PVC for human blood containing an anticoagulant solution

Parameters	Results	Standards and Limits	
	Sample 2	Ph. Eur.	DIN ISO 3826
Resistance to centrifugation	complies[Ph Eur]	5000 *g* for 10 min. no leakage perceptible and no permanent distortion occur	5000 *g* for 30 min. T = 4 ^{0}C and T = 37 ^{0}C no leakage perceptible and no permanent distortion occur
Resistance to stretch (%)	3.82[Ph Eur]	20 N	20 N
Leakage	complies[Ph Eur]	Internal pressure: 100 kPa for 10 min.	Internal pressure: 67 kPa for 10 min.
Vapor permeability	complies[Ph Eur]	T = 5 ± 1 ^{0}C RH = 50 ± 5 % for 6 weeks Loss in mass: max 2 %	T = 5 ± 1 ^{0}C RH = 50 ± 5 % for 21 days Loss in mass: max 1 %
Emptying under pressure	complies[Ph Eur]	Internal pressure: 40 kPa The container empties in less than 2 min.	Internal pressure: 40 kPa The container empties in less than 2 min.
Speed of filling	complies[Ph Eur]	Internal pressure: 9.3 kPa The volume of liquid which flows into the container in 8 min. is not less than the nominal capacity of the container	Internal pressure: 9.3 kPa The volume of liquid which flows into the container in 8 min. is not less than the nominal capacity of the container
Resistance to temperature variations	complies[Ph Eur]	T = - 80 ^{0}C for 24 hours T = 50 ^{0}C for 20 min.	T = - 80 ^{0}C for 24 hours T = 50 ^{0}C for 12 hours
Transparency	complies[Ph Eur]	Primary opalescent suspension (1 : 16)	Primary opalescent suspension (1 : 16)
Appearance	complies	Internal specification	
Dimensions	complies	Internal specification	
Thickness of wall (mm)	0.37	Internal specification	

n = 6

The thickness of the wall of the tested PVC bags for water solutions for intravenous infusion and blood and blood products varies within the range of 0.33-0.38 mm, declared by the manufacturer. The tested PVC bags also meet the other physical requirements important for the quality of the containers (Table 1 and 2).

Parameters such as resistance to centrifugation, leakage, empting under pressure, speed of filling are specific for assessment of the quality of the PVC containers for human blood. These PVC bags also meet the requirements for resistance to stretching that is important for the containers' quality. Among the tested containers, there were no examples of tearing or prolonged deformation of the material during the application of a force of 20 N, due to the elastic properties of the plastic containers. A larger percentage of stretching, without tearing or prolonged deformation of the material, implies better elastic properties.

Chemical tests

The identification of the main polymer, poly(vinyl chloride) and the corresponding plastificator for PVC containers, di(2-ethylhexyl) phthalate (DEHP), was done using IR spectroscopy, in comparison with the referent IR spectra (3) and the IR spectra of the standard substances.

After the separation of the plastificator DEHP and PVC (extraction with diethyl ether in an apparatus by Soxlet) in the appropriate PVC packaging, they were re-identified by the IR method, which confirms their presence. A thin layer of the sample in tetrahydrofuran was applied to a NaCl plate and the spectra were recorded in the range from 4000 to 600 cm^{-1}. The resulting IR spectra are shown in Fig. 1.

The results of the chemical tests on investigated PVC bags are given in Table 3 and 4.

The requirements for the quality of the PVC packaging are regulated by Ph. Eur., DIN and ISO standards. In order to make a complete evaluation of the investigated PBC bags' quality, all the parameters prescribed in these standards were included.

The requirements for the physical parameters of plastic bags for water solutions for intravenous infusion, except for its transparency, are not specified by Ph. Eur., unlike the DIN standard, which sets out exact regulations; the confirmation of

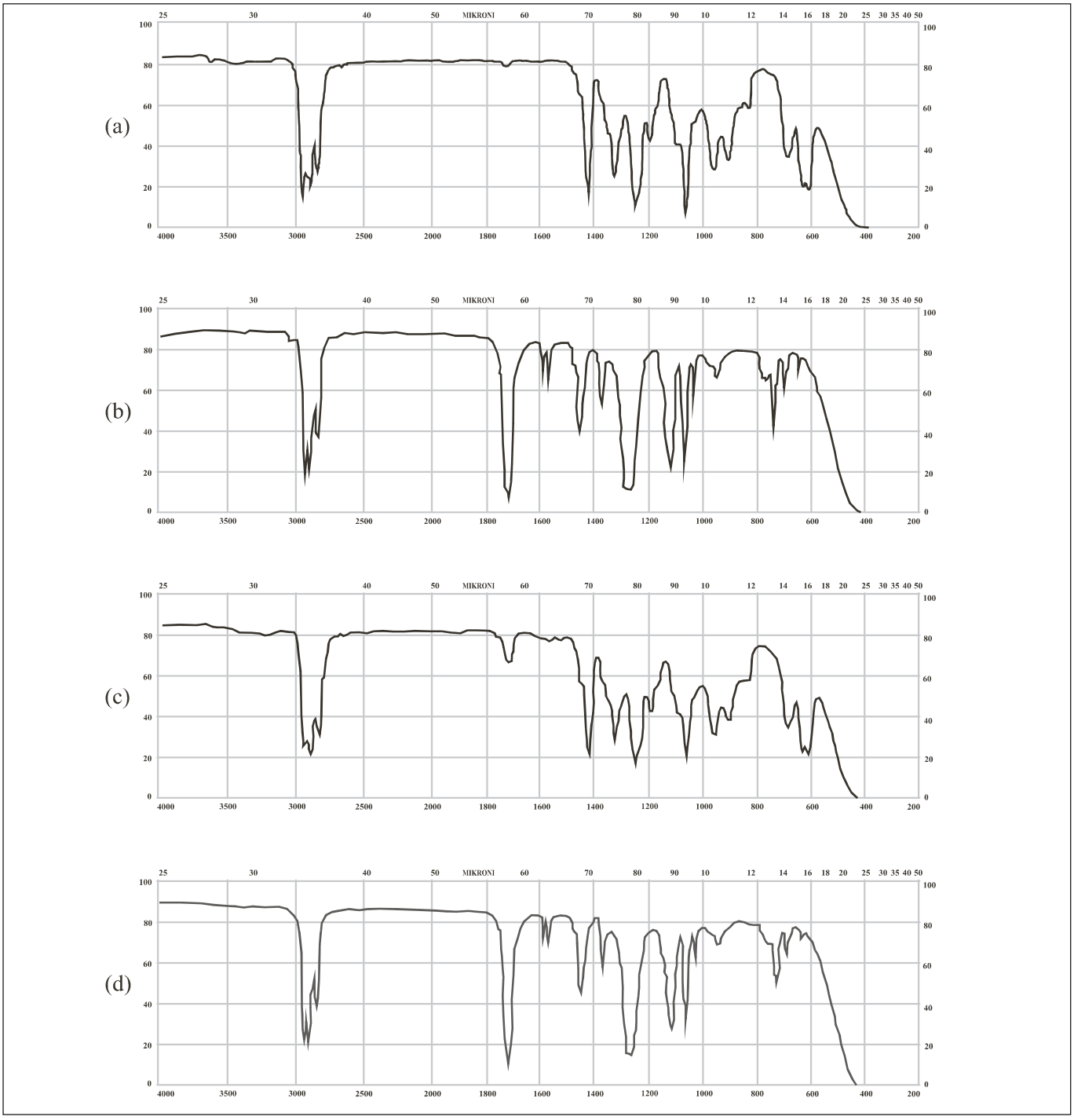

Fig. 1. IR spectra of PVC (a) and DEHP (b), standard substances; PVC (c) and DEHP (d) after their separation from sample 1

the presence of impurities such as SO_4^{2-}, NH_4^+, and Cl^-, as part of the chemical tests prescribed for PVC is not prescribed in Ph. Eur. for PVC bags for water solutions for intravenous infusion, whereas such regulations are upheld by the DIN standard. Furthermore, Ph. Eur. does not require tests for the presence of heavy metals in all types of plastic packaging, whereas DIN and DIN ISO standards do require the test for heavy metals represented as Pb^{2+} or their individual determination, for example: Ba, Cr, Cu, Pb, Sn, Cd, and Al for plastic packaging for water solutions for intravenous infusions, and Ba, Pb, Sn and Cd for plastic packaging for blood and blood products. In contrast to Ph. Eur., the DIN standard also requires testing for mechanical impurities in plastic bags for water solutions for intravenous infusions with the exact number and size of the particles.

In addition, the allowed presence of Cl^- as an impurity in PVC packaging for blood and blood products is 0.4 ppm and 4 ppm according to Ph. Eur. and DIN ISO standards respectively.

Table 3. Results of chemical tests on PVC containers for aqueous solutions for intravenous infusion

Parameters	Results	Standards and Limits	
	Sample 1	Ph. Eur.	DIN 58 363 - 15
Appearance of solution clarity/color	complies$^{Ph\ Eur}$	Clear and colorless solution	Clear solution, not more opalescent than reference suspension
Acidity or alkalinity	complies$^{Ph\ Eur}$	max. 0.4 ml 0.01 mol/L NaOH or max. 0.8 ml 0.01 mol/L HCl / 4 % of the nominal capacity of the container	max. 0.8 ml 0.01 mol/L NaOH or max. 0.8 ml 0.01 mol/L HCl / 20 ml
pH (4.0 - 4.5)	5.56$^{DIN\ 13098}$	/*	/*
Mechanical particles	complies$^{DIN\ 58\ 363\ -15}$	/*	Particles ≥ 2 μm: max. 200/ml Particles ≥ 5 μm: max. 20/ml
Absorbance (230 - 360 nm)	0.020 $^{Ph\ Eur}$ (250 nm)	max. 0.200	max. 0.250
Oxidisable substances (mlA - mlSl) 0.002 mol/L $KMnO_4$	0.65 ml $^{Ph\ Eur}$	max. 1.5 ml	max. 3.0 ml
SO_4^{2-}	complies $^{DIN\ 58\ 363-15}$	/*	10 ppm
NH_4^+	complies$^{DIN\ 58\ 363-15}$	/*	0.8 ppm
Cl^-	complies$^{DIN\ 58\ 363-15}$	/*	4 ppm
Residue on evaporation (mg/100 ml)	2.57$^{DIN\ 58363-15}$	/*	5.0
Heavy metals (ppm)	Pb = 0.00 Cd = 0.00 Sn = 0.00 (DIN 58 363-15)	/*	1. Pb^{2+}: 1.6 ppm 2. AAS Ba, Cr, Cu, Pb: 1 ppm Sn, Cd: 0.1 ppm Al: 0.01 ppm

n = 6; /* parameter is not prescribed for examination

The total content of the plastificator DEHP and the liquid stabilizators is determined by gravimetric means, after a 16-hour extraction period with diethyl ether in an apparatus by Soxlet. The content of the PVC polymer is determined gravimetrically after dissolving the residue, obtained from extraction, in cyclohexanon and its precipitation with methanol. The content of the fillers and solid stabilizators are represented by the undissolved part in cyclohexanon, as dry residue.

According to the specifications of Ph. Eur., the content of the PVC polymer in PVC primary containers intended for water solution for intravenous infusions and blood and blood products should be at least 55%. The determined content of the PVC polymer in the samples is above the required minimum, and the necessary elasticity of the PVC bags is obtained by the addition of a plastificator in content of max. 40 %, as specified in Ph. Eur.

The content of extractive di(2-ethylhexyl)phthalate (DEPH), used as a plastificator, is also tested in order to determine the PVC containers' quality. Determination of the content of DEPH extracted from the solvent is accomplished through a calibration graph constructed by the absorbances of the solutions of

Table 4. Results of chemical tests on sterile containers of plasticised PVC for human blood containing an anticoagulant solution

Parameters	Results	Standards and Limits	
	Sample 2	Ph. Eur.	DIN ISO 3826
Appearance of solution	complies[DIN ISO]	/*	Clear solution, not more opalescent than reference suspension II
Volume of anticoagulant solution	complies[Ph Eur]	± 10 % from the stated volume of anticoagulant solution	/*
Spectrophotometric examination of anticoagulant sol. (250 - 350 nm)	0.030[Ph. Eur] (280 nm)	The absorbance at the maximum at 280 nm is not greater than 0.5	/*
Acidity or alkalinity	complies[Ph Eur]	max. 0.4 ml 0.01 mol/L NaOH or max. 0.8 ml 0.01 mol/L HCl / 4 % of the nominal capacity	max. 0.4 ml 0.01 mol/L NaOH or max.0.8 ml 0.01 mol/L HCl / 10 ml sol.
Absorbance 230 - 360 nm	no absorbance[Ph Eur]	max. 0.300 (230 – 250 nm) max. 0.100 (251 – 360 nm)	max. 0.200
Oxidisable substances (mlA - mlSl) 0.002 mol/L $KMnO_4$	0.45 ml [Ph Eur]	max. 2.0 ml/8 % of the nominal capacity of the container	max. 2.0 ml/20 ml sol.
NH_4^+ (ppm)	complies[Ph Eutr]	2 ppm	2 ppm
Cl^- (ppm)	complies[Ph Eutr]	0.4 ppm	4 ppm
Extractable di(2-ethylhexyl)-phthalate (DEHP) mg/100ml	complies [Ph. Eur] (Table 4)	10.0 mg/100 ml (volume: 300 – 500 ml) 13.0 mg/100 ml (volume: 150 – 300 ml) 14.0 mg/100 ml (volume to 150 ml)	10.0 mg/100 ml
Vinyl chloride	complies*	1 ppm	1 ppm
PVC	complies (Table 3)*	min. 55 %	/*
Plasticizers and liquid stabilizers	complies (Table 3)*	max. 40%	/*
Residue on evaporation (mg/100 mg)	0.2[Ph Eur]	max. 3.0 mg/100 ml	max. 3.0 mg/100 ml
Heavy metals (ppm)	Pb = 0.00 Cd = 0.00 Sn = 0.00 (DIN ISO 3826)	/*	AAS Ba, Pb: 1 ppm Sn, Cd: 0.6 ppm
Ash (mg/g)	0.1[DIN ISO 3826]	/*	1 mg/g

n = 6 * - internal procedure;
* - parameter is not prescribed for examination

Table 5. Results of determination of PVC polymer and additives in PCV bags

Sample	PVC polymer (%)	Plastificator* and liquid stabilizators (%)	Fillers and solid stabilizators (%)	Total (%)
1	71.05	28.95	traces	100
2	63.66	36.44	traces	100

*plastificator - di(2-ethylhexyl)phthalate (DEHP)

DEHP, standard substance in the concentration range of 2 to 20 mg/100 ml, at λ=272 nm. The regression line estimated by linear least-squares regression analysis is represented by the equation: y = 0.0271 + 0.0231x, with a correlation coefficient of 0.9994. The content of vinyl chloride in the PVC packaging is determined by the method of gas chromatography (head space), FID detector and S/S column, ¼, 6 m (15% Diethylhexylsebacate /Chromosorb W DMCS, 80/100 mesh). The chromatogram of vinyl chloride, standard substance, and the chromatograms of vinyl chloride (VC) in PVC bags are given in Fig. 2.

The retention time for vinyl chloride, standard substance is approximately 4 minutes. The absence of a peak which corresponds to the retention time of vinyl chloride, standard substance, is noticeable in the chromatograms obtained from samples 1 and 2, implying total polymerization of the vinyl chloride - monomer in the process of production of the tested PVC containers. The concentration of the prepared standard solution of vinyl chloride of 1 ppm, at the same time represents the maximum allowed presence of VC in the PVC packaging, taking into consideration its toxicity and the possibility of its migration into the solution.

Biological tests

The most widely used tests for the biological study of this type of containers are: the pyrogen test, abnormal toxicity, the test for haemolysis and sterility (Ph. Eur.) and permeability of microorganisms (DIN).

The pyrogen test (4) is used to determine the presence of pyrogen substances of non-microbiological origin, most often originating from the packaging material.

The plastic masses are inert and do not show a toxic effect if the polymerization of the polymer is complete. If the final product is not well purified it could contain a substance or an additive which is not chemically bonded to the polymer. The monomers, plastificators, stabilizators, catalysts, fillers and other additives, which are molecules with a small molecular weight, can easily migrate into the solution and display a toxic effect. Toxicity could also be a result of the migration of the glue and the ink used in the printing of the label into the solution. Beside the monomer and the additives, the presence of tin as a form of impurity could also lead to a hemolysis of the erythrocytes (5). Due to these, for the evaluation of plastic packaging quality, the test for abnormal toxicity and the test for hemolysis are also conducted.

Table 6. Content of extractive DEPH, obtained by calibration graph

Sample	Absorbance, λ=272 nm	Concentration (mg/100 ml) (max. 10 mg/100 ml)
1. (bag with capacity of 500 ml)	0.1599	5.76
2. (primary bag with capacity of 400 ml)	0.1506	5.36

A sterility test is prescribed only for sterile bags of plasticised poly(vinyl chloride) for human blood containing an anticoagulant solution (sample 2), following the membrane filtration procedure outlined in Ph. Eur.

The plastic packaging should not be permeable to microorganisms, as a secondary contamination of the product. The permeation of microorganisms is controlled by the appropriate thickness of the walls of the plastic packaging. A thickness of the plastic wall of 0.04 mm, prevents the permeation of microorganisms into the solution. As the walls at the joining points could be thinner, the thickness of the walls of the plastic packaging should be at least 0.1 mm.

A cultivating medium where the samples (PVC bags) were kept during the examination was innoculated with *Bacillus subtilis* varieties Niger NCTC 10073. The cultivating medium in the tested PVC bags stayed clear after the proposed time of incubation, which indicates the impermeability of the plastic packaging to the tested microorganism.

The tested primary containers intended for pharmaceutical preparations is apyrogen, nontoxic, sterile, and does not cause haemolysis to the erythrocytes and it is impermeable to microorganisms.

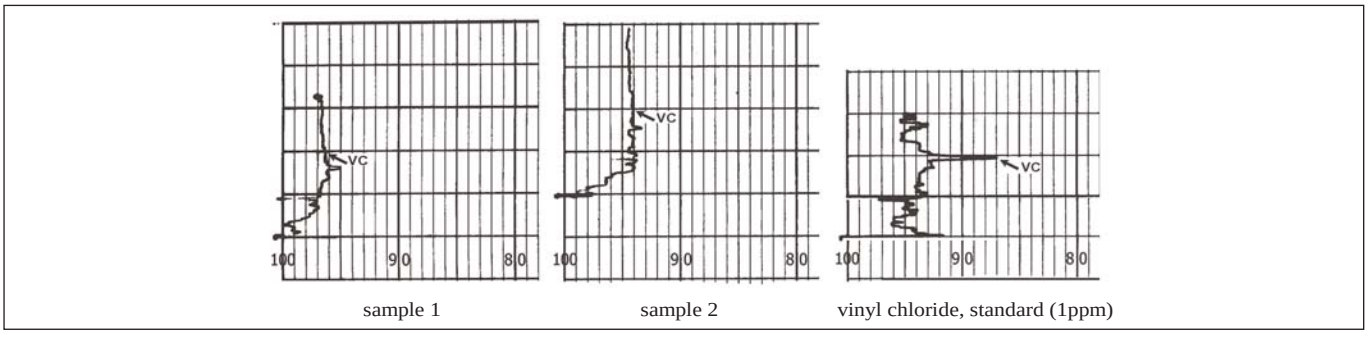

Fig 2. Chromatograms of determination of vinyl chloride in tested PVC containers and vinyl chloride, standard substance (1 ppm) in N,N dimethylacetamid

Table 7. Results of biological tests on PVC bags

Sample	Pyrogen test Ph Eur	Abnormal toxicity Ph. Eur	Sterility Ph Eur	Permeability to microorganisms DIN ISO	Haemolytic value (%) Ph Eur (max 10%)					
					I cell	control cell I	Δ %	II cell	control cell II	%
1	complies	complies	/*	complies	8.12	17.36	**9.24**	51.42	60.81	**9.39**
2	complies	complies	complies	**/***	8.87	17.36	**8.49**	50.97	60.81	**9.84**

Standards and limits			
DIN 58363 – 15 (Sample 1)	DIN ISO 3826 (Sample 2)	Ph. Eur.	
/*	Containers comply with test for sterility (membrane filtration)	Containers comply with test for sterility (membrane filtration)	Sterility
Haemolytic value not greater than 10 %	Haemolytic value not greater than 10 %	Haemolytic value not greater than 10 %	Haemolytic effects in buffered systems
Complies with test for pyrogens	Complies with test for pyrogens	Complies with test for pyrogens	Pyrogens
Complies with test for abnormal toxicity	Complies with test for abnormal toxicity	Complies with test for abnormal toxicity	Abnormal toxicity
Containers are not permeable to microorganisms	/*	/*	Permeability to microorganisms
Containers do not challenge mutation on cell culture	Containers do not challenge mutation on cell culture	/*	Cytotoxicity

Conclusion

The requirements for PVC container quality are regulated by Ph. Eur., DIN and DIN ISO standards. The specifications should encompass the parameters prescribed in Ph. Eur, DIN and DIN ISO standards for a more detailed evaluation of PVC container quality, and synchronize the allowed ranges of tolerance for certain parameters, as well.

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Резиме

Параметри за процена на квалитетот на PVC амбалажа наменета за фармацевтски препарати

Анета Димитровска[1], Лилјана Угринова[1], Сузана Трајковиќ-Јолевска[1], Славица Танчева[2]

[1]Институт за испитување и контрола на лекови, Фармацевтски факултет, Универзитет „Св. Кирил и Методиј“, Водњанска 17, 1000 Скопје, Македонија, [2]ОХИС А.Д., 1000 Скопје, Македонија

Клучни зборови: поли(винил хлорид) амбалажа, фармацевтски препарати, процена на квалитет

Направен е преглед на параметрите за процена на квалитетот на поли(винил хлорид) амбалажа наменета за фармацевтски препарати. Барањата за квалитет на PVC амбалажата пропишани според Ph. Eur., DIN и DIN ISO стандардите се разликуваат во однос на предвидените параметрите за физички, за хемиски и за биолошки испитувања. Исто така, пропишани се и различни граници на дозволено отстапување на одделни параметри. Споредбата на параметрите пропишани според Ph. Eur., DIN и DIN ISO стандардите за овој вид амбалажа е направена со цел да се изврши поцелосна процена на квалитетот на PVC амбалажата.
