Effect of Partial Replacement of Di(2-ethyl hexyl)phthalate, by a Polymeric Plasticizer, on the Permeability and Leaching Properties of Poly(vinyl chloride)

M. C. Sunny,[1,2] P. Ramesh,[2] K. E. George[1]

[1]*Department of Polymer Science and Rubber Technology, Cochin University of Science and Technology, Kochi 682 022, India*
[2]*Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Poojapura, Thiruvananthapuram 695 012, Kerala, India*

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ABSTRACT: Acrylonitrile butadiene rubber (NBR) was used as a polymeric plasticizer in poly(vinyl chloride) (PVC) for the partial replacement of di(2-ethyl hexyl)phthalate (DEHP). The effect of this partial replacement on DEHP leaching from the PVC was evaluated at 10, 25, and 40°C. The study shows that the incorporation of NBR reduces the rate of DEHP leaching, the reduction being prominent at lower temperatures. Gas permeability of the NBR-modified samples was also evaluated at the above temperatures using oxygen and carbon dioxide. A reduction in gas permeability is observed in NBR-modified samples compared to the PVC plasticized with DEHP alone particularly in the case of carbon dioxide. Water vapor transmission rates of the NBR-modified samples are higher than that of the control sample. The NBR-modified PVC sample was found to be noncytotoxic in the *in vitro* cytotoxic evaluation both by direct contact and test on extract methods. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 4720–4727, 2006

Key words: acrylonitrile butadiene rubber; di(2-ethyl hexyl)phthalate; plasticizer leaching; poly(vinyl chloride)

INTRODUCTION

Flexible poly(vinyl chloride) (PVC) is extensively used in medical field as blood bags, intravenous or total parenteral nutrition bags, tubing, catheters, etc.[1–4] To make PVC soft and flexible, a phthalate ester, di(2-ethyl hexyl)phthalate (DEHP), is commonly used as a plasticizer in medical products.[5] Several studies have indicated that as DEHP is not chemically bound to PVC, it leaches out from medical products into the media, which comes in contact with it.[6–9] There is mounting concern for the exposure to the phthalate ester through various medical procedures such as intravenous therapy, enteral and parenteral nutrition support, blood transfusion, hemodialysis and peritoneal dialysis, cardiopulmonary bypass, and extracorporeal membrane oxygenation.[10–13] Although DEHP is suggested to be of low acute toxicity, long-term exposure may adversely affect the human being.[14] The DEHP risk assessment on human health identified several areas of concern with critical effects on kidneys, testes, fertility, and development.[15,6] Various studies indicated that the potential risk of DEHP exposure is presumably higher for infants, particularly infants at an early and more sensitive stage of their development, and pregnant women.[7,16–19] Attempts have been made in many laboratories to reduce the leaching of DEHP[20–22] or to find out an alternate safe plasticizer.[23,24]

As plasticizers are generally liquids and not chemically bound to the polymer, they escape from the polymer matrix due to volatility during storage or get extracted to the medium while in use. The loss of plasticizer from the polymer will adversely affect the properties like flexibility, clarity, and so on of the product.[25] The problem of plasticizer loss can be alleviated by the use of polymeric type materials as plasticizers. Moreover, the polymeric plasticizers offer low volatility, high resistance to extraction, and low leachability at elevated temperatures.[26]

The blending of two or more structurally different polymers provides a convenient and economical route to obtain a polymeric material with tailor-made properties to meet specific needs.[27] In our earlier investigation, we have reported that the partial replacement of DEHP in PVC with polymeric plasticizers viz, nitrile rubber (NBR), carboxylated nitrile

Correspondence to: K. E. George (kegeorge@cusat.ac.in).

rubber (XNBR), and epoxidized natural rubber (ENR), reduced the DEHP leaching.[28] Of the three elastomers used, NBR was found to be the most promising one with respect to improved mechanical properties and reference to DEHP leaching characteristics. The blends of PVC/NBR have extensively been studied and NBR was found to be highly compatible with PVC.[29,30] Being miscible with PVC and uniformly dispersed in PVC phase, NBR is being used as a compatibilizer in many PVC/rubber blends.[31] Alloys of NBR with plasticized PVC were described as thermoplastic elastomers because they combine ease of melt processing with flexibility and rubber elasticity.[32] These alloys show better low temperature flexibility and improved abrasion resistance, which are the two prime properties of the materials used for blood and blood component storage applications.[32,33] Nitrile rubber (NBR) is regarded as one of the commercially available elastomers that are used in biomedical applications, generally in *in vitro* situations. Binary polyblends of plasticized PVC and NBR have been studied for medical applications.[34] However, for the blood storage application, the gas and water permeability of the material are also of cardinal importance. This study thus investigates the gas permeability and water vapor transmission characteristics of NBR-modified PVC systems. The temperature dependence of permeability as well as DEHP leaching is also addressed in this study.

MATERIALS AND METHODS

Materials

Suspension grade poly(vinyl chloride) (PVC) with *K* value of 66–69, di(2-ethyl hexyl)phthalate (DEHP; Indo-Nippon India), epoxidized oil (Indiofil Chemicals, India), Ca-Zn stabilizer (ALA-Chemicals, India), phosphite chelator (ALA-Chemicals, India), and NBR (acrylonitrile content 34%, Gujarat Apar Polymers, India) were used as received.

Preparation of blends

Compounding of PVC was carried out in an ordinary high-speed mixer with the apposite amounts of additives as given in Table I. Blends of PVC and NBR at four different NBR loadings (Table I) were prepared by mixing the polymers in a Haake Torque rheometer (Model: Rheomix-600) fitted with cam rotors at 160°C using a rotor speed of 40 rpm. For this, compounded PVC was initially melted in the mixer for 1–2 min. Masticated rubber strips were then added to the molten PVC and allowed to mix till the mixing torque was stabilized. The blend thus obtained was passed through a laboratory two-roll mill set at 2 mm-nip setting to get a sheet, which was subsequently compression-molded between aluminum foils at 160°C for 3 min at a pressure of 100 kg/cm^2 in an electrically heated press (Santhosh Industries, India) to obtain sheets of dimensions 120 mm × 120 mm × 0.3 mm.

TABLE I
Composition of Control and NBR-Modified PVC[a]

Material	A (Control)	B	C	D	E
PVC	100	100	100	100	100
Polymeric plasticizer (NBR)	–	7.5	15	25	25
DEHP	40	32.5	25	15	–
Di-octyl adipate	10	10	10	10	–
Epoxidized oil	7	7	7	7	–
Ca-Zn stabilizer	2.5	2.5	2.5	2.5	–
Phosphite chelator	0.5	0.5	0.5	0.5	–

[a] All values are in grams. The compositions A, B, C, and D are designated as Control, NBR-7.5, NBR-15, and NBR-25 respectively in the article.

Leaching studies

Studies on DEHP leaching from the control and NBR-modified PVC samples were carried out in *n*-hexane at three different temperatures viz. 10, 25, and 40°C. Preweighed samples were kept immersed in 10 mL of *n*-hexane. The samples were taken out at different intervals of time over a period of 72 h, the weights of the dried samples were taken. From the difference in weights, the amount of DEHP leached out into the medium was determined. The values reported are the average of three values.

The possibility of leaching of NBR from NBR-modified PVC samples was also determined by assessing the amount of material leached out to the medium of *n*-hexane in 72 h at 40°C from the modified samples having maximum amount of NBR (25 phr) and without any additives (composition E, Table I).

Gas permeability studies

The gas permeability measurements were made using samples of 120 mm diameter and 0.3 mm thickness. The samples were preconditioned according to ASTM D618-96.[35] The gas permeability measurements were carried out using oxygen and carbon dioxide in a manometric gas permeability tester (Model L-100, 2402/1, Switzerland) at three different temperatures (10, 25, and 40°C) as per ASTM D1434-98.[36]

Density measurements

The densities of the samples were calculated using a Sartorius precision balance (LA 230S, Sartorius, Germany) with the help of a specific gravity kit. The

density (ρ) of the samples were calculated using the formula (Sartorius Manuel):

$$\rho = \frac{W_a \rho_{fl}}{0.99983G} + 0.0012 \quad (1)$$

where W_a is the weight of the solid in air; ρ_{fl}, the density of water at the test temperature; 0.99983, the correction factor; G, the buoyancy of the immersed solid; and 0.0012, the density of air under standard conditions.

Hardness test

Shore A hardness of the control PVC and NBR-modified PVC samples were measured using a durometer (Blue steel Engineers, India) as per ASTM D2240-97.[37]

Water permeability testing

Water vapor transmission rates (WVTRs) of the samples for 24 h were measured using an in-house setup. The technique used to measure WVTR was a modification of the wet cup method described by ASTM E96-95.[38] In this method the test film covered a 100 mL beaker filled with distilled water. The mass of water lost from the beaker was measured as a function of time and the WVTR was calculated from the steady state region using eqs. (2) and (3). Thickness of the sample was measured using a thickness gauge at a minimum of 15 positions. The standard deviation of thickness for each specimen was less than 5%. A window of known area was cut from two sheets of aluminum foils and the sample was thoroughly fixed in between them. Then the aluminum foils with the test sample was mounted on the beaker with the help of adhesive tape. A control set up was also made without the samples.

$$\text{WVTR} = \frac{\text{Mass of } H_2O \text{ lost}}{\text{Time} \times \text{Area}} \quad (2)$$

$$\text{Sp WVTR} = \frac{\text{Mass of } H_2O \text{ lost}}{\text{Time} \times \text{Area}} \times \text{thickness} \quad (3)$$

Cytotoxicity studies

In vitro cell culture cytotoxicity evaluation of PN25 was carried out both by direct contact assay and test on extracts with a monolayer of L929 mouse fibroblast cells according to ISO standards.[39] Briefly, L929 cells were subcultured from stock culture (ATCC, USA) by tripsinized and seeded onto multi-well tissue culture plates (Nunc, Denmark). Cells were fed with minimum essential medium (MEM) supplemented with bovine serum and incubated at (37 ± 2)°C in humid atmosphere containing 5% carbon dioxide. When the cells attained subconfluency, the test samples (circular disc having 4 mm diameter) were kept in contact with the cells in triplicate for direct contact assay. After incubation at (37 ± 2)°C for 24 ± 1 h, cell culture was examined microscopically using a phase contrast inverted microscope (Leica DMIL, Germany) for cellular response around the test sample. The morphology of the cells was assessed in comparison with negative (ultra high molecular weight polyethylene) and positive control (organotin-stabilized PVC). Cellular responses were scored as 0, 1, 2, or 3 according to none, slightly, moderately, or severely cytotoxic.

For test on extract, the extract was prepared by incubating the sample with media containing serum (0.1 g/mL) for 24 ± 1 h at (37 ± 2)°C. Extract of test sample, negative control (ultra high molecular weight polyethylene), and positive control (dilute phenol) in triplicate were placed on subconfluent monolayer of L-929 cells. After incubation at (37 ± 2)°C for 24 ± 1 h, cell culture was examined microscopically for cellular response and scored as 0, 1, 2, 3, or 4 according to none, slight, mild, moderate, or severely cytotoxic.

RESULTS AND DISCUSSION

DEHP leaching studies: Effect of using NBR at different temperatures

Various analytic methods have been reported for evaluating DEHP leaching from PVC articles and have indicated that DEHP leaching phenomenon is strongly influenced by the solvent used for extraction.[40–42] Here, *n*-hexane has been selected as a leaching solvent to study the leaching trend of DEHP from control PVC and the NBR-modified systems having different NBR and DEHP contents. Figures 1–3 show the extent of DEHP leaching from control and the NBR-modified samples at 10, 25, and 40°C. The cumulative amounts of DEHP leached out per weight of the sample with leaching time are illustrated in these figures. The results indicate that the leaching of DEHP into the medium from control is very fast and it reaches maximum level within 8 h irrespective of temperature variation. But in the case of NBR-modified samples, the DEHP leaching at 40°C was attained in 18 h, whereas at 10°C the leaching reached to the maximum level only in 24–48 h. It was further observed that the amount of DEHP leached out from NBR-modified samples was strongly influenced by the temperature as well as the content of NBR. It may be seen from the graphs that the amount of DEHP leached out is directly proportional to the temperature and inversely proportional to the NBR content. It has been reported

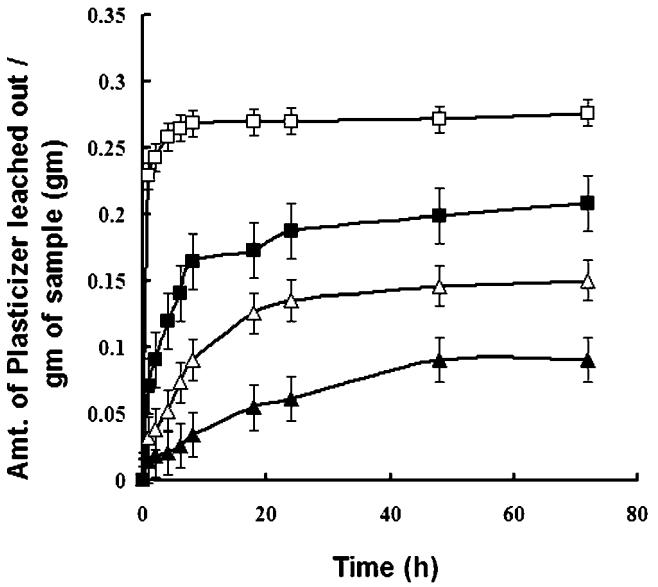

Figure 1 DEHP leaching at 10°C with time. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

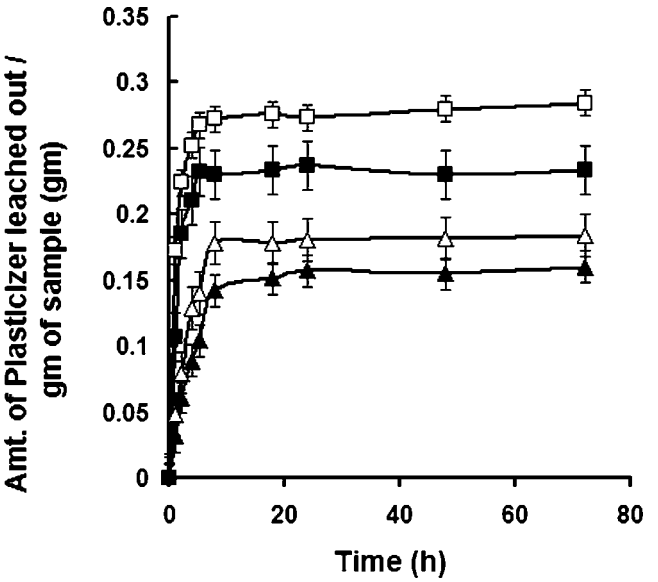

Figure 3 DEHP leaching at 40°C with time. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

that nitrile rubber has got an affinity toward conventional liquid plasticizers.[43] So the slow down in DEHP leaching pattern in NBR-modified samples could be due to the affinity of the incorporated NBR toward DEHP. No measurable quantity of weight loss was observed in the leaching studies of the PVC samples modified with 25 phr NBR alone at 40°C for 72 h in *n*-hexane, which shows that the loss of polymeric plasticizer is absent due to leaching.

Figure 4 shows the comparison of the percentage leaching of DEHP at different temperatures at the end of 72 h. It can be observed that the maximum retardation in leaching obtained by substituting DEHP by polymeric plasticizers is at lower temperatures. The leaching, transferring, and diffusion phenomenon of relatively small molecules through flexible polymers may be described by Fick's law applied to one dimension and may be expressed by the equation

$$\frac{M_t}{M_\infty} = 2\left[\frac{Dt}{\pi l^2}\right]^{1/2} \tag{4}$$

where, M_t and M_∞ are the measured quantity of DEHP migrated at time t and time infinity (72 h in

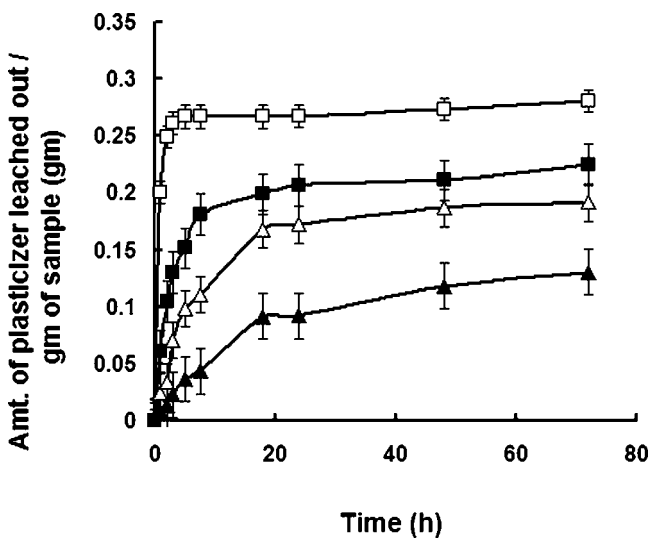

Figure 2 DEHP leaching at 25°C with time. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

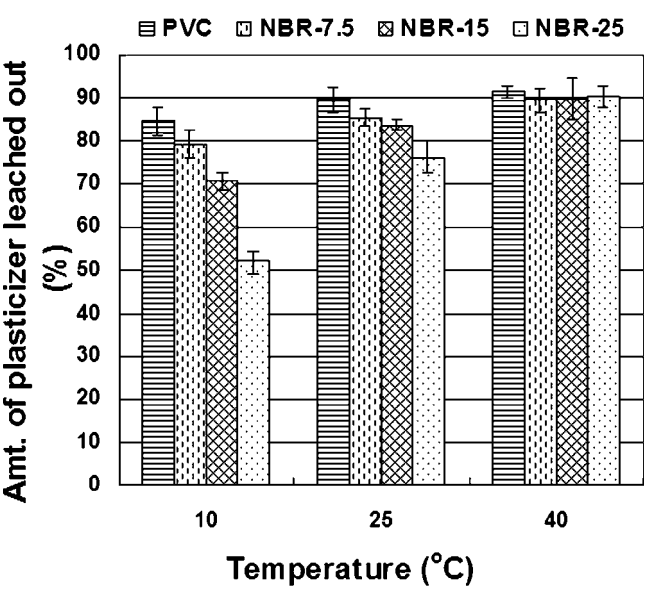

Figure 4 Temperature dependence of DEHP leaching from various systems in 72 h.

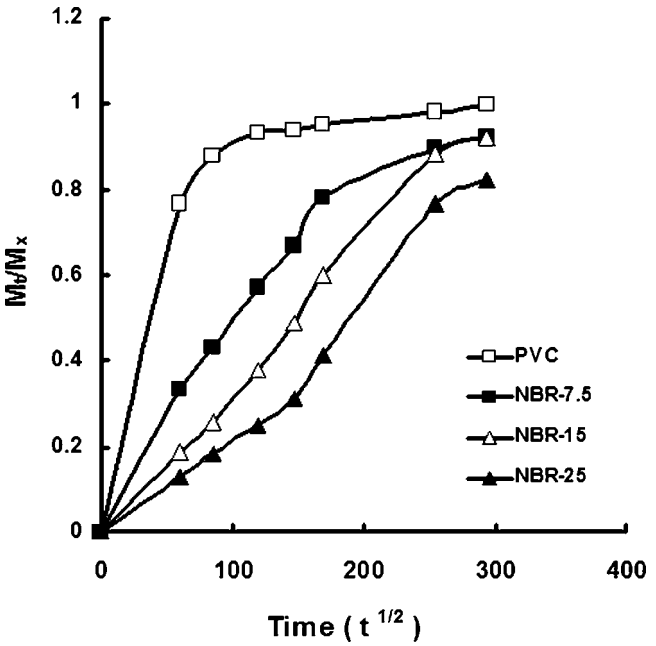

Figure 5 Plot of M_t/M_∞ versus $t^{1/2}$ for various systems at 10°C. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

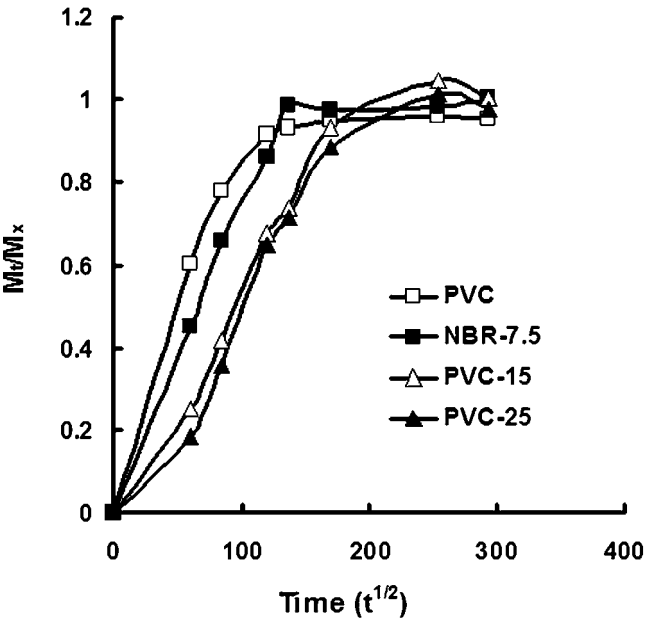

Figure 7 Plot of M_t/M_∞ versus $t^{1/2}$ for various systems at 40°C. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

the present study), D is the diffusion coefficient unrelated to the DEHP concentration, and l is the thickness of specimen. Plots of M_t/M_∞ versus $t^{1/2}$ for various systems at 10, 25, and 40°C are depicted in the Figures 5–7, respectively.

As illustrated, M_t steeply increases at initial period and then gradually reaches equilibrium. Furthermore, the time at which M_t reaches the plateau, decreased with increasing temperature. It suggests that DEHP leaching takes place very intensively at early stage in high temperature. According to the eq. 4, a plot of M_t/M_∞ versus $t^{1/2}$ should yield a straight line of slope $2(Dt/\pi l^2)^{1/2}$. So, from the slopes, diffusion coefficient of each system were calculated and expressed in the Table II. The high and low D values correspond to the large and small amounts of DEHP leaching, respectively. The results indicate that except at 40°C, the diffusion coefficient decreases with increase of NBR content in the system. In other words, the increase of NBR content decreases the DEHP leaching rate, but at 40°C the rate of DEHP leaching for all modified samples is more compared to the control PVC. This could be due to the differential expansion of PVC and NBR, since the coefficient of thermal expansion of PVC (6.6–7.3 $\times$ 10^{-5}) and that of NBR (19.6 $\times$ 10^{-5}) are different, at higher temperatures polymeric chains of the individual

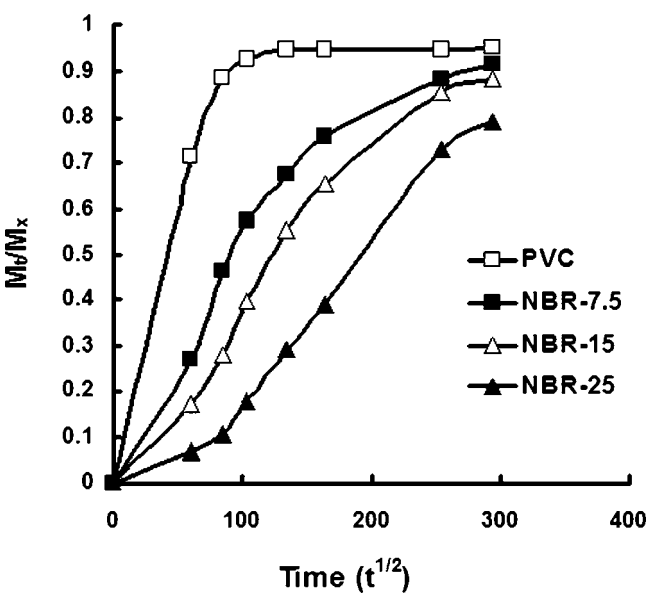

Figure 6 Plot of M_t/M_∞ versus $t^{1/2}$ for various systems at 25°C. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

TABLE II
Diffusion Coefficient of Control and NBR-Modified PVC

	Diffusion coefficient (10^{-8}) (cm^2/s)		
Sample	10°C	25°C	40°C
PVC	14.2	17.2	17.1
NBR-7.5	12.1	14.0	22.8
NBR-15	7.4	10.7	19.8
NBR-25	5.3	6.3	28.0

TABLE III
Oxygen and Carbon Dioxide Permeability of Control and NBR-Modified PVC at 10°C, 25°C, and 40°C

Material	Temperature (°C)	Permeability (cm^3/m^2 day) Oxygen	Carbon dioxide	Ratio (CO_2/O_2)
PVC	10	671 ± 90	1934 ± 105	2.88
	25	1153 ± 182	4371 ± 255	3.79
	40	2250 ± 327	8226 ± 470	3.66
NBR-7.5	10	448 ± 6	976 ± 35	2.18
	25	1348 ± 136	3613 ± 179	2.68
	40	2385 ± 60	5681 ± 234	2.38
NBR-15	10	315 ± 17	536 ± 12	1.70
	25	1365 ± 25	2953 ± 263	2.16
	40	1901 ± 42	4242 ± 426	2.23
NBR-25	10	286 ± 14	413 ± 9	1.44
	25	1072 ± 83	2797 ± 103	2.61
	40	1810 ± 95	3710 ± 196	2.05

components in the blends may undergo differential expansion, which could lead to the generation of small spaces that facilitate faster migration of the liquid plasticizer into the medium. Even though the rate of DEHP leaching is more at higher temperatures, the total availability of DEHP per gram of the sample is less compared to control.

Permeability studies

The stability and survival of the blood components for prolonged periods depends on the storage conditions as well as the O_2 and CO_2 permeability of the materials. During storage, blood components, for example, the platelets convert glucose, present in the anticoagulant, to lactic acid and CO_2.[44] The CO_2 thus produced lowers the pH, which in turn adversely affects the survival of the blood components. However, the presence of O_2 suppresses the conversion of glucose to lactic acid and CO_2.

Gas permeability values of the control and three different NBR-modified systems are given in the Table III. A reduction in O_2 and CO_2 permeability was observed for all modified samples compared to that of control and the reduction being more prominent for CO_2. It was further noticed that the replacement of DEHP with NBR gradually reduces the gas permeability of the NBR-modified samples. It has been indicated that the gas transmissibility of PVC formulation was dependent on the total amount of

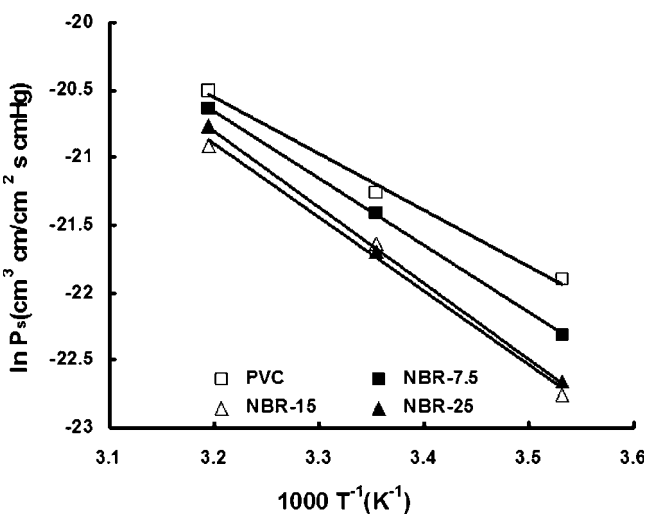

Figure 8 Temperature dependence of oxygen permeability. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

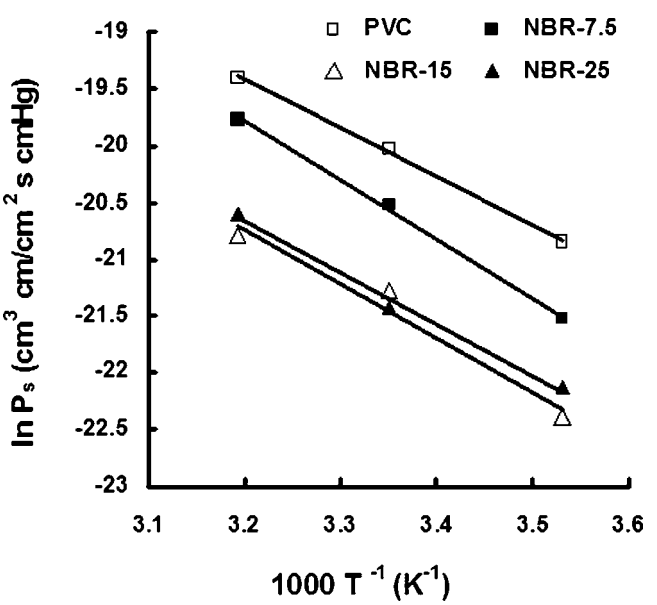

Figure 9 Temperature dependence of carbon dioxide permeability. □: Control PVC, ■: NBR-7.5, △: NBR-15, ▲: NBR-25.

TABLE IV
Density Measurements Data for Control and Modified Samples

Sample	Density (g/cm^3)
Control PVC	1.21 ± 0.0023
NBR-7.5	1.209 ± 0.0035
NBR-15	1.207 ± 0.0069
NBR-25	1.215 ± 0.0015

the liquid plasticizer present and the lower transmissibility was obtained with lower plasticizer content.[44]

Plots of ln P versus $1/T$ for O_2 and CO_2 permeabilities of control and NBR-modified PVC samples at 10, 25, and 40°C are shown in Figures 8 and 9, respectively. A linear relationship is obtained in the temperature range of 10–40°C. This indicates that the Arrhenius expression governs the temperature dependence of permeabilities of control and NBR-modified PVC samples.

Density data for NBR-modified PVC samples (Table IV) indicated only marginal variation from that of the control. The statistical evaluation of the data was found to have no significant variation in the densities of NBR-modified samples except the sample containing 25 phr NBR content.

Table V shows the shore A hardness of control and modified samples. An increase in hardness values are seen with an increase in NBR content in the NBR-modified PVC samples, but the values are within the tolerance of the medical bag applications.

Specific WVTR of control and NBR-modified PVC samples at 25°C are shown in Figure 10. It is apparent from the figure that NBR influences the specific WVTR of the modified samples, which indicates that the diffusion of water vapor through the sheets increased with the increase of NBR content and reached to a maximum value for the system having 15 phr NBR content. Further increase in NBR content was found to have no appreciable effect in the WVTR.

To evaluate the possibility of the toxicity of NBR-modified PVC samples, a preliminary cytotoxicity evaluation of the sample having high NBR content (25 phr) was carried out using mouse fibroblast cells. Cytotoxicity testing is a rapid, standardized, sensitive, and inexpensive means to determine whether a material contains significant quantities of biologically harmful extractables. Neither the sample nor its extracts induced any morphological changes to the cells confirming the nontoxic nature of the NBR modification. The morphology of the cells growing on the surface of the material (scored as zero) is depicted in Figure 11(a). It is clear from the figure that the typical spindle morphology of L929 was retained even after 24 h of contact with NBR-modified PVC. Similar result obtained for the test performed on the extract of the sample, as given in Figure 11(b), indicates that there was no toxic material leached out of the sample.

TABLE V
Hardness of Control and Modified Samples

Sample	Shore A hardness
Control PVC	83.83 ± 1
NBR-7.5	85.0 ± 1
NBR-15	85.33 ± 1
NBR-25	89.33 ± 1

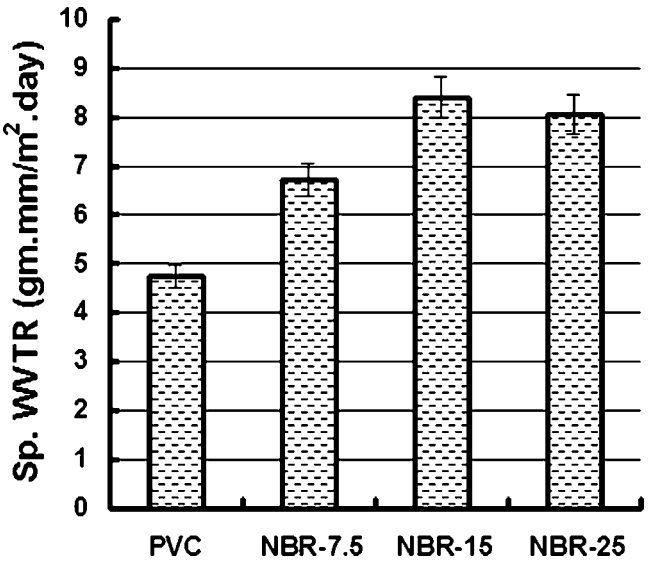

Figure 10 Specific water vapor transmission rate of control and NBR-modifie-d PVC samples at 25°C.

CONCLUSIONS

In this investigation, NBR was used in flexible PVC formulation for the partial replacement of DEHP to minimize the use of leachable plasticizers. The incorporation of NBR was found to reduce the leaching of DEHP, considerably at lower temperatures. Reduction of DEHP leaching from PVC medical products minimizes the risk of DEHP contamination of the media, which comes in contact with it. Furthermore, reduced leaching of DEHP alleviates the problems of stiffening, mechanical property deterioration, and transparency of PVC. The nontoxic nature of the material is revealed in the preliminary toxicity evaluation by *in vitro* cytotoxicity studies. The reduction in gas permeability and high WVTR of the modified-PVC samples indicate that the modified material could be used in medical field for the

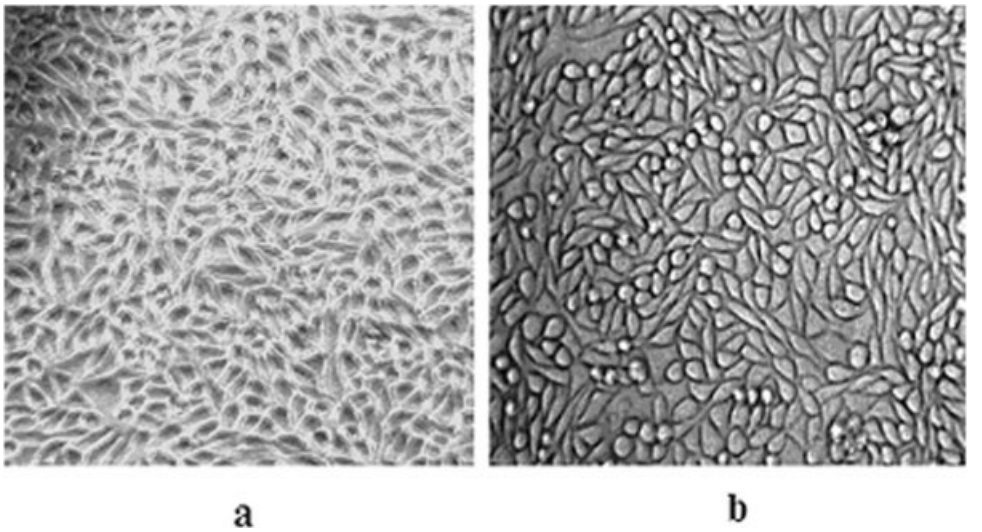

Figure 11 L929 cells incubated with (a) NBR-25 (direct contact) and (b) extract from NBR-25 (test on extract) over 24 h.

applications, which need only short term contact of body fluids rather than long term storage purposes.

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