Release of Dithiocarbamates into Artificial Sweat from Latex Vulcanizates: Effects of the Accelerator Type and Storage Time

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ABSTRACT: The release of commonly used dithiocarbamate accelerators, namely, zinc diethyldithiocarbamate (ZDEC), zinc dibutyldithiocarbamate (ZDBC), zinc dibenzyldithiocarbamate, zinc isobutyldithiocarbamate, and zinc diisononyldithiocarbamate, into artificial sweat from natural rubber latex vulcanizates was studied. The extent of release of ZDEC was much higher than that of ZDBC or other higher homologues, as indicated by high-performance liquid chromatography analysis. The effect of the storage time on the extent of release of ZDEC into artificial sweat from vulcanizates prepared with various amounts of ZDEC was studied. The result showed that ZDEC migrated significantly to the surface of the vulcanizates upon storage, and the amount that migrated increased with an increase in the shelf time. Moreover, the amount of ZDEC that migrated increased with an increase in the amount of ZDEC added to the latex formulations. The rate of migration, as determined from the slopes of the migration curves, was dependent on the residual ZDEC content, which in turn depended on the initial level of ZDEC incorporated during latex compounding. The analysis of the migration data showed that the migration followed a Fickian behavior, and the diffusion coefficient of ZDEC was slightly dependent on the concentration. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 2055–2061, 2006

Key words: diffusion; rubber; additives; high performance, liquid chromatography (HPLC)

INTRODUCTION

Natural rubber latex is the material of choice for medical-glove manufacturing because of its superior barrier protection, puncture resistance, strength, durability, fit, comfort, and elasticity. However, irritation and type IV allergies from natural rubber latex products, especially gloves, have been a matter of serious concern over the past 2 decades. These allergic reactions are caused by residual chemicals such as dithiocarbamates, thiurams, thiazoles, and antioxidants retained in the finished latex products.[1–6] Irritation and type IV allergy are rarely severe but pose serious and possibly career-threatening problems in individuals, especially healthcare workers. Studies have shown that nearly 85% of the patients with glove intolerance have irritation, or type IV allergy, or both.[7–9] Besides, dermatologists in Finland and United Kingdom have reported that the most common types of chemicals inducing type IV allergy in the general population are rubber chemicals[10–12]

Zinc dialkyldithiocarbamates are widely used as vulcanization accelerators as they possess the very active vulcanization time–temperature cycle required in the manufacture of natural rubber latex products.[13] Different types of zinc dialkyldithiocarbamates are currently used for the manufacture of dipped goods made of natural rubber latex. A comparative evaluation of the toxic and allergenic potential of some of these dithiocarbamate accelerators has been carried out by various researchers.[14–16] Nakamura et al.[14] reported that dithiocarbamates exhibited strong cytotoxicity among different types of rubber chemicals, and the order of their cytotoxicity potential was as follows: zinc dimethyldithiocarbamate (ZDMC) > zinc diethyldithiocarbamate (ZDEC) = zinc pentamethylenedithiocarbamate (ZPC) > zinc ethylphenyldithiocarbamate (ZEPC) > zinc dibutyldithiocarbamate (ZDBC). The embryotoxicity of different dithiocarbamates was reported to be in the order of ZDEC > ZEPC > ZDBC.[15] De Jong et al.[16] ranked different dithiocarbamates in the order of ZDEC > ZPC > ZDMC > ZDBC for their allergenicity, as determined by local lymph node assays. Knudsen et al.[17] reported that gloves releasing higher amounts of dithiocarbamates and/or thiurams into artificial sweat

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TABLE I
Formulation Recipes with Different Dithiocarbamate Accelerators

Ingredient[a]	Formulation code				
	DE-1	BU-1	IBC-1	BZ-1	DN-1
60% natural rubber latex	100	100	100	100	100
10% KOH	0.3	0.3	0.3	0.3	0.3
50% sulfur	0.75	0.75	0.75	0.75	0.75
50% ZDEC	0.5	—	—	—	—
50% ZDBC	—	0.5	—	—	—
50% ZIBC	—	—	0.5	—	—
50% ZBEC	—	—	—	0.5	—
50% ZDNC	—	—	—	—	0.5
50% ZnO	0.5	0.5	0.5	0.5	0.5

[a] On a dry weight basis

elicited a greater number of positive reactions during patch tests than those releasing smaller amounts. The purpose of the patch test is to determine whether a finished natural rubber latex product contains residual chemicals that might cause a skin reaction in individuals. The induction of immunogenic allergic reactions is known to depend on many factors, such as the allergenic potential, the concentration of the allergen, the ability of the allergen to permeate the skin surface, and the quantity of the allergen released into human sweat.[18] Besides, the migration may lead to an increase in the concentration of residual chemicals at the surface of the gloves when they are stored for longer periods and thereby increase the chances of allergy. It has been reported that the residual chemicals migrate from the bulk of a rubber product when it is stored over time.[19,20]

The reduction of type IV allergy is important in the wake of an increasing number of unpleasant occupational allergic incidents associated with the use of natural rubber latex products. The judicious selection of a dithiocarbamate accelerator for products that are intended to come into contact with skin is required to minimize the incidence of allergic elicitations. Data on the inherent allergenic and toxic potential of different dithiocarbamates are available, but their extent of release from latex vulcanizates into physiological media under simulated-use conditions is still lacking. This study assesses the extent of release of five commonly used dithiocarbamate accelerators, namely, ZDEC, ZDBC, zinc dibenzyldithiocarbamate (ZBEC), zinc isobutyldithiocarbamate (ZIBC), and zinc diisononyldithiocarbamate (ZDNC), from in-house prepared latex vulcanizates into artificial sweat, a physiologically simulated medium that closely mimics the end-use conditions of gloves. The effect of the storage time on the extent of release of ZDEC from latex vulcanizates into artificial sweat was also evaluated. The migration data were applied in a mathematical equation to estimate the diffusion coefficient of ZDEC.

EXPERIMENTAL

Materials

Double-centrifuged natural rubber latex (60%), conforming to Bureau of Indian Standards specifications (IS 11001-1984), was used. ZDEC and ZDBC were obtained from National Organic Chemical Industries, Ltd. (Mumbai, India), and ZBEC was acquired from Bayer AG (Leverkusen, Germany). ZIBC and ZDNC were obtained from R.T. Vanderbilt Co., Inc. (Norwalk, CT, United States), and Robinson Brothers, Ltd. (England), respectively. Dichloromethane, acetone [high-performance liquid chromatography (HPLC) grade], hexane, ether, sodium chloride, and urea were obtained from local sources. Lactic acid was procured from Sigma–Aldrich (St. Louis, MO, United States).

Effect of the accelerator type on dithiocarbamate release

Preparation of the latex vulcanizates

The effect of the dithiocarbamate type on the extent of dithiocarbamate release into artificial sweat was studied with latex vulcanizates containing 0.75 pphr sulfur and 0.5 pphr each of the dithiocarbamate accelerators. The natural rubber latex vulcanizates were prepared with five different dithiocarbamate accelerators according to the formulations given in Table I. The ingredients, on a dry weight basis (pphr), were added to the latex. Chemicals such as sulfur, zinc oxide, and dithiocarbamates were made into dispersions in water via ball milling for 48–72 h. Potassium hydroxide was added as a 10% aqueous solution. The dispersions were added to the latex one by one in the same order as given in the formulation recipes with a 10-min interval between each addition. The compounded latex was matured for 19 h and cast on leveled glass plates. The cast sheets were allowed to air-dry for at least 48 h. The air-dried sheets were then vulcanized at 120°C for 15 min. The vulcanized latex sheets were

TABLE II
Composition of Artificial Sweat

Constituent	Weight (%)
Sodium chloride	0.5
Lactic acid	0.1
Urea	0.1
Deionized water	To make 100

subjected to leaching in water at 50–55°C for 15 min four times. A leaching ratio (water-to-rubber ratio) of 100 was maintained. Additional leaching in water at room temperature for 24 h was also performed. The leached sheets were dried in an air oven at 70°C for 30 min.

Extraction in artificial sweat

The latex vulcanizates prepared with different dithiocarbamate accelerators were extracted in artificial sweat to study the effect of the accelerator type on the extent of release into the sweat solution. Artificial sweat was prepared according to the composition given in European Standard EN1811:1998(E) (Table II). The pH of the artificial sweat solution was adjusted to 6.5 ± 0.1 by the addition of a 1% aqueous ammonia solution. The latex sheets (2 g) were cut into pieces of approximately 2 × 0.5 cm^2 and added to 100 mL of an artificial sweat solution in a 250-mL, round-bottom flask. The extraction was carried out at 37 ± 2°C for 24 h with constant mechanical shaking. The sweat solution was then extracted with 40 mL of dichloromethane five times. The solvent fraction in each extraction was collected and distilled off with a rotary evaporator at 60°C to recover the residue and was subjected to HPLC to quantify the amount of dithiocarbamates released into artificial sweat, that is, sweat-extractable dithiocarbamates. The extraction in artificial sweat was performed within a week after the preparation of the latex vulcanizates.

Quantification of dithiocarbamates released into artificial sweat

A number of chromatographic techniques have been used for the quantification of allergologically relevant accelerators.[21–23] Zinc dialkyldithiocarbamates were reported to undergo metal-exchange reactions with the stainless steel parts of the HPLC column.[24] To avoid these exchange reactions, zinc dithiocarbamates were converted into their respective copper complexes. The residue obtained after the sweat extraction of latex sheets was redissolved in 10 mL of dichloromethane. Five milliliters of this solution was pipetted out and mixed with 1.7 mL of a 0.01*M* aqueous ammoniacal cupric sulfate solution. The mixture was then vortexed for 2 min to obtain the copper–dithiocarbamate complex quantitatively.[25,26] The dichloromethane layer was separated and evaporated off to recover the residue. This residue was redissolved in 5 mL of acetone for analysis by HPLC.

The HPLC system consisted of a Waters 510 pump, C18 column, and 7725 Rheodyne injector (Waters, Inc., Milford, MA, United States). The presence of a copper–dithiocarbamate complex was detected with a variable-wavelength ultraviolet detector (model 486) set at 435 nm. Separation was achieved in a column (4.6 × 75 mm) packed with C_{18} material (3.5 μm). The mobile phase was acetone–water (90:10 v/v). A flow rate of 1.0 mL/min was used. Known quantities of ZDEC, ZDBC, ZIBC, ZBEC, and ZDNC were converted into their respective copper complexes and used as standards. The amount of sweat-extractable dithiocarbamates from latex sheets was determined quantitatively by a comparison with the respective standard.

Effect of the storage time on the release of ZDEC

The effect of the storage time on the amount of ZDEC released into artificial sweat was investigated. Latex vulcanizates containing a fixed quantity of sulfur (0.5 pphr) and various amounts of ZDEC (concentrations ranging from 0.5–1.0 pphr) were prepared according to the formulations given in Table III. The sheets were then packed in polythene bags, sealed, and stored under the ambient conditions for 1, 8, 24, and 48 weeks. The average room temperature was 28°C, and the relative humidity ranged from 70 to 80%. At the end of the storage period, the latex sheets were extracted in artificial sweat to determine the amount of ZDEC released into artificial sweat. The procedure for the extraction and quantification is already described. The significance of the results was determined with an analysis of variance method (significance level = 0.05).

Quantification of residual dithiocarbamates

The amount of dithiocarbamates released into dichloromethane was taken as the residual dithiocarbamate

TABLE III
Formulation Recipes with Various Amounts of ZDEC

Ingredient[a]	Formulation code		
	DE-2	DE-3	DE-4
60% natural rubber latex	100	100	100
10% KOH	0.3	0.3	0.3
50% sulfur	0.5	0.5	0.5
50% ZDEC	0.5	0.82	1.0
50% ZnO	0.5	0.5	0.5

[a] On a dry weight basis.

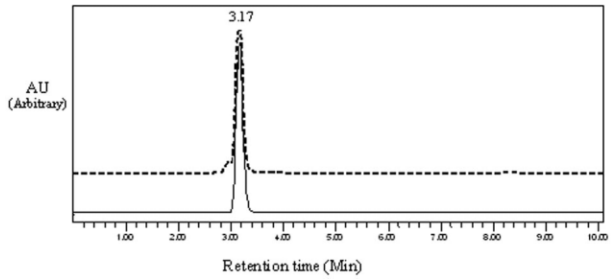


Figure 1 Chromatogram of copper complexes of (—) standard ZDEC and (- - -) the sweat extract of a latex vulcanizate containing ZDEC.

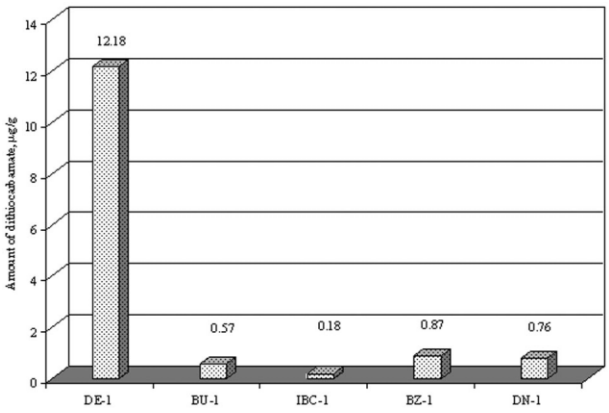


Figure 2 Amount of dithiocarbamates released into artificial sweat from latex vulcanizates.

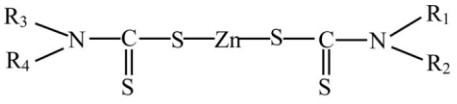
content in the latex vulcanizates. Latex sheets prepared according to the formulations given in Table III were extracted in dichloromethane at room temperature for 24 h to determine the amount of residual ZDEC and ZDBC following vulcanization. Vulcanizates using formulations DE-1 and BU-1 were also extracted in dichloromethane to determine the amounts of residual ZDEC and ZDBC, respectively. The solvent was distilled off at 60°C to recover the residue and subjected to HPLC, as detailed earlier, to determine the residual dithiocarbamate in the latex vulcanizates.

RESULTS AND DISCUSSION

Effect of the accelerator type

Latex vulcanizates containing equal amounts of different dithiocarbamates accelerators were prepared and extracted in artificial sweat to study the effect of the accelerator type on the extent of dithiocarbamate release. Figure 1 shows a typical chromatogram obtained for the sweat extract of the latex vulcanizate containing ZDEC and the standard ZDEC compound. The chromatogram of the latex vulcanizate gave a peak around 3.17 min that was characteristic of ZDEC, indicating that the ZDEC residues were released into artificial sweat from the latex sheets. Figure 2 shows the amounts of different dithiocarbamates released into the artificial sweat from the latex vulcanizates prepared according to the formulations given in Table I. It is evident that the extent of release of ZDEC into artificial sweat from the latex sheets was substantial ($\sim$12 μg/g) in comparison with that of ZDBC or higher homologues, despite the use of the same level of dithiocarbamate accelerators for vulcanization. Negligible quantities ($<$1 μg/g) of ZDBC, ZIBC, ZBEC, and ZDNC were released into artificial sweat from the latex vulcanizates. This variation in the extent of release of ZDEC from other dithiocarbamates into artificial sweat was attributed to the difference in their solubility in rubber. The general structure of the dithiocarbamates is given in Scheme 1. The structure shows that dithiocarbamates differed only in the nature of the N-substituted alkyl/aryl group. ZDEC contained a nonbulky ethyl group as the N-substituted alkyl group. In contrast, all other dithiocarbamate compounds contained bulky alkyl or aryl groups with higher hydrocarbon contents, which made them more rubber-soluble than ZDEC. Solubility experiments with dithiocarbamates in natural rubber showed that the solubility of ZDBC was much higher than that of ZDEC.[27,28] The limit of solubility of ZDEC and ZDBC in natural rubber was 0.8 and 2.0 pphr, respectively.[27] The high rubber solubility of ZDBC explained its substantially lower extent of release into artificial sweat compared with that of ZDEC. A similar argument holds for ZIBC, the isomeric counterpart of ZDBC. ZDNC is also reported to have high solubility in rubber leading to a low release in artificial sweat.[13,29]

Another factor that governs the amount of sweat-extractable dithiocarbamates is the residual dithiocarbamate content. The amounts of residual dithiocarbamates in vulcanizates containing ZDEC (DE-1) and ZDBC (BU-1) were compared. Vulcanizate BU-1 con-



ZDEC, R_1, R_2, R_3, R_4 = Ethyl (i.e., $-CH_2-CH_3$)

ZDBC, R_1, R_2, R_3, R_4 = Butyl (i.e., $-CH_2-CH_2-CH_2-CH_3$)

ZBEC, R_1, R_2, R_3, R_4 = Benzyl (i.e., $-CH_2-C_6H_5$)

ZIBC, R_1, R_2, R_3, R_4 = Isobutyl (i.e. $-CH_2-CH(CH_3)-CH_3$)

ZDNC, R_1, R_2, R_3, R_4 = Isononyl (i.e. $-CH_2-CH(CH_3)-(CH_2)_5-CH_3$)

Scheme 1 General structure of dithiocarbamates.

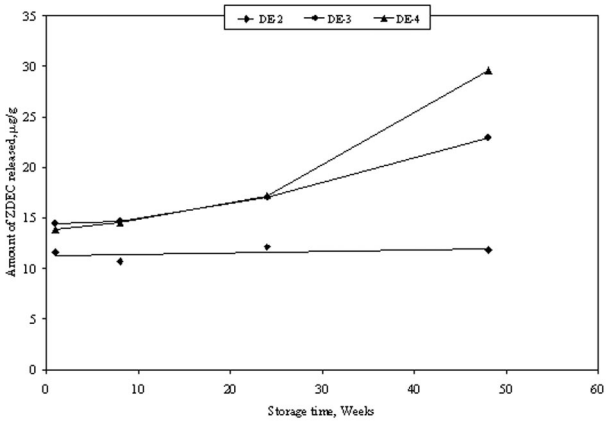


Figure 3 Amount of ZDEC released into artificial sweat from latex vulcanizates stored for different periods (DE-2, DE-3, and DE-4 compounded with 0.5, 0.82, and 1.0 pphr ZDEC, respectively).

tained a higher amount of residual ZDBC (4 mg/g) than vulcanizate DE-1, which contained 1 mg/g residual ZDEC. Despite containing high levels of residual ZDBC, vulcanizate BU-1 released negligible amounts of ZDBC into sweat. Therefore, it may be inferred that the higher solubility of ZDBC in rubber is a major factor controlling its release into artificial sweat.

Effect of the storage time

The effect of the storage time on the extent of dithiocarbamate release into artificial sweat was studied with latex vulcanizates containing various amounts of ZDEC, the highest migrating accelerator as indicated by the previous study. Figure 3 shows the variation in the amount of ZDEC released into artificial sweat from latex vulcanizates with the storage time. Within the time frame of the experiment, the results indicated that the amount of sweat-extractable ZDEC significantly increased with an increase in the storage time ($p < 0.05$). The increase in the amount of sweat-extractable ZDEC upon storage was attributed to the migration of ZDEC residues through the rubber phase. Lederer et al.[20] reported that the magnitude of change in the curative concentration across the rubber interface increased with increasing storage time, indicating the migration of curatives. The extent of migration depended on the nature of the curative and the rubber matrix.[20,30] It has been reported that accelerators with high rubber solubility show a lower tendency to migrate across the rubber phase to the surface of the rubber article.[13] ZDEC, being less rubber-soluble, migrated across the natural rubber vulcanizate to the surface of the vulcanizate over a period of time; this resulted in an increase in its concentration at the surface, which in turn accounted for the increase in the amount of sweat-extractable ZDEC.

It was also found that the sweat-extractable ZDEC varied with the concentration of ZDEC added initially to the latex formulations. With an increase in the amount of ZDEC added to the latex formulations, the amount of sweat-extractable ZDEC from the vulcanizates tended to increase upon storage (Fig. 3). This could be explained by the residual ZDEC content in the vulcanizates. Figure 4 shows the amount of the residual ZDEC in the latex vulcanizates. The residual ZDEC content increased with an increase in the amount of the initial level of ZDEC in the formulations. As the residual ZDEC content increased, it migrated to the surface of the vulcanizates at a faster rate, and this resulted in an increase in its concentration at the surface. This accounted for the increase in the amount of sweat-extractable ZDEC with an increase in the initial ZDEC content. The rate of migration of ZDEC across the rubber phase was calculated from the slope of the curves in Figure 3.[19] The slopes of the curves for DE-2, DE-3, and DE-4 are 0.02, 0.19, and 0.34, respectively. It is apparent that there was a steady increase in the slope as the initial level of ZDEC was increased, indicating that the rate of migration depended on the initial ZDEC content in the latex vulcanizates. The residual ZDEC content was directly proportional to the initial ZDEC content in the formulations (Fig. 4). It is, therefore, implied that the higher the amount is of residual ZDEC, the higher the extent is of migration through the rubber phase (Fig. 3).

The diffusion coefficients of ZDEC could be calculated with the migration data obtained in this study. Detailed migration studies of additives through rubber by various researchers have shown that the migration is controlled by diffusion obeying Fick's second law.[19,28] The migration model given in eq. (1), based on Fick's second law, has been extensively used for the assessment of the migration of additives:[28,31]

$$\frac{M_t}{M_0} = \frac{2}{l}\left(\frac{D_p t}{\pi}\right)^{0.5} \quad (1)$$

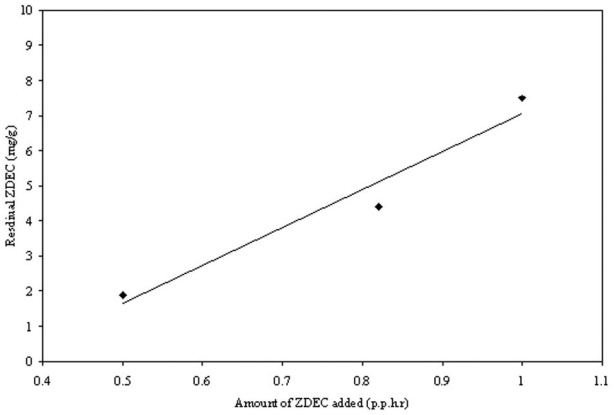


Figure 4 Variation of the residual ZDEC content with respect to the amount of ZDEC added initially to the latex formulations.

where M_t is the amount of the additive that has migrated at storage time t (s), M_0 is the total amount of the migrant in the rubber, D_p is the diffusion coefficient of the migrant, and l is the thickness of the polymer film. The diffusion coefficients of ZDEC at each concentration were calculated from a plot of M_t/M_0 versus $\sqrt{t}$ with initial migration data and linear regression analysis. Figure 5 shows a typical plot of M_t/M_0 versus $\sqrt{t}$, indicating that the migration of ZDEC followed the characteristic Fickian behavior; that is, the amount of ZDEC that migrated was linearly related to the square root of time. The diffusion coefficient was calculated with the migration data available at each concentration and is given in Table IV. The data of the diffusion coefficient of ZDEC confirmed that the there was a slight concentration dependence for the diffusion coefficients, probably due to the presence of a number of additives and the high concentration of ZDEC in the rubber matrix.[32] A similar observation was made by Lederer et al.,[20] who reported a small rationalizable effect of concentration on the diffusion coefficient of curatives in a rubber matrix.

This study generated meaningful data regarding the extent of release of residual dithiocarbamates into artificial sweat. The release profile of different dithiocarbamates into artificial sweat will help manufacturers to select suitable accelerators for products that come into direct and prolonged contact with the body. The release studies of ZDEC into artificial sweat with time showed that ZDEC migrated to the surface of the latex vulcanizates upon storage for long periods, such as 48 weeks. In the case of DE-3 and DE-4, the increase in the ZDEC content was marginal up to 24 weeks, and then there was a steep rise in the ZDEC content with storage for 48 weeks. However, in the case of DE-2, there was not much change in the ZDEC content even up to 48 weeks. Therefore, it can be inferred that the extent of migration of ZDEC increased with an increase in the amount of residual ZDEC. It follows that a high residual ZDEC content in latex vulcanizates may increase the concentration of ZDEC at the surface of the vulcanizates when they are stored for long periods. The observations made in this study consolidate the fact that the use of migrating accelerators such as ZDEC will lead to an accumulation of ZDEC at the surface of latex sheets over a period of time, thereby increasing the risk of allergic elicitations.

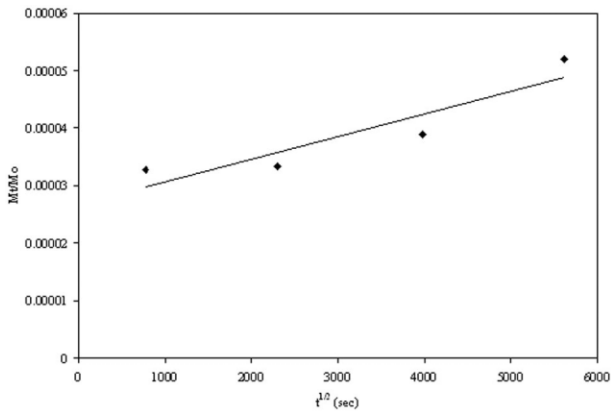


Figure 5 Typical plot of M_t/M_0 versus $\sqrt{t}$ with the migration data of latex vulcanizates compounded with 0.82 pphr ZDEC.

TABLE IV
D_p Values of ZDEC at Different Concentrations

Initial level of ZDEC (pphr)	Dp (cm^2/s), at 28 deg C
0.5	2.07×10^{-9}
0.82	3.94×10^{-9}
1.0	4.14×10^{-9}

CONCLUSIONS

Despite the use of the same levels of dithiocarbamates, higher quantities of ZDEC were released into sweat solutions in comparison with ZDBC and other higher homologue dithiocarbamates. Within the time frame of the study, the amount of sweat-extractable ZDEC from latex vulcanizates increased with an increase (1) in the storage time and (2) in the amount of residual ZDEC, which in turn depended on the amount of ZDEC added initially to the latex formulations. The analysis of the data indicated that the migration followed a typical Fickian behavior. The diffusion coefficient of ZDEC was slightly dependent on the concentration.

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