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A NEW METHODOLOGY TO EVALUATE THE MECHANICAL PROPERTIES OF ELASTOMERIC CLOSURES

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ABSTRACT

A quantitative method was developed to evaluate the mechanical properties of elastomeric closures commonly used in liquid parenteral dosage forms. The new methodology was based on the compression of individual stoppers facing upwards, with a stainless steel probe attached to an Instron testing machine. The Instron recorded the maximum force exerted by the closure at a preset rate and displacement value. The mechanical properties were also evaluated with the standard needle penetration force test. The compression test was found to be more sensitive in ascertaining differences in the mechanical properties of stoppers compared to the needle penetration test. Changes in the mechanical properties of closures exposed to various concentrations of acetate buffer, pH and buffer species were also evaluated in this study. The mechanical properties of all stoppers tested were affected by the acetate buffer concentration, even though their physical appearance did not change. The compression force was significantly decreased with an increase in buffer concentration, whereas the needle penetration force values were not significantly different. Since there was no significant effect of pH or citrate buffer species on the mechanical properties of closures, the changes in compression force observed were attributed to the acetate buffer species. In addition, an increase in the duration of the autoclaving cycle significantly affected the mechanical properties of

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polyisoprene stoppers, whereas the properties of bromo and chlorobutyl stoppers remained unchanged.

INTRODUCTION

The selection of a suitable elastomeric closure is an important decision in the development of a parenteral vial product. The primary function of the closure is to establish an integral seal that will assure sterility of the product at the time of use. In addition, it must permit removal of the product, usually by penetration either single or multiple with a hypodermic needle.

Typical elastomers used for closures are high molecular weight flexible polymers with characteristic viscoelastic properties (1,2). The viscous component of these closures ensures an effective seal on the parenteral vial and the elasticity maintains a residual seal force against the top of the vial.

Usually, important rheological properties defining the rubber formulations such as durometer hardness, tensile strength, modulus, and compression set are examined. However, the relevance of these properties to the performance requirements of finished elastomeric closures has been questioned (2). Furthermore, the stress-strain tests mentioned above are usually conducted by the closure manufacturer on stock rubber, rather than on the molded closures. Other initial screening tests for functional characteristics on rubber closures include, testing for leakage rate (3), relative coring tendency, moisture vapor transmission and needle penetration and resealability (4). A 10% coring rate is an acceptable limit for the stoppers in pharmaceutical industry. However, the rationale for this limit is unknown (5). The moisture vapor transmission test is usually conducted to qualify a new formulation and is not routinely conducted on the closures. The needle penetration and resealability test is used as a comparative test against formulations of established performance characteristics, rather than a test for functional integrity of the stopper. Excellent reviews on the physical, chemical, functional and stability testing requirements for elastomeric rubber closures are available in the literature (6,7).

The overall purpose of these studies was to develop a quantitative method for evaluating the mechanical properties of elastomeric closures

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used in liquid parenteral dosage forms. The objectives of these studies included the evaluation of changes in the mechanical properties of rubber stoppers exposed to various concentrations of acetate buffer, pH and buffer species. The results from the new methodology are compared with those from the standard needle penetration force test.

MATERIALS AND METHODS

Materials

Gray 13 mm closures of various polymeric compositions were supplied by The West Co., Phoenixville, PA. The stoppers used in the study included, bromobutyl stoppers (4416 and 1816), a natural rubber (polyisoprene) stopper (1134), a chlorobutyl/isoprene blend stopper (1888) and a 4416 stopper coated with a special polymeric coating identified by the proprietary name of Purcoat®. Reagent grade acetic acid, sodium acetate, citric acid and sodium citrate were obtained from Fisher Scientific (Fairlawn, NJ).

Methods

Effect of Buffer Concentration and Autoclaving cycles

Three different concentrations of acetate buffer (0.025M, 0.1M and 1.0M) at pH 4.0 were prepared. Citrate buffer at pH 4.0 and acetate buffer at pH 5.0, each at a concentration of 0.1M, were also prepared. The buffer solutions were filled into 10 mL vials, which were sealed and stored inverted at 45°C for eight weeks prior to testing.

A portion of the filled vials were also autoclaved at 121°C for either 30 minutes or 60 minutes. The vials were allowed to cool to room temperature and then were stored inverted at 45°C for eight weeks prior to testing. The results obtained from these studies were compared with those from non-autoclaved vials by the methods described below.

Closures of each polymeric composition were also tested immediately after washing to obtain baseline values for the mechanical properties prior to autoclaving and storage.

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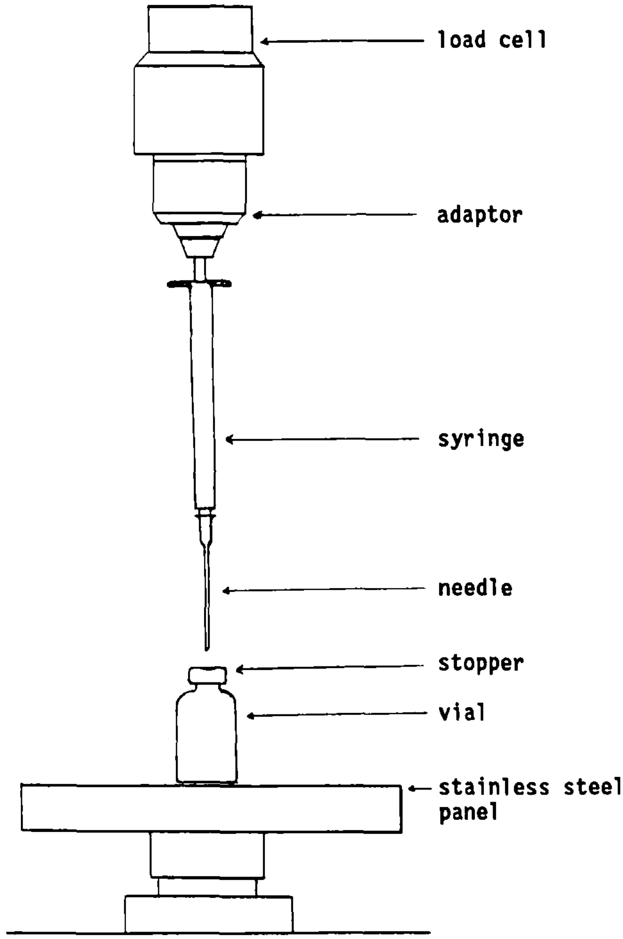

SCHEMATIC 1

Instron Testing Machine set-up for performing the needle penetration test.

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Testing Procedures

An INSTRON Testing Machine (model 4200) equipped with a 50 lb compression load cell and interfaced with an IBM computer was used to perform the needle penetration and the compression test.

Needle Penetration Force Test

This test measured the load needed to penetrate the closure with a disposable 18-gauge needle at a preset crosshead speed of 10 mm/minute

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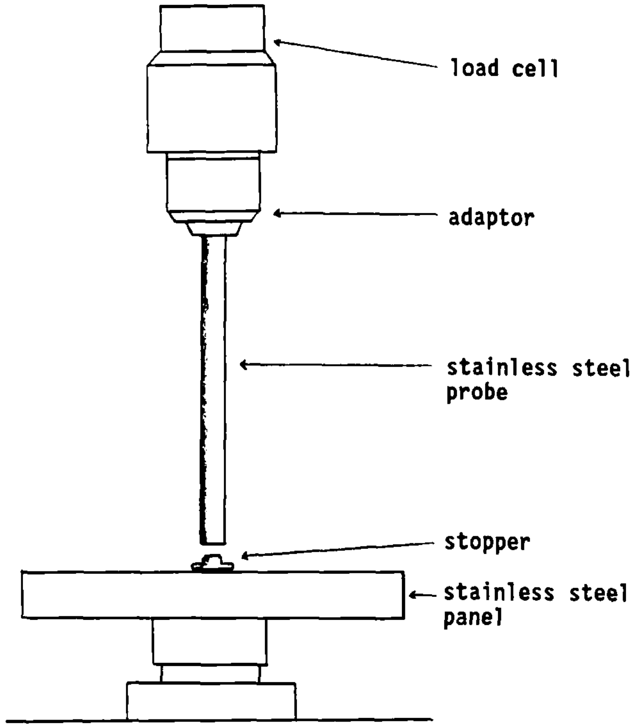

SCHEMATIC 2

Instron Testing Machine set-up for performing the compression test.

(Schematic 1). The needle (with the needle point extending downward) was attached on a 1 mL syringe affixed to the load cell with an adaptor. The test was conducted by placing the vial sealed with the stopper on the stainless steel panel below the mobile crosshead. The load cell with the syringe was allowed to travel down until the needle penetrated the stopper. A minimum of six stoppers were tested. The required penetration force was measured in terms of load values in units of grams.

Compression Force Test

The stopper was removed from the vial and placed on the stainless steel panel, with the side (plug) exposed to the liquid facing upwards. The test is based on the compression of closures with a stainless steel probe attached to the load cell with an adaptor (Schematic 2). The

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TABLE 1

Physical Properties* of the Polymeric Formulation of the Elastomeric Stoppers

Stopper	Tensile (psi)	300% Modulus (psi)	Elongation (%)
4416	1200	400	780
1816	885	285	755
1888	621	257	510
1134	2260	1000	530

* Data provided by the West Company

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INSTRON recorded the resistance to compression as a function of the maximum load exerted on the stopper at a preset rate and displacement value. A crosshead speed of 5 mm/minute was used and a predetermined displacement value was chosen based upon the molding of the closure studied. A minimum of six stoppers were tested. The compression force was measured in terms of load values in units of kilograms.

Statistical Analysis

The data for the effect of acetate buffer concentration and duration of the autoclaving cycles on the mechanical properties of closures, were analyzed using analysis of variance (ANOVA), followed by Duncan's test to detect differences between the mean values using SAS. The effects of pH and different buffer species were analyzed by a two-tailed Student's t-test.

RESULTS AND DISCUSSION

The physical properties of the polymeric formulations of the various stoppers used in this study are listed in Table 1. Tensile strength is the force per unit area which is applied at the time of rupture of an elastomeric rubber sample. Modulus is the amount of stress or pull

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required to stretch an elastomer to a given elongation. This property expresses the stiffness of an elastomer and is related to durometer hardness. Elongation is a property defined as the percent of an elastomer's original length versus the length when stretched to its breaking point. The data shown in Table 1 suggest that the natural rubber stoppers (1134) possess excellent physical properties as compared to halobutyl (4416 and 1816) and halobutyl/polyisoprene (1888) stoppers. Preliminary studies, using the 4416 stopper, showed that the needle penetration force increased with a decrease in the gauge of the disposable needle used. These results were expected, since the stopper will exert a higher resistance to the larger gauge needle which is thicker and has a larger needle tip surface area. The 18-gauge needle was selected to perform the needle penetration test since it resulted in the highest load values with the lowest variability. The effect of crosshead speed on the penetration load was also investigated as part of validating the test. It was shown that increasing the crosshead speed from 5 mm/min to 20 mm/min resulted in an increase in needle penetration force. However, the increase in penetration force above a speed of 10 mm/min was not significant and therefore, this speed was chosen for the needle penetration force test. Initial studies had also indicated that the use of the same needle for multiple penetration tests resulted in an increased force for each subsequent penetration. This was postulated to be due to the blunting of the needle. Therefore, it was decided that a new needle should be used for each test to simulate conditions of actual use.

Evaluation of the mechanical properties of closures

The data for the mechanical properties of the different closures unexposed to buffers or autoclaving cycles, are listed in Table 2. The results showed that the properties of halobutyl stoppers (4416 and 1816) were comparable, but they were significantly different from those of polyisoprene (1134) stoppers and halobutyl/isoprene blend stoppers (1888). The needle penetration force for polyisoprene stoppers (1134) was significantly higher than that for halobutyl (4416 and 1816) and halobutyl/isoprene blend stoppers (1888). These results correlate with the tensile strength values of the polymeric formulations listed in Table 1. On the other hand, the compression load for the polyisoprene (1134) stoppers was significantly lower than that for halobutyl stoppers. This

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TABLE 2

Mechanical properties of processed elastomeric closures

Stopper	Needle Penetration Force (gm)	Compression Load (Kg)
4416	396 ± 20[a]	15.25 ± 0.37[a]
4416Purcoat®	373 ± 20[a]	15.02 ± 0.78[a]
1816	349 ± 10[b]	13.82 ± 0.61[b]
1888	234 ± 16[c]	8.46 ± 0.26[c]
1134	496 ± 50[d]	5.76 ± 0.78[d] *

[a,b,c,d] same letters indicate no significant difference at $p<0.05$
* test performed at different displacement value (1 mm) due to stopper molding

lower compression load was artifactual because of the molding of the 1134 stoppers (V-38) as compared to the molding (V-35) of the other stoppers. To accommodate the different moldings, the compression test was conducted at a displacement value of 1 mm for 1134 stoppers and 5 mm for the other stoppers. Within the stoppers with the same mold, the halobutyl/isoprene blend (1888) stoppers, exhibited the lowest compression load. Purcoat®, which is applied uniformly on all surfaces of the stopper, did not significantly affect the mechanical properties of halobutyl stoppers.

__Needle Penetration Force Test__

Table 3 shows the effect of various acetate buffer concentrations and autoclaving cycles on the needle penetration force values for halobutyl stoppers (4416, 4416Purcoat and 1816), halobutyl/isoprene blend (1888) stoppers, and polyisoprene (1134) stoppers. Although the penetration force values were different for the various stoppers based upon polymeric composition, no statistically significant differences were observed within each stopper under different conditions. Polyisoprene (1134) stoppers were significantly affected, both, by the concentration of acetate buffer and by the duration of the autoclaving cycle. In that, the needle penetration force was inversely proportional to the concentration of the buffer, as well as the duration of the autoclaving cycle. Although

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TABLE 3

Effect of Acetate Buffer Concentration at pH 4.0 and Autoclaving Cycle on the Needle Penetration Force Values of Closures

Stopper	Autoclaving Cycle	Needle Penetration Force (gm) Acetate Buffer Concentration 0.025M	0.1M	1.0M
4416	Non-autoclaved	414 ± 19	403 ± 38	437 ± 37
	30 minutes	407 ± 22	419 ± 31	386 ± 20
	60 minutes	382 ± 32	416 ± 33	384 ± 15
4416Purcoat®	Non-autoclaved	448 ± 29	395 ± 38	423 ± 22
	30 minutes	442 ± 42	411 ± 16	419 ± 41
	60 minutes	417 ± 34	424 ± 34	421 ± 39
1816[a]	Non-autoclaved	393 ± 35	345 ± 18	350 ± 25
	30 minutes	375 ± 40	348 ± 32	323 ± 18
	60 minutes	361 ± 30	319 ± 25	317 ± 21
1888[a]	Non-autoclaved	251 ± 17	285 ± 36	240 ± 16
	30 minutes	237 ± 8	280 ± 26	228 ± 15
	60 minutes	241 ± 16	265 ± 14	229 ± 14
1134[a,b,c]	Non-autoclaved	598 ± 69	494 ± 51	354 ± 36
	30 minutes	501 ± 28	453 ± 65	345 ± 32
	60 minutes	477 ± 39	428 ± 40	346 ± 48

[a]significantly different at $p<0.05$ from 4416 and 4416Purcoat® stoppers

[b]significantly different at $p<0.05$ for duration of autoclaving cycle

[c]significantly different at $p<0.05$ for acetate buffer concentration

the exact reason for this finding is unclear, it may be partially explained on the basis of the properties imparted by the different polymeric composition of the closures. Polyisoprene stoppers have excellent physical properties due to the degree of unsaturation of the elastomer present in the stopper, as compared to butyl and halobutyl stoppers. The latter possess excellent chemical properties, due to saturation of the reactive double bonds in the main chain of the

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TABLE 4

Effect of pH, Buffer Species and Autoclaving Cycle on the Needle Penetration Force Values of Closures

Stopper	Autoclaving Cycle	Needle Penetration Force (gm) pH 4.0 0.1M Acetate	pH 4.0 0.1M Citrate	pH 5.0 0.1M Acetate
4416	Non-autoclaved	403 ± 38	414 ± 44	418 ± 29
	30 minutes	419 ± 31	399 ± 25	426 ± 25
	60 minutes	416 ± 33	415 ± 43	426 ± 34
4416Purcoat®	Non-autoclaved	395 ± 38	431 ± 10	414 ± 37
	30 minutes	411 ± 16	431 ± 32	427 ± 43
	60 minutes	424 ± 34	419 ± 30	416 ± 28
1816[a,c]	Non-autoclaved[#]	345 ± 18	394 ± 38	410 ± 52
	30 minutes	348 ± 32	402 ± 16	412 ± 36
	60 minutes	319 ± 25	369 ± 25	408 ± 40
1888[a,c]	Non-autoclaved	285 ± 36	290 ± 25	232 ± 18
	30 minutes	280 ± 26	267 ± 18	241 ± 16
	60 minutes[*]	265 ± 14	268 ± 24	247 ± 26
1134[a]	Non-autoclaved	494 ± 51	502 ± 62	513 ± 59
	30 minutes[c]	453 ± 65	465 ± 47	530 ± 37
	60 minutes	428 ± 40	456 ± 45	451 ± 46

[a]significantly different at $p<0.05$ from 4416 and 4416Purcoat® stoppers

[c]significantly different at $p<0.05$ for different pH values

[#]significantly different at $p<0.05$ for different buffer species

[*]not significantly different a $p<0.05$ for different pH values

elastomer. Furthermore, the curing system used for 1134 stoppers was sulfur, and that for 1888 stoppers was phenolic resin. The halobutyl stoppers (4416 and 1816) employed unconventional curing systems. These differences may contibute to the effect of buffer and autocalving on 1134 closures.

The effect of pH and duration of the autoclaving cycle for two different buffers at a fixed concentration of 0.1M, on the needle

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penetration force, is shown in Table 4. The data showed a significant effect of pH for 1816 stoppers. Also, there was variability within the 1888 stoppers in the needle penetration force values, for stoppers autoclaved for different lengths of time. Since there was no difference between pH 4.0 and 5.0 (0.1M acetate buffer) for the 4416, 4416Purcoat® and 1134 stoppers, and due to the variability in the data, the effect of pH on the needle penetration force for closures was at best ambiguous. Furthermore, there was no significant difference between the needle penetration force values, at pH 4.0 for citrate and acetate buffers for all the stoppers studied.

<u>Compression Force Test</u>

The effect of acetate buffer concentration and duration of the autoclaving cycle on the compression force of stoppers is shown in Table 5. The results demonstrated a reduction in the compression load with increasing acetate buffer concentrations for all bromobutyl (4416, 4416Purcoat® and 1816) stoppers. The data for chlorobutyl/polyisoprene stoppers (1888) showed no significant difference between the compression force values for various buffer concentrations. These results for 1888 stoppers may be due to the complete penetration of the stainless steel probe into the plug of the closure. The Instron essentially yielded the same compression load for all conditions tested. This phenomenon was not observed with any of the other stoppers. The polymeric coating of Purcoat® resulted in a marginal protection of the bromobutyl stoppers against the increasing buffer concentrations as compared to the uncoated 4416 stoppers. For example, in case of the non-autoclaved 4416 stoppers exposed to 1.0M acetate buffer for eight weeks at 45°C, the compression load for the 4416Purcoat stoppers was 12.67 kg; whereas that for the uncoated 4416 stoppers was 10.82 kg.

The effects of pH and autoclaving cycle for two different buffer species at a fixed concentration of 0.1M on the compression force of the various stoppers are shown in Table 6. These results showed no significant differences in the compression force values at the two pH values (0.1M acetate buffer) for any stopper tested. This alluded to the lack of contribution of the pH to the changes in the compression force of the stoppers. Since, Table 5 did show significant differences at pH 4.0

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TABLE 5

Effect of Acetate Buffer Concentration at pH 4.0 and Autoclaving Cycle on the Compression Force Values of Closures

Stopper	Autoclaving Cycle	Compression Force (Kg) Acetate Buffer Concentration 0.025M	0.1M	1.0M
4416[c]	Non-autoclaved	15.71 ± 0.99	12.40 ± 0.29	10.82 ± 0.75
	30 minutes	14.23 ± 1.23	12.70 ± 0.56	10.36 ± 0.50
	60 minutes	15.05 ± 1.16	12.69 ± 0.80	10.73 ± 0.75
4416Purcoat®[c]	Non-autoclaved	15.18 ± 0.76	13.99 ± 0.44	12.67 ± 0.80
	30 minutes	16.60 ± 0.98	13.61 ± 0.37	12.75 ± 0.70
	60 minutes	16.30 ± 0.77	13.58 ± 0.24	12.84 ± 0.71
1816[a,c]	Non-autoclaved	14.92 ± 1.54	12.03 ± 0.60	9.54 ± 0.47
	30 minutes	14.04 ± 1.05	12.25 ± 0.49	9.24 ± 0.43
	60 minutes	14.54 ± 0.88	12.21 ± 0.53	9.40 ± 0.27
1888[a]	Non-autoclaved	7.72 ± 0.36	7.54 ± 0.62	7.16 ± 0.38
	30 minutes	7.52 ± 0.30	7.01 ± 0.56	7.22 ± 0.39
	60 minutes	7.97 ± 0.71	6.72 ± 0.43	7.35 ± 0.33
1134[a,b,c]	Non-autoclaved	5.56 ± 0.59	3.72 ± 0.43	2.19 ± 0.31
	30 minutes	4.10 ± 0.40	2.61 ± 0.12	1.82 ± 0.21
	60 minutes	2.78 ± 0.47	2.53 ± 0.21	1.36 ± 0.16

[a]significantly different at $p<0.05$ from 4416 and 4416Purcoat® stoppers

[b]significantly different at $p<0.05$ for duration of autoclaving cycle

[c]significantly different at $p<0.05$ for acetate buffer concentration

for increasing concentrations of acetate buffer, the changes in the mechanical properties were attributed to the acetate species rather than the pH itself. Furthermore, at pH 4.0, the compression load values for citrate buffer samples were significantly higher than those for acetate buffer samples in the cases of 1888 and 1134 stoppers. This was also indicative of the contribution of acetate buffer species to the changes measured by the compression test. The compression force values for the

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TABLE 6

Effect of pH, Buffer Species and Autoclaving Cycle on the Compression Force Values of Closures

Stopper	Autoclaving Cycle	Compression Force (Kg) pH 4.0 0.1M Acetate	pH 4.0 0.1M Citrate	pH 5.0 0.1M Acetate
4416	Non-autoclaved*	12.40 ± 0.29	13.75 ± 0.77	12.42 ± 0.79
	30 minutes	12.70 ± 0.56	13.09 ± 0.10	12.63 ± 0.74
	60 minutes	12.69 ± 0.80	13.30 ± 0.37	12.55 ± 0.52
4416Purcoat®[a]	Non-autoclaved	13.99 ± 0.44	13.53 ± 0.67	13.55 ± 0.84
	30 minutes	13.61 ± 0.37	13.70 ± 0.47	14.29 ± 0.33
	60 minutes*	13.58 ± 0.24	14.67 ± 0.69	13.93 ± 0.77
1816	Non-autoclaved	12.03 ± 0.60	12.27 ± 0.90	12.60 ± 0.53
	30 minutes	12.25 ± 0.49	11.94 ± 1.30	12.80 ± 0.38
	60 minutes	12.21 ± 0.53	12.77 ± 0.84	12.60 ± 0.59
1888[a,c]	Non-autoclaved	7.54 ± 0.62	8.75 ± 0.74	6.76 ± 0.17
	30 minutes	7.01 ± 0.56	9.24 ± 0.23	7.07 ± 0.37
	60 minutes	6.72 ± 0.43	9.41 ± 0.32	6.87 ± 0.48
1134[a,b,c]	Non-autoclaved	3.72 ± 0.43	6.01 ± 0.59	3.41 ± 0.46
	30 minutes**	2.61 ± 0.12	5.92 ± 0.57	1.96 ± 0.33
	60 minutes	2.53 ± 0.21	5.45 ± 0.15	2.29 ± 0.30

[a]significantly different at $p<0.05$ from 1816 and 4416 stoppers

[b]significantly different at $p<0.05$ for duration of autoclaving cycle

[c,*]significantly different at $p<0.05$ for different buffer species

[**]significantly different at $p<0.05$ for different pH values

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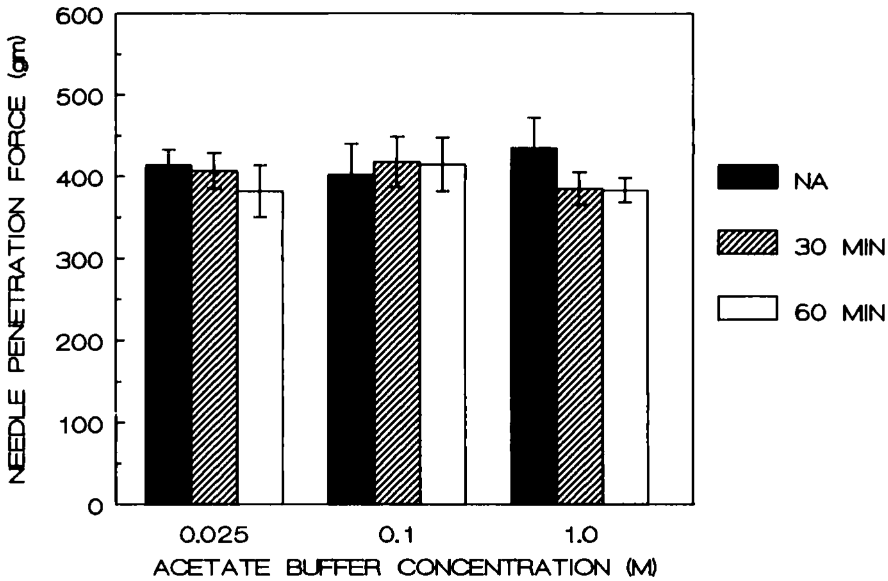

FIGURE 1

Effect of acetate buffer concentration and autoclaving cycle on the needle penetration force of 4416 stoppers.

4416 stoppers were higher for the citrate buffer samples, when compared to the acetate buffer samples. However, the compression force values of 1816 stoppers showed no significant effect of buffer species or pH. The exact reason for the different behavior of the 1816 stoppers, which are identical to 4416 (both being bromobutyl), is unknown. However, 1816 is the predecessor for the 4416 stopper. In the improved 4416 stoppers, magnesium is added as a scavenger for excess bromine to reduce the extractables from this stopper. This slight difference in the polymeric composition may be the factor that influences the behavior of these two stoppers under the conditions tested. No significant differences were observed in the compression force values of 4416Purcoat® stoppers exposed to different pH and buffer species. The polymeric coating of Purcoat® is probably the cause for the lack of noticeable differences in the compression force values of these stoppers.

Although the exact reason for the discriminatory capability of the compression test is not known, it is possible that the evaluation of a

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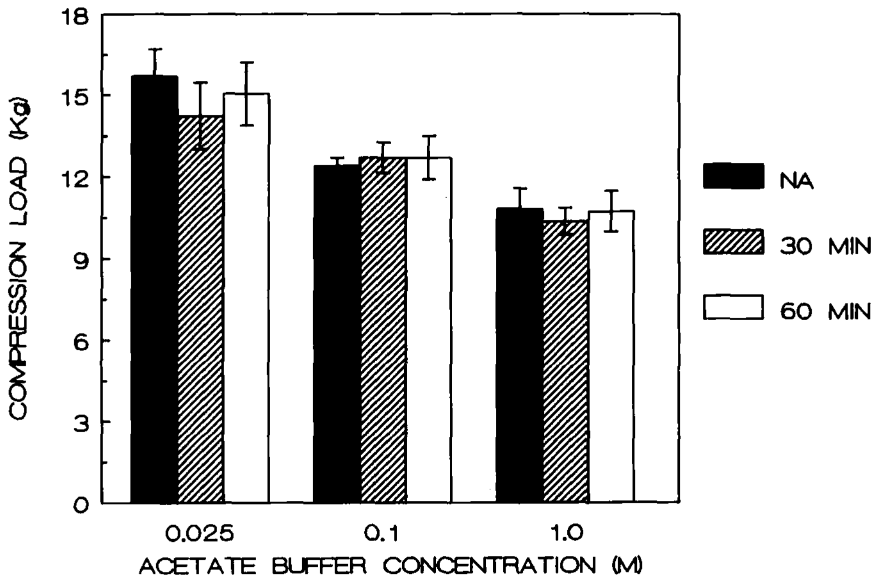

FIGURE 2

Effect of acetate buffer concentration and autoclaving cycle on the compression load of 4416 stoppers.

larger surface area of the stopper may be a contributing factor. The compression test entails the testing of the entire surface area of the stopper exposed to the liquid, whereas, the needle penetration force test only examines a small portion of the stopper surface. Figures 1 and 2 show the distinction in the capabilities of ascertaining the differences in the mechanical properties of 4416 stoppers, between the needle penetration force and compression test, respectively. It should be noted that the compression test is only applicable to detect changes in the closures of the same molding.

However, both tests were functional in case of 1134 stoppers (Figures 3 and 4). This may be due to the difference in the chemical composition of the rubber closures. As mentioned earlier, polyisoprene stoppers possess excellent physical properties, but poor chemical properties due to their degree of unsaturation. The double bonds of polyisoprene stoppers may react with the acetate and/or acetic acid in the

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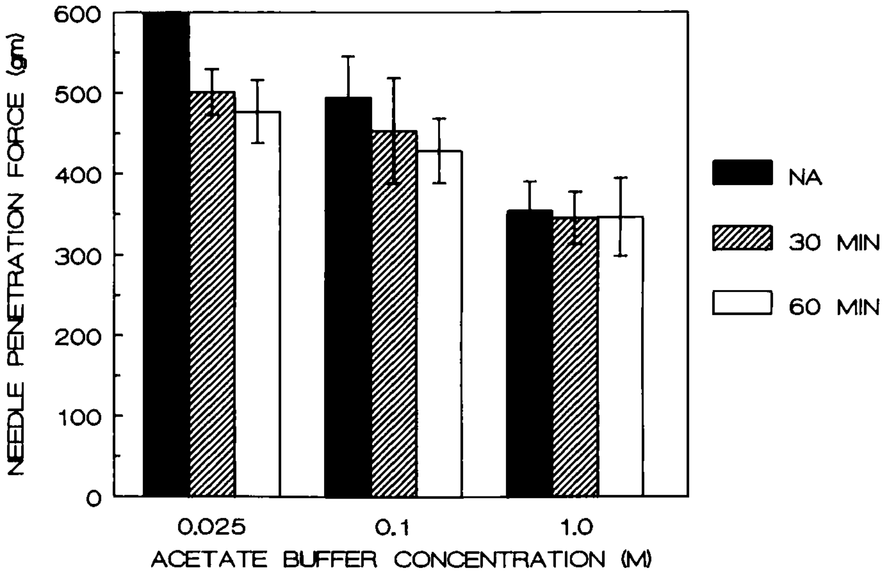

FIGURE 3

Effect of acetate buffer concentration and autoclaving cycle on the needle penetration force of 1134 stoppers.

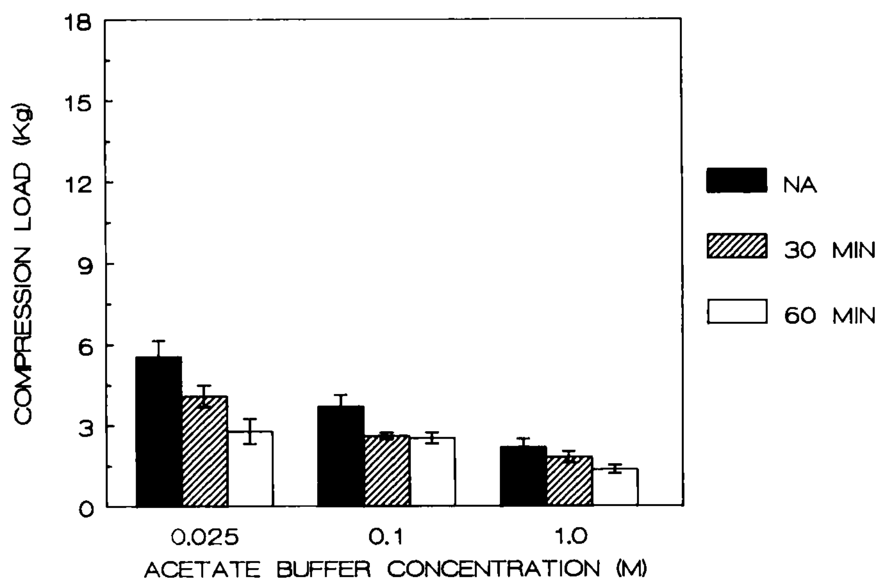

FIGURE 4

Effect of acetate buffer concentration and autoclaving cycle on the compression load of 1134 stoppers.

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buffer and change the polymeric composition considerably. Therefore, due to the magnitude of this chemical change, it is likely that the needle penetration test is capable of detecting the effects of autoclaving and buffer concentrations on this particular stopper.

CONCLUSIONS

A method was developed that allowed for the quantitative evaluation of elastomeric stoppers commonly used in parenteral products. It was shown that the new methodology, which was based on the compression of the stoppers at a preset displacement value, was able to discern changes in the mechanical properties of stoppers exposed to various conditions. These changes were not detected by the needle penetration force test.

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