

Compatibility of ¹⁴C-Labeled Phenylephrine Hydrochloride in Polyethylene Nasal Spray Containers

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Abstract □ The interaction of phenylephrine hydrochloride with low density polyethylene containers was investigated using ¹⁴C-labeled phenylephrine hydrochloride. In the first part of the study, nasal spray bottles with and without dip tubes containing 0.25 and 0.5% ¹⁴C-phenylephrine hydrochloride were evaluated at temperatures of 7, 22, 40, and 50°. No losses of ¹⁴C-phenylephrine hydrochloride were observed. Units stored at 40 and 50° showed apparent increases in concentration of the ¹⁴C-phenylephrine hydrochloride. This reflected the loss of water from these units, the loss being confirmed by gravimetric data. This demonstrated a technique for the observation of solvent loss by means of a radioisotopic method. In the second part of the study, the influence of two preservatives, benzalkonium chloride (1:5000) and thimerosal (1:5000) on the phenylephrine hydrochloride-polyethylene container interaction was investigated. The data indicated apparent binding of phenylephrine hydrochloride to low density polyethylene by means of a preservative agent. Interaction was most significant at room temperature, with elevated temperature disrupting the apparent weak binding.

Keyphrases □ Phenylephrine hydrochloride, ¹⁴C-labeled—interaction with low density polyethylene nasal spray containers, effect of preservatives □ Polyethylene nasal spray containers—interaction with ¹⁴C-phenylephrine hydrochloride, effect of preservatives □ Drug-plastic interactions—¹⁴C-phenylephrine hydrochloride and polyethylene nasal spray containers □ Nasal spray containers, polyethylene—interaction with ¹⁴C-phenylephrine hydrochloride, effect of preservatives □ Preservatives, benzalkonium chloride and thimerosal—effect on binding of phenylephrine hydrochloride to polyethylene containers □ Plastic (polyethylene) nasal spray containers—interaction with phenylephrine hydrochloride, effect of preservatives □ Liquid scintillation spectrometry—used to study interaction of ¹⁴C-phenylephrine hydrochloride with polyethylene

Many different products are packaged in plastics today. Among the first to recognize the versatility and practicality of plastics for packaging were the cosmetic and pharmaceutical manufacturers. The use of plastic containers in the pharmaceutical and cosmetic industry has multiplied rapidly to include a wide range of products. The plastic most frequently used in the manufacture of molded pharmaceutical and cosmetic containers is polyethylene.

Despite the widespread and increasing use of poly-

ethylene containers to package drug and cosmetic preparations, limited information is available in the literature as to the compatibility of medicinal agents and solutions with polyethylene containers. One potential problem is that solutions of a drug in contact with a plastic can lead to sorption of the drug by the plastic, resulting in a significant loss of potency. Another major consideration encountered with polyethylene is that it is permeable in varying degrees to liquids, gases, and volatile substances.

Marcus *et al.* (1) and Kim and Autian (2) studied the sorption of certain bacteriostatic agents and several weak organic acids by polyethylene syringes. Using conventional analytical techniques, they determined that no sorption had occurred after 1 week of storage at 5, 30, and 50°. Neuwald and Schmitzek (3) found that preservative solutions stored in low and high density polyethylene containers showed no apparent reduction in preservative concentration resulting from sorption into plastics. Schoenwald and Belcastro (4) demonstrated the sorption of chlorobutanol by polyethylene strips stored in ¹⁴C-labeled chlorobutanol solution. At present, there appears to be no satisfactory general method for predicting which plastic material should be used for one drug or another.

Parlman (5-7) was one of the first to study permeability of polyethylene with regard to containers. He developed an empirical method of determining the transmission rates of certain liquids through polyethylene. More recently, Salame and Pinsky (8) developed the Permachor method for estimating the permeabilities of organic liquids in polyethylene. One reason why permeation data often do not agree is that the particular plastic material influences the permeation rate, so great variations can occur in plastics even when manufactured under the same generic name (9).

One popular treatment employed for the symptomatic relief of nasal congestion is the administration of sympathomimetic-containing nasal solutions from polyethylene squeeze bottles. Phenylephrine hydrochloride is

Table I—Sample Grouping, Part A

Temperature	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution		0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	
	Group 1 Units with Dip Tubes	Group 2 Units without Dip Tubes	Group 3 Units with Dip Tubes	Group 4 Units without Dip Tubes
7°	Subgroup A Units: 1-5 101-105	Subgroup A Units: 6-10 106-110	Subgroup A Units: 41-45 141-145	Subgroup A Units: 46-50 146-150
22°	Subgroup B Units: 11-15 111-115	Subgroup B Units: 16-20 116-120	Subgroup B Units: 51-55 151-155	Subgroup B Units: 56-60 156-160
40°	Subgroup C Units: 21-25 121-125	Subgroup C Units: 26-30 126-130	Subgroup C Units: 61-65 161-165	Subgroup C Units: 66-70 166-170
50°	Subgroup D Units: 31-35 131-135	Subgroup D Units: 36-40 136-140	Subgroup D Units: 71-75 171-175	Subgroup D Units: 76-80 176-180

Table II—Sample Groupings, Part B

Temperature	—0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution—				—0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution—			
	Benzalkonium Chloride (1:5000)		Thimerosal (1:5000)		Benzalkonium Chloride (1:5000)		Thimerosal (1:5000)	
7°	Units	1-5	Units	101-105	Units	41-45	Units	141-145
22°	Units	6-10	Units	106-110	Units	46-50	Units	146-150
40°	Units	11-15	Units	111-115	Units	51-55	Units	151-155
50°	Units	16-20	Units	116-120	Units	56-60	Units	156-160

Table III—Mean Disintegrations per Minute (d.p.m.) for 0.25% ¹⁴C-Phenylephrine Hydrochloride Solution, Part A

Weeks	Mean d.p.m. Units 1-5, 7°, DT ^a	Mean d.p.m. Units 6-10, 7°, NDT ^b	Mean d.p.m. Units 11-15, 22°, DT	Mean d.p.m. Units 16-20, 22°, NDT	Mean d.p.m. Units 21-25, 40°, DT	Mean d.p.m. Units 26-30, 40°, NDT	Mean d.p.m. Units 31-35, 50°, DT	Mean d.p.m. Units 36-40, 50°, NDT
0	19,963	19,963	19,963	19,963	19,963	19,963	19,963	19,963
0.28	20,135	20,079	19,729	19,857	19,876	20,002	20,079	20,315
0.57	19,958	20,059	20,036	19,893	20,136	19,842	20,295	20,215
1.1	19,762	20,125	20,027	19,991	20,090	20,038	20,372	20,157
2.0	20,020	20,132	19,871	19,976	20,073	19,926	20,083	20,337
3.0	19,773	19,871	19,935	19,945	20,032	20,258	20,353	20,522
4.0	19,696	19,997	20,054	19,929	20,307	20,044	20,621	20,730
6.0	20,085	20,245	20,015	19,902	20,185	20,168	20,771	21,090
8.0	20,065	19,807	20,004	20,002	20,289	20,277	20,609	21,473
10.0	19,932	20,018	19,916	19,981	20,387	20,330	21,339	22,329
16.0	—	—	—	—	20,354	20,703	21,848	23,785
20.0	—	—	—	—	20,395	20,456	21,983	23,803

^a DT = dip tube. ^b NDT = no dip tube.

perhaps the most widely employed agent for this purpose, being the main ingredient in a large number of commercial products available for over-the-counter as well as prescription sales.

The intent of this investigation was to study the behavior of phenylephrine hydrochloride in the complete polyethylene spray bottle unit as it is sold to the consumer. Internal liquid scintillation spectrometry was employed for studying phenylephrine hydrochloride concentrations throughout the study because it is more sensitive to minute changes in concentration than are traditional assay methods.

While previous studies of drug-plastic interactions have been concerned with single-component systems, the use of internal liquid scintillation spectrometry permitted the study of a multicomponent system. One reason for not studying a multicomponent system by traditional methods is that the method of analysis can become quite complex. The ¹⁴C-phenylephrine hydrochloride could be studied in the presence of various unlabeled components to see what effect they might have on its interaction with the polyethylene.

EXPERIMENTAL

Polyethylene spraying bottles were used throughout the study¹. These bottles were made to contain 15 ml. of liquid and were supplied with dip tube, sprayhead, and screw-on cap.

The ¹⁴C-phenylephrine hydrochloride², with a specific activity of 6.02 mc./mmole, was determined by the manufacturer to have a radiochemical purity greater than 99%. To confirm this value, the upper layer of a butanol-acetic acid-water (5:1:3) solution was used as the developing solvent for the paper chromatographic analysis of the ¹⁴C-phenylephrine hydrochloride. Development of the chromato-

gram was followed by autoradiography on X-ray film, sectioning of the chromatogram, and scintillation counting. A radiochemical purity of greater than 98% was indicated.

Four main groups comprised Part A of the study. Group 1 contained 0.25% ¹⁴C-phenylephrine hydrochloride solution in spray containers complete with dip tubes, while Group 2 units had the dip tubes removed. Groups 3 and 4 contained 0.5% ¹⁴C-phenylephrine hydrochloride, with Group 3 spray containers being complete and Group 4 containers being without dip tubes.

Each main group was divided into four subgroups of five spray units each. One subgroup was stored at each of the following temperatures: 7, 22, 40, and 50°. Table I depicts the grouping of the units. A duplicate set of units was prepared for all four primary groups. These duplicate units were prepared to study weight loss and to determine the effects, if any, of repeated sample withdrawals on the results obtained with the primary groups.

In Part B of the study, the effects of two preservatives, benzalkonium chloride (1:5000) and thimerosal (1:5000), on the behavior of the ¹⁴C-phenylephrine hydrochloride-polyethylene interaction were studied. The units stored at 7 and 22° in Part A (from both the primary and duplicate groups) were used for Part B. No change occurred in these units during the first 10 weeks of Part A of the study.

The preservative solutions were added in such a manner as to yield a final volume of 10.1 ml. in each unit. All units used in Part B were assembled complete with dip tubes. Grouping of the units according to preservative and storage temperature is depicted in Tables II and III.

The spray containers were stored at the respective temperatures in the upright position in both parts of the study. Partitioned cardboard trays, open at the top, were constructed to store the spray units. Each partitioned carton held 20 spray containers.

A 100-μl. Hamilton³ microliter syringe with a Chaney adapter was used to withdraw 100-μl. samples from the spray containers. A scintillator solution (0.4% 2,5-diphenyloxazole in equal parts of toluene and 2-ethoxyethanol) was used for all samples.

A two-channel, ambient temperature, internal liquid scintillation spectrometer⁴, equipped with automatic sample changer and print-out, was used throughout the study. Each sample was counted at

¹ Spray bottles No. 25163, N-7/4, Wheaton Plastic, Millville, NJ 08332

² Tracerlab, Waltham, Mass.

³ Hamilton Co., Whittier, Calif.

⁴ Tri-Carb model 2002, Packard Instrument Co., Inc., LaGrange, Ill.

Table IV—Mean Disintegrations per Minute (d.p.m.) for 0.5% ¹⁴C-Phenylephrine Hydrochloride Solution, Part A

Weeks	Mean d.p.m. Units 41-45, 7°, DT ^a	Mean d.p.m. Units 46-50, 7°, NDT ^b	Mean d.p.m. Units 51-55, 22°, DT	Mean d.p.m. Units 55-60, 22°, NDT	Mean d.p.m. Units 61-65, 40°, DT	Mean d.p.m. Units 66-70, 40°, DT	Mean d.p.m. Units 71-75, 50°, DT	Mean d.p.m. Units 76-80, 50°, NDT
0	20,680	20,680	20,680	20,680	20,680	20,680	20,680	20,680
0.28	20,825	20,725	20,546	20,809	20,873	20,728	20,808	20,836
0.57	20,618	21,072	20,720	20,716	20,765	20,756	20,892	20,857
1.1	20,617	20,411	20,879	20,669	20,624	20,772	20,856	20,769
2.0	20,689	20,690	20,563	20,543	20,734	20,861	21,057	20,546
3.0	20,826	20,635	20,846	20,644	20,828	20,737	20,761	20,850
4.0	20,653	20,759	20,847	20,660	20,795	20,714	21,197	21,106
6.0	20,552	20,739	20,808	20,635	20,912	20,917	21,231	21,622
8.0	20,441	20,735	20,724	20,547	20,842	21,011	21,622	21,762
10.0	20,623	20,645	20,624	20,611	20,860	20,999	22,177	22,048
16.0	—	—	—	—	21,342	21,366	22,912	23,726
20.0	—	—	—	—	21,199	21,135	22,788	23,410

^a DT = dip tube. ^b NDT = no dip tube.

optimum gain for a 1-min. interval, with the instrument set to subtract the background count rate automatically. Net counts per minute (c.p.m.) ranged from approximately 14,000 to 16,000. A counting error of less than 1% was obtained, and the counting efficiency was around 78% throughout the investigation. By using a toluene-¹⁴C internal standard, the absolute count rate was calculated according to the method described by Wang and Willis (10). All further calculations were based upon the disintegrations per minute (d.p.m.) obtained.

Each container in the duplicate set of units was weighed on an analytical balance at the beginning and at the end of Part A to determine moisture loss. In addition, two units from each subgroup of the duplicate set were weighed periodically. Weighings were conducted each time sampling of the primary group was performed.

RESULTS

Drug-Plastic Interaction: Part A—Table I lists the solution groups investigated in Part A of the study. The mean disintegra-

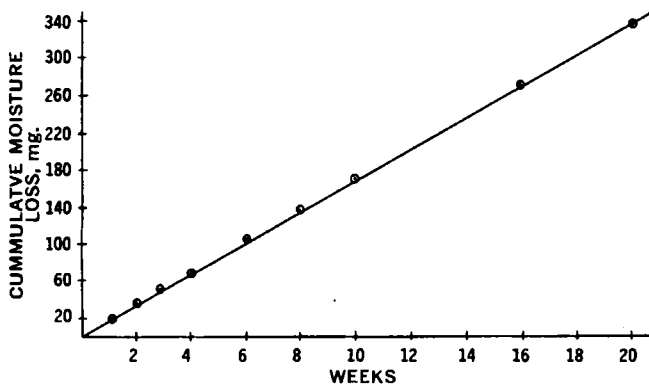


Figure 1—Example of a typical weight loss curve for a unit stored at 40°.

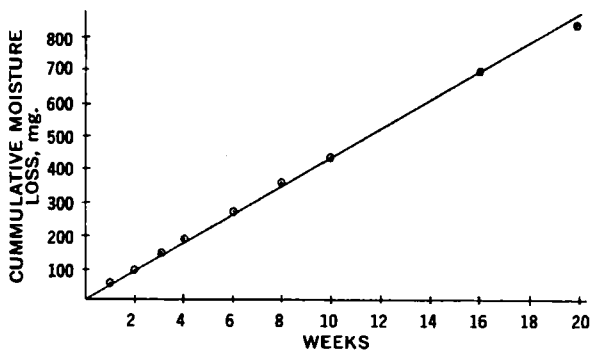


Figure 2—Example of a typical weight loss curve for a unit stored at 50°.

tions per minute for each five-container group is listed in Tables III and IV. The three major parameters investigated were the effects of solution concentration, temperature, and container components on possible drug-plastic interaction.

The data presented in Table III show that no loss of ¹⁴C-phenylephrine hydrochloride occurred in any of the 0.25% solutions. The disintegrations per minute values at the end of 10 weeks were of the same magnitude as the initial values or greater. Table IV shows similar results for the 0.5% ¹⁴C-phenylephrine hydrochloride. In all cases, group disintegrations per minute values either remained the same or increased during 10 weeks of storage at 7, 22, 40, or 50°. An increase in concentration of the ¹⁴C-phenylephrine hydrochloride had no apparent effect on the behavior of the phenylephrine hydrochloride toward the polyethylene. No sorption was demonstrated, indicating complete compatibility of the drug with the container and its components. There was no difference seen in the units without dip tubes. All units behaved in identical fashion at each temperature regardless of the presence or absence of dip tube components.

Reference to Tables III and IV shows that no loss of ¹⁴C-phenylephrine hydrochloride occurred at any of the four temperatures studied. There was no increase or decrease for any of the groups stored at 7 and 22°. Elevated temperatures failed to promote any loss of ¹⁴C-phenylephrine hydrochloride through sorption. There was an apparent gain in disintegrations per minute values, however, for each group stored at 40 and 50°. This gain was attributed to the loss of solvent from the spray containers.

Moisture Loss: Part A—Each unit in the duplicate set of units from Part A was weighed at the beginning of the study and at the end of 10 weeks. The units stored at 40 and 50° were also weighed again at the end of 16 and 20 weeks. The weight loss for each unit, represented as percent weight loss after 10 weeks, is listed in Table V. Table VI lists the percent weight loss for each unit stored at 40 and 50° for Weeks 11-16 of the study, while Table VII shows the percent weight loss for these units for Weeks 17-20. Since there was a corresponding increase in disintegrations per minute with weight

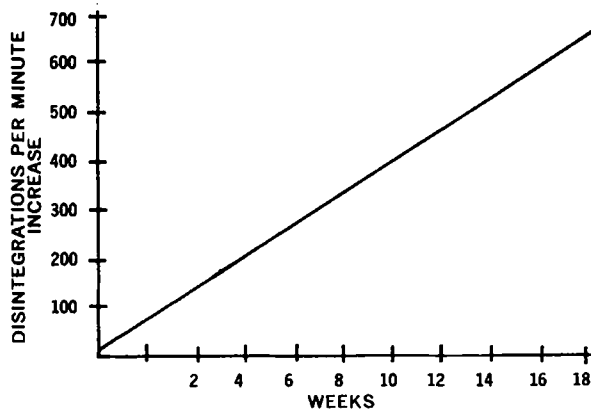


Figure 3—Average moisture loss as reflected by disintegrations per minute increase for a typical group of units stored at 40°.

Table V—Weight Loss Tabulation for First 10 Weeks of Study, Part A

Group Description	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution		0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	
	Unit Number	Percent Weight Loss	Unit Number	Percent Weight Loss
Storage at 7°, units with dip tubes	101	0.030	141	0.044
	102	0.203	142	0.233
	103	0.954 ^a	143	0.015
	104	0.034	144	0.492 ^a
	105	0.031	145	0.017
Storage at 7°, units without dip tubes	106	0.029	146	0.182
	107	0.029	147	0.023
	108	0.028	148	0.044
	109	0.025	149	0.012
Storage at 22°, units with dip tubes	110	0.033	150	0.082
	111	0.280	151	0.271
	112	0.295	152	0.268
	113	0.280	153	0.263
Storage at 22°, units without dip tubes	114	0.276	154	0.272
	115	0.282	155	0.269
	116	0.993	156	0.540
	117	0.286	157	0.267
Storage at 40°, units with dip tubes	118	0.280	158	0.283
	119	0.258	159	0.275
	120	0.274	160	0.277
	121	2.274	161	2.443
Storage at 40°, units without dip tubes	122	1.794	162	1.767
	123	1.740	163	3.130 ^a
	124	1.745	164	1.708
	125	1.726	165	1.738
Storage at 50°, units with dip tubes	126	1.753	166	1.643
	127	1.673	167	1.705
	128	1.819	168	1.747
	129	1.764	169	1.691
Storage at 50°, units without dip tubes	130	2.445	170	1.788
	131	4.512	171	4.158
	132	4.673	172	4.403
	133	5.741	173	4.639
Storage at 50°, units with dip tubes	134	5.111	174	4.666
	135	5.294	175	9.099 ^a
	136	4.444	176	4.071
	137	4.636	177	4.277
Storage at 50°, units without dip tubes	138	5.007	178	4.411
	139	5.001	179	4.536
	140	5.232	180	4.706

^a Denotes unit improperly sealed.

loss of the solutions studied, the weight loss was attributed to permeation of the solvent, water, through the polyethylene container. Average percent moisture loss values for all groupings as demonstrated by weight loss are listed in Table VII.

The presence or absence of dip tubes did not affect the moisture loss. Groups having no dip tubes showed moisture losses of the same magnitude as their counterparts with dip tubes. The average 10-week percent moisture loss for all groups stored at 7° was 0.031%, while the average loss was 0.275% for groups stored at 22°. Groups stored at 40 and 50° showed average moisture losses of 1.8 and 4.7%, respectively, during the first 10 weeks. Weight loss data for the second 10-week segment of Part A show an additional average moisture loss of 2.0% for units stored at 40° and of 4.4% for units stored at 50°.

Representative units of each group stored at 40 and 50° were weighed periodically during the first 10 weeks of the study, at the end of 16 weeks, and again at the end of 20 weeks. Figures 1 and 2 show the moisture loss curves for typical units stored at 40 and 50°. Water was lost from the units at a constant rate, the average loss being approximately 19 mg./week for units stored at 40° and 45.5 mg./week for units stored at 50°.

The loss of solvent from the polyethylene spray bottles was also reflected in the increased disintegrations per minute values at the end of 10, 16, and 20 weeks. The percent increase in disintegrations per minute values for both primary (regularly sampled) and duplicate (unsampled until Week 10) groups stored at 40 and 50° is shown in Table VIII. Reference to Table VIII shows that at the end of 10

Table VI—Weight Loss Tabulation for Weeks 11-16 and 17-20 of Study, Part A

Group Description	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution		0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	
	Unit Number	Percent Weight Loss	Unit Number	Percent Weight Loss
Weeks 11-16				
Storage at 40°, units with dip tubes	121	1.076	161	1.440
	122	1.430	162	1.496
	123	1.521	163	1.531
	124	0.972	164	1.079
	125	1.223	165	0.923
Storage at 40°, units without dip tubes	126	1.382	166	1.452
	127	1.350	167	0.990
	128	1.824	168	1.076
	129	1.075	169	0.962
Storage at 50°, units with dip tubes	130	1.290	170	0.982
	131	2.289	171	2.097
	132	2.546	172	2.333
	133	2.823	173	2.528
Storage at 50°, units without dip tubes	134	2.874	174	2.625
	135	2.995	175	2.823
	136	2.398	176	2.062
	137	2.680	177	2.203
Storage at 50°, units with dip tubes	138	4.324	178	3.031
	139	2.880	179	2.881
	140	2.907	180	2.636
	Weeks 17-20			
Storage at 40°, units with dip tubes	121	0.638	161	0.836
	122	0.628	162	0.939
	123	0.669	163	0.615
	124	0.689	164	0.607
	125	0.898	165	0.618
Storage at 40°, units without dip tubes	126	0.629	166	1.206
	127	0.816	167	0.614
	128	1.032	168	0.615
	129	0.836	169	0.845
Storage at 50°, units with dip tubes	130	0.635	170	0.601
	131	1.547	171	1.353
	132	1.663	172	1.502
	133	1.808	173	1.635
Storage at 50°, units without dip tubes	134	1.890	174	1.707
	135	1.998	175	1.827
	136	1.493	176	1.327
	137	1.612	177	1.433
Storage at 50°, units with dip tubes	138	2.160	178	1.578
	139	1.825	179	1.647
	140	1.915	180	3.059

weeks the percent increase in disintegrations per minute values for both primary and duplicate groups stored at 40° compares favorably with the percent weight loss data. While the percent increase in disintegrations per minute values after 10 weeks for the duplicate units stored at 50° compares favorably with the weight loss data, higher losses were reflected by the primary or regularly sampled units. The higher losses in these units may be attributed to their regular sampling, additional moisture loss occurring each time a unit was opened and a withdrawal made. These data are valuable in projecting what might be observed during normal patient use of these products.

The disintegrations per minute values for all groups stored at 40 and 50° continued to increase during the second 10-week period. The percent increase in disintegrations per minute values for the 20-week period compares favorably with the weight loss data for that period. Figures 3 and 4 show the moisture loss curves for groups stored at 40 and 50°, respectively, as reflected by the disintegrations per minute increase. The solid lines in Figs. 3 and 4 represent the lines of best fit for the data as determined by least-squares calculations.

Container Suitability: Part A—The results of Part A demonstrate that low density polyethylene containers are suitable for the packaging of aqueous solutions of phenylephrine hydrochloride. Phenylephrine hydrochloride showed no interaction with the polyethylene polymer at any of the temperatures studied. Furthermore, phenyl-

Table VII—Mean Moisture Loss in Percentages for All Groups as Determined Gravimetrically, Part A

Group Description	Percent Moisture Loss					
	After 10 Weeks		After 16 Weeks		After 20 Weeks	
	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution
Storage at 7°, with dip tubes	0.031	0.025	—	—	—	—
Storage at 7°, without dip tubes	0.028	0.040	—	—	—	—
Storage at 22°, with dip tubes	0.283	0.268	—	—	—	—
Storage at 22°, without dip tubes	0.274	0.276	—	—	—	—
Storage at 40°, with dip tubes	1.856	1.738	3.100	3.031	3.805	3.755
Storage at 40° without dip tubes	1.891	1.713	3.275	2.805	4.068	3.582
Storage at 50° with dip tubes	5.066	4.446	7.771	6.947	9.551	8.552
Storage at 50°, without dip tubes	4.864	4.400	7.902	6.962	9.703	8.772

Table VIII—Mean Moisture Loss in Percentages for Primary and Duplicate Groups Stored at 40 and 50°, Determined Radioactively, Part A

Group Description	After 10 Weeks		After 16 Weeks		After 20 Weeks	
	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.25% ¹⁴ C-Phenylephrine Hydrochloride Solution	0.5% ¹⁴ C-Phenylephrine Hydrochloride Solution
	Primary group, 40°, with dip tubes	2.1	0.9	4.5	3.2	2.2
Duplicate group, 40°, with dip tubes	1.6	1.7	—	—	2.1	2.0
Primary group, 40°, without dip tubes	1.8	1.5	3.7	3.3	2.5	2.2
Duplicate group, 40°, without dip tubes	2.1	0.7	—	—	1.7	0.9
Primary group, 50°, with dip tubes	6.9	7.2	9.4	10.7	10.1	10.2
Duplicate group, 50°, with dip tubes	5.4	4.3	—	—	8.1	7.4
Primary group, 50°, without dip tubes	11.8	6.6	19.1	14.7	19.2	13.2
Duplicate group, 50°, without dip tubes	4.7	4.8	—	—	9.2	6.6

ephrine hydrochloride demonstrated no visual evidence of decomposition when stored at 7, 22, or 40° in combination with 2% sodium bisulfite. At 50°, no decomposition was evident after 10 weeks had elapsed. By the end of 16 weeks, the characteristic brownish color of degraded phenylephrine hydrochloride was evident.

The polyethylene containers studied presented a good barrier to moisture transmission. Water permeation through the container walls was negligible at 7° and only 0.03%/week at room temperature (22°). At elevated temperatures, the losses were about 0.2%/week at 40° and 0.45%/week at 50°. Overall, low density polyethylene was shown to be an adequate container for packaging of aqueous solutions of phenylephrine hydrochloride utilizing a radioisotopic method of investigation.

Drug-Plastic Interaction: Part B—In Part B, the influence of two preservatives, benzalkonium chloride (1:5000) and thimerosal (1:5000), on the phenylephrine hydrochloride-polyethylene container interaction was investigated. Table II lists the different solution groups investigated in Part B. Mean disintegrations per minute values for each five-container group are listed in Tables IX and X. Table XI shows the net percentage increase or decrease in disintegrations per minute values for each of the groups investigated in Part B.

Both benzalkonium chloride and thimerosal were found to cause a slight interaction of the ¹⁴C-phenylephrine hydrochloride with the polyethylene container. At 7°, the average loss for all units was 1.0%

after 14 weeks of storage. At 22°, the loss of ¹⁴C-phenylephrine hydrochloride averaged 2.6% after 14 weeks, with the average loss values ranging from 1.9 to 3.0%. The decrease in phenylephrine hydrochloride concentration for groups stored at 22° is depicted in Fig. 5.

After 14 weeks at 40°, there was a small increase in the average disintegrations per minute values. The increase averaged 0.23% for 14 weeks. When this value is compared to the average disintegrations per minute increase (1.75% for 14 weeks) for the unpreserved solutions stored at 40°, a difference of approximately 1.5% is indicated. Thus, there was an apparent 1.5% loss of ¹⁴C-phenylephrine hydrochloride offsetting the loss of moisture from the container.

The average percent disintegrations per minute increase for units preserved with benzalkonium chloride and stored at 50° was approximately 0.5%/week or about the same magnitude as the increase per week (0.53%) for unpreserved solutions stored at 50° in Part A. The disintegrations per minute increase for units preserved with thimerosal was greater than that of the units preserved with benzalkonium chloride. The average percent disintegrations per minute increase for the thimerosal-preserved units was 0.71%/week. If the percent increase in average disintegrations per minute values for the thimerosal-preserved units is projected over a 20-week period, a gain of 14.2% is indicated. This value compares favorably with the range

Table IX—Mean Disintegrations per Minute (d.p.m.) for 0.25% ¹⁴C-Phenylephrine Hydrochloride, Preservative Solutions, Part B

Weeks	Mean d.p.m. Units 1-5, Benzalkonium Chloride, 7°	Mean d.p.m. Units 101-105, Thimerosal, 7°	Mean d.p.m. Units 6-10, Benzalkonium Chloride, 22°	Mean d.p.m. Units 106-110, Thimerosal, 22°	Mean d.p.m. Units 11-15, Benzalkonium Chloride, 40°	Mean d.p.m. Units 111-115, Thimerosal, 40°	Mean d.p.m. Units 16-20, Benzalkonium Chloride, 50°	Mean d.p.m. Units 116-120, Thimerosal, 50°
0	17,794	19,830	17,903	19,746	17,820	19,913	17,934	19,856
1	17,848	20,114	17,934	19,826	18,107	19,701	18,294	20,376
3	17,982	20,028	18,014	19,642	18,025	20,236	18,515	20,490
5	18,358	19,960	17,751	19,612	18,040	20,280	18,613	20,946
7	17,960	19,642	17,632	19,507	17,869	19,700	18,509	20,798
9	17,645	19,549	17,607	19,364	17,937	19,859	18,932	21,044
12	17,981	19,822	17,595	19,592	17,882	20,120	18,734	21,468
14	17,927	19,461	17,485	19,136	17,857	19,774	19,168	21,819

Table X—Mean Disintegrations per Minute (d.p.m.) for 0.5% ¹⁴C-Phenylephrine Hydrochloride, Preservative Solutions, Part B

Weeks	Mean d.p.m. Units 41-45, Benzalkonium Chloride, 7°	Mean d.p.m. Units 141-145, Thimerosal, 7°	Mean d.p.m. Units 46-50, Benzalkonium Chloride, 22°	Mean d.p.m. Units 146-150, Thimerosal, 22°	Mean d.p.m. Units 51-55, Benzalkonium Chloride, 40°	Mean d.p.m. Units 151-155, Thimerosal, 40°	Mean d.p.m. Units 56-60, Benzalkonium Chloride, 50°	Mean d.p.m. Units 156-160, Thimerosal, 50°
0	18,455	20,377	18,596	20,404	18,485	20,383	18,555	20,388
1	18,722	20,791	18,567	20,658	18,675	20,630	18,919	20,949
3	18,694	20,510	18,700	20,519	18,870	20,663	19,166	20,990
5	18,848	20,847	18,331	20,468	18,804	20,824	19,172	21,634
7	18,410	20,386	18,216	20,102	18,386	20,382	19,219	21,422
9	18,634	20,181	18,053	20,115	18,529	20,466	19,528	21,702
12	18,395	20,434	18,149	20,042	18,515	20,454	19,610	22,338
14	18,252	20,171	18,043	20,006	18,703	20,434	19,899	22,408

Table XI—Net Percentage Increase or Decrease in Group Disintegrations per Minute Averages for 0.25% and 0.5% ¹⁴C-Phenylephrine Hydrochloride, Preservative Solutions, Part B

Concentration of ¹⁴ C-Phenylephrine Hydrochloride, %	Group Description		Weeks							
	Preservative	Storage Temperature	1	3	5	7	9	12	14	
0.25	Benzalkonium chloride	7°	+0.3	+1.1	+3.1	-0.6	-0.8	+1.1	+0.7	
0.25	Thimerosal	7°	+1.4	+1.0	+0.7	-0.9	-1.4	0	-1.9	
0.5	Benzalkonium chloride	7°	+1.4	+1.3	+2.1	-0.2	+1.0	-0.3	-1.0	
0.5	Thimerosal	7°	+2.0	+0.6	+2.3	0	-0.9	+0.3	-1.0	
0.25	Benzalkonium chloride	22°	+0.2	+0.6	-0.8	-1.5	-1.7	-1.7	-2.3	
0.25	Thimerosal	22°	+0.4	-0.5	-0.7	-1.2	-1.9	-0.8	-3.0	
0.5	Benzalkonium chloride	22°	+0.2	+0.5	-1.4	-2.0	-2.9	-2.4	-3.0	
0.5	Thimerosal	22°	+1.2	+0.6	+0.3	-1.4	-1.4	-1.8	-1.9	
0.25	Benzalkonium chloride	40°	+1.6	+1.2	+1.2	+0.3	+0.6	+0.3	+0.3	
0.25	Thimerosal	40°	-1.0	+1.6	+1.8	-1.0	-0.3	+1.0	-0.7	
0.5	Benzalkonium chloride	40°	+1.0	+2.0	+1.7	-0.5	+0.2	+0.2	+1.2	
0.5	Thimerosal	40°	+1.2	+1.4	+2.2	0	+0.4	+0.3	+0.2	
0.25	Benzalkonium chloride	50°	+2.0	+3.2	+3.8	+3.2	+5.6	+4.5	+6.9	
0.25	Thimerosal	50°	+2.6	+3.2	+5.5	+4.7	+6.0	+8.1	+9.9	
0.5	Benzalkonium chloride	50°	+2.0	+3.3	+3.3	+3.6	+5.2	+5.7	+7.2	
0.5	Thimerosal	50°	+2.8	+3.0	+6.1	+4.8	+6.4	+9.5	+9.9	

of percent increase in disintegrations per minute values for unpreserved solutions from Part A listed in Table X. Overall, the moisture loss (as reflected by increased average disintegrations per minute values) for the preserved solutions stored at 50° was the same as that for the unpreserved solutions studied in Part A.

Study of the data from Part B reveals that there is an apparent interaction between the ¹⁴C-phenylephrine hydrochloride and the polyethylene container caused by both preservatives. The interaction was strongest at room temperature (22°), with apparent binding

of ¹⁴C-phenylephrine hydrochloride as high as 3.0% after 14 weeks. An increase in temperature appears to disrupt the interacted system. For example, at 40° the net loss of ¹⁴C-phenylephrine hydrochloride was 1.5%. At 50°, no loss was shown.

The data further reveal that there is no apparent overall trend visible as to any difference between the solutions containing thimerosal or benzalkonium chloride or between solutions containing 0.25% as opposed to 0.5% ¹⁴C-phenylephrine hydrochloride. Since the preservative is the limiting factor in the interaction, a

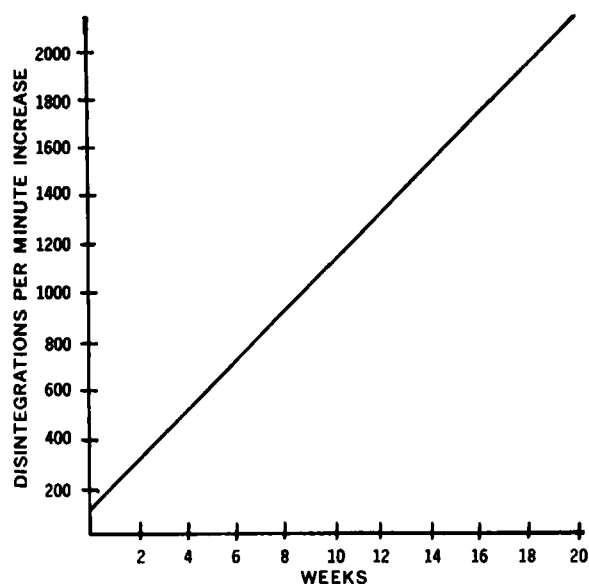


Figure 4—Average moisture loss as reflected by disintegrations per minute increase for a typical group of units stored at 50°.

change in preservative concentration would probably alter the percentage lost or bound. Accelerated stability studies at elevated temperatures could not be used to predict the long-term stability of these units at room temperature since the results showed that elevated temperatures disrupt the interaction between container and preservative-drug.

A study of the preservatives as the labeled compound would reveal more about their role in this study and about possible serious loss of preservative due to interaction with the polyethylene container.

SUMMARY

The utility of radioisotopic techniques in evaluating container performance of pharmaceutical packaging was demonstrated by the use of ¹⁴C-phenylephrine hydrochloride to investigate the compatibility of phenylephrine hydrochloride in low density polyethylene containers. Phenylephrine hydrochloride in aqueous solution apparently does not bind with low density polyethylene as a blow molded container. Moisture loss from low density polyethylene containers was clearly demonstrated by use of radioisotopic means as well as by conventional gravimetric techniques. It was demonstrated that, at room temperature, phenylephrine hydrochloride binds either to or in combination with a preservative (thimerosal or

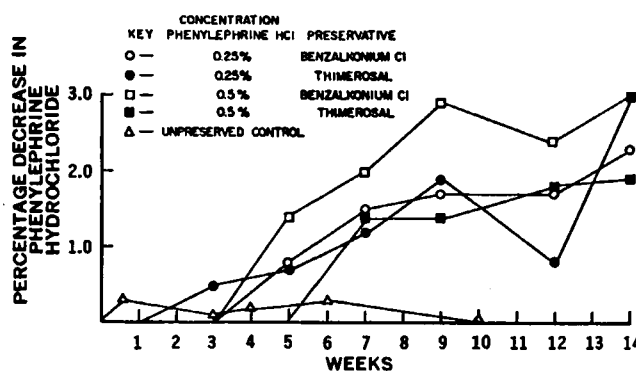


Figure 5—Average percentage decrease of phenylephrine hydrochloride for groups stored at 22° (Part B).

benzalkonium chloride) to produce an interacted system with low density polyethylene. In this study an elevated temperature disrupted the weak binding. This indicates the necessity of always evaluating polyethylene packaging of liquid pharmaceutical products at room temperature to avoid the possibility of erroneous conclusions based on accelerated testing.

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