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Polymer Sorption of Nitroglycerin and Stability of Molded Nitroglycerin Tablets in Unit-Dose Packaging

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Abstract □ The sorption of nitroglycerin by thermoplastic polymers and the stability of molded nitroglycerin tablets in strip packaging were studied. The polymers investigated varied greatly in their affinity for nitroglycerin, the order of decreasing affinity being: vinyls ≫ low density polyethylene > ionomers > high density polyethylene. With the proper choice of packaging, molded nitroglycerin tablets stabilized with povidone maintained acceptable potency for up to 2 years at 26° when strip packaged in unit doses. Chemical decomposition (hydrolysis) of nitroglycerin also was investigated. Povidone accelerated the decomposition of nitroglycerin; at high temperature, decomposition was a significant factor in tablet stability for tablets containing povidone.

Keyphrases □ Nitroglycerin—sorption by thermoplastic polymers and stability of molded tablets in various strip packages, effect of povidone □ Sorption—nitroglycerin by thermoplastic polymers in various packaging materials □ Stability—molded nitroglycerin tablets in various strip packages, effect of povidone □ Packaging materials, various—sorption by thermoplastic polymers and stability of molded nitroglycerin tablets, effect of povidone □ Povidone—effect on stability of molded nitroglycerin tablets in various strip packages □ Tablets, molded—nitroglycerin, sorption by thermoplastic polymers and stability in various strip packages □ Dosage forms—molded nitroglycerin tablets, sorption by thermoplastic polymers and stability in various strip packages □ Vasodilators, coronary—nitroglycerin, sorption by thermoplastic polymers and stability of molded tablets in various strip packages, effect of povidone

Recently, the stability of nitroglycerin tablets has been studied extensively (1–4). Nitroglycerin tablets potentially can lose potency in four ways: chemical decomposition, loss to the atmosphere by vaporization, intertablet migration, and sorption by packaging materials. Nitroglycerin undergoes thermal decomposition at elevated temperature (5) and may undergo basic hydrolysis (6). However, nitroglycerin decomposition in tablets has not been demonstrated.

At 25°, the air space above nitroglycerin tablets contains 1–7 μg of nitroglycerin/liter (4), the exact figure depending on the formulation. Thus, when nitroglycerin tablets are exposed to adequate circulation of room air, measurable losses in potency occur within a few days *via* vaporization (1, 2). Intertablet migration of nitroglycerin, resulting in decreased content uniformity upon aging, is a serious problem with conventional molded tablets (1, 4). Because of the migration problem, stabilizing additives have been incorporated into tablets (1, 4). The stabilizing additive lowers the vapor pressure of nitroglycerin sufficiently to prevent most of the migration that would otherwise occur (4).

Sorption of nitroglycerin by packaging materials may also have serious consequences for tablet stability (2–5, 7, 8). Conventional tablets strip packaged in an aluminum foil–low density polyethylene laminate lost 90% of their nitroglycerin to the package (7). Sorption losses were less for stabilized tablets (2). However, none of the strip

packaging studied maintained adequate tablet potency for the stabilized molded tablets (2).

This study concerned the sorption of nitroglycerin by packaging materials and the corresponding stability of nitroglycerin tablets in strip packaging. Previous studies considered only packaging with low density polyethylene as the thermoplastic component (*i.e.*, the thermoplastic material directly exposed to the tablet that is needed to seal the package). Vinyls, ionomers, and high density polyethylene may also be used as the thermoplastic component or heat-seal film. It will be demonstrated that with proper selection of packaging, stabilized molded nitroglycerin tablets maintain acceptable potency for up to 2 years at 26° when packaged in unit doses.

EXPERIMENTAL

Materials—The nontablet nitroglycerin samples were the same as previously described (4). Except when specifically noted otherwise, the tablets were commercial lots[1] stabilized with povidone, present as 1% of the total tablet weight. Packages I–IX were obtained commercially[2].

Procedures—*Assay Methods*—Tablets were assayed by one of two methods: Method A, an adaptation of Bell's method (9), which is essentially the same as that described by Fusari (3); and Method B, whereby nitroglycerin is extracted from an aqueous solution of the tablets into isooctane and then analyzed by the method of Wells *et al.* (10). Method B has been automated for unit-dose analysis of the tablets.

Nitroglycerin was extracted from the packaging by shaking the packaging with ethanol until the concentration of nitroglycerin in ethanol did not change (1–2 days). The nitroglycerin–ethanol solution was assayed according to Method B, omitting the isooctane extraction step. In several cases, a second extraction of the packaging was made to verify that no nitroglycerin remained. Except for Package IX, blank experiments with packaging devoid of nitroglycerin demonstrated that assay interference from the package was negligible. A large blank was obtained with Package IX. When extracted with isooctane instead of ethanol, this problem was eliminated. Therefore, package assays on Package IX were performed by extraction with isooctane.

Dinitroglycerin was determined by semiquantitative TLC following the procedure of Page *et al.* (11).

Packaging Procedures—Tablets packaged in strip packaging, 30 tablets/pouch, were heat sealed using a laboratory packaging apparatus[3]. Tablets strip packaged in unit dose, one tablet/pouch, were packaged using production machinery[4].

Film Thickness Measurement—The thickness of a heat-seal polymer was determined by weighing a known area of polymer film of known density (12). The heat seal was separated from the packaging either by soaking in aqueous hydrochloric acid (foil-containing packages) or by soaking in butyl acetate (Packages VI and VIII).

X-Ray Scattering Measurements—X-ray scattering data were obtained using an X-ray diffractometer[5] with copper radiation and a nickel filter.

Solubility Measurements—Saturation concentrations of nitroglycerin in the heat-seal polymer for a given package were determined by exposing only the heat-seal film to nitroglycerin vapor from 10% nitroglycerin on lactose. Sample holders were constructed from the cutoff top of a high density polyethylene bottle and the corresponding screw cap. A disk of packaging was placed in the cap with the heat-seal film exposed, and the bottle top was screwed down tightly. This procedure effectively eliminated vapor phase contact between nitroglycerin and the side of packaging not covered with the heat-seal film under investigation. Thus, the nitroglycerin sorbed by the packaging was sorbed only by the heat-seal film, assuming that permeation of the aluminum foil was negligible.

The samples (in the holders) were then placed in a glass desiccator containing a large excess of nitroglycerin, a moderate vacuum was applied (~10 Torr), and the desiccator was sealed. The nitroglycerin content of the packaging was assayed after several equilibration times, and the saturation value was taken as the nitroglycerin content after equilibrium was achieved (1–2 months).

[1] Eli Lilly and Co., Indianapolis, Ind.

[2] Package I: aluminum foil–vinyl; Anaconda Aluminum Co., Louisville, KY 40203. Package II: paper, polyethylene, aluminum foil–vinyl; Aluminum Co. of America, Pittsburgh, PA 15219. Package III: aluminum foil–vinyl; F-200, Aluminum Co. of America, Pittsburgh, PA 15219. Package IV: high density polyethylene film; B-74, American Can Co., Greenwich, CT 06830. Package V: cellophane, polyethylene, aluminum foil–low density polyethylene; Ivers Lee, Division of Becton-Dickinson, West Caldwell, NJ 07006. Package VI: nylon, Saran–low density polyethylene. Package VII: Surlyn 1707 film; du Pont, Wilmington, Del. Package VIII: nylon, Saran–Surlyn 1601, du Pont, Wilmington, Del. Package IX: paper, polyethylene, aluminum foil–Surlyn 1604; FL 1674, Rexham Corp., Hemington, NJ 08822. The foil had been treated with an adhesion promotor identified as Rexham REP01.

[3] Sentinel impulse heat sealer, model 125C, Packaging Industries, Hyannis, Mass.

[4] Model VPH4, Wrap-Ade, Clifton, N.J.

[5] Norelco, Mt. Vernon, N.Y.

Table I—Hydrolysis of Nitroglycerin in Nitroglycerin–Povidone Systems [a]

Weight Ratio, Povidone to Nitroglycerin	Nitroglycerin Loss, %[b]		Dinitroglycerin Content, %[c]	
	1.5 years, 25°	1.5 years, 25° plus 1 month, 50°	1.5 years, 25°	1.5 years, 25° plus 1 month, 50°
0.22	2	11	1	2
0.65	7	22	4	7
1.04	12	22	3	9
1.56	—	—	4	8
2.13	—	—	5	8

[a] Samples were prepared by dry blending povidone and 10% nitroglycerin trituration on β-lactose. [b] Determined from nitroglycerin assay on initial and aged samples. [c] Expressed as weight percent of total nitroglycerin compounds (*i.e.*, dinitroglycerin and trinitroglycerin); determined by semiquantitative TLC procedure.

RESULTS

The chemical decomposition of nitroglycerin *via* hydrolysis was studied for nitroglycerin–povidone–lactose systems (Table I). Both 1,2-dinitroglycerin and 1,3-dinitroglycerin were present in the aged samples in roughly equal amounts. Dinitroglycerin content is expressed as weight percent of the total nitroglycerin compounds. Within the uncertainty of the data, both the nitroglycerin loss and dinitroglycerin content were independent of the povidone concentration above a weight ratio of 0.6. Although the TLC assay is only semiquantitative, the data demonstrate that a significant fraction of the nitroglycerin loss was due to hydrolysis of the trinitro ester to dinitroglycerin species.

High temperature stability of tablets containing povidone are compared with other formulations in Table II. Potency loss at high temperature was significantly greater with the povidone-containing formulation. TLC analysis showed significant amounts of the 1,2- and 1,3-dinitroglycerin moieties in the aged povidone formulation but only trace amounts in other formulations.

X-ray diffraction patterns were obtained from the heat-seal films investigated (Fig. 1). Diffraction patterns from the ionomers of Packages VII and VIII were similar to the one shown in Fig. 1 for the ionomer of Package IX. The vinyls were completely amorphous and gave no peaks in the diffraction pattern. The peaks at $2\theta = 21°$ and $2\theta = 24°$ are characteristic of polyethylene crystallinity. The peak at $2\theta = 4°$ from the ionomer is characteristic of ionomers and may be caused by clustering of cations (13). Taking the intensity and sharpness of the diffraction peaks as an index of crystallinity, the crystallinity of the heat-seal films decreased in the order: high density polyethylene ≫ low density polyethylene (VI) > low density polyethylene (V) > ionomers > vinyls.

Saturation levels of nitroglycerin in the heat-seal films of various packages are summarized in Table III.

Potency losses of 0.4-mg stabilized tablets stored in various pouch-type packages are summarized in Table IV. The corresponding package assays are also listed. If it is assumed that chemical decomposition in the pouch package is identical to that in the control package (~300 tablets in glass with tin-lined screw cap), the package assay, in micrograms per square

Table II—Potency Loss of 0.3-mg Tablets at High Temperature: Comparison of Formulations [a]

Formulation	Potency Loss, %	
	6 months, 37°	6 months, 45°
Conventional tablet, no stabilizer	9	7
Stabilized tablet, 1% povidone	17	36
Stabilized tablet[b], polyethylene glycol	—	8

[a] Tablets were stored in screw-capped glass bottles with rayon stuffing, 100 tablets/bottle. [b] Nitrostat, Parke-Davis and Co.

Table III—Heat-Seal Film Sorption of Nitroglycerin at Saturation (Nitroglycerin Source Was 10% Nitroglycerin on Lactose) [a]

Package[b] (Heat-Seal Thickness)	Sorption of Nitroglycerin 25°, μg/cm²	37° μg/cm²	37° wt. %
I (4.2 μm)	210	180	24.8
II (3.8 μm)	160	130	20.8
III (3.2 μm)	160	130	24.0
IV (53 μm)	1.5	1.4	0.028
V (19 μm)	52	40	2.3
VII (69 μm)	20	25	0.39
IX (26 μm)	20	22	0.89

[a] Nitroglycerin vapor pressure, in Torr, is (4) 5.5×10^{-4} at 25° and 22×10^{-4} at 37°. [b] See Footnote 2 in the text.

centimeter, will be identical (within experimental error) to the corresponding potency loss when no nitroglycerin leaves the package through diffusion. With Packages VII and IV, and perhaps with Package II, the potency loss was significantly greater than the package sorption, suggesting diffusion of nitroglycerin through the package.

Data regarding the rate of nitroglycerin removal from the heat-seal films of packages are summarized in Table V. The experimental data are compared with values calculated from the appropriate solution of Fick's law (14):

$$F(t) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left[-\frac{D(n+\frac{1}{2})^2\pi^2 t}{l^2}\right] \quad \text{(Eq. 1)}$$

where $F(t)$ is the fractional attainment of equilibrium, *i.e.*, $F(t) = 1$ at infinite time when all nitroglycerin is removed from the packaging; D is the diffusion coefficient of nitroglycerin in the film; l is the thickness of the film for Package V and is one-half the film thickness for Package VII (*i.e.*, diffusion occurs from both sides of the film); and t is time.

The assumption in Eq. 1 is that the distribution of nitroglycerin in the heat-seal film is initially homogeneous. The values of D were chosen to give the best fit of Eq. 1 to the data. With Package VII, agreement between diffusion theory and experimental data was excellent. For Package V, agreement was good only at times greater than about 10 hr. At small times, nitroglycerin release by the package was slower than predicted by *simple* diffusion theory (Eq. 1).

Table VI and Fig. 2 compare the stability of nitroglycerin tablets in unit-dose strip packages of Package IX with the stability in both conventional packaging and the control package (~300 tablets in glass with tin-lined screw cap). In Table VI, the third and fourth columns give the parameters evaluated by a least-squares fit of the data to the equation:

$$\ln N = \ln N_0 - k_1 t \qquad t \geq 1 \text{ month} \qquad \text{(Eq. 2)}$$

where k_1 is the first-order rate constant reflecting chemical decomposition of nitroglycerin, N is the tablet potency at time t, and N_0 is the tablet potency extrapolated to zero time. The difference between the N_0 values for the control package and the unit-dose package represents the quantity of nitroglycerin absorbed by the heat-seal film of the unit-dose package. The uncertainty given for k_1 is the standard deviation of this parameter. The last column of Table VI summarizes the mean content uniformities for a number of package–tablet–temperature combinations. The measure of content uniformity used here is the relative standard deviation for the assay of 30 tablets when the assay results are expressed in weight of nitroglycerin per unit tablet weight.

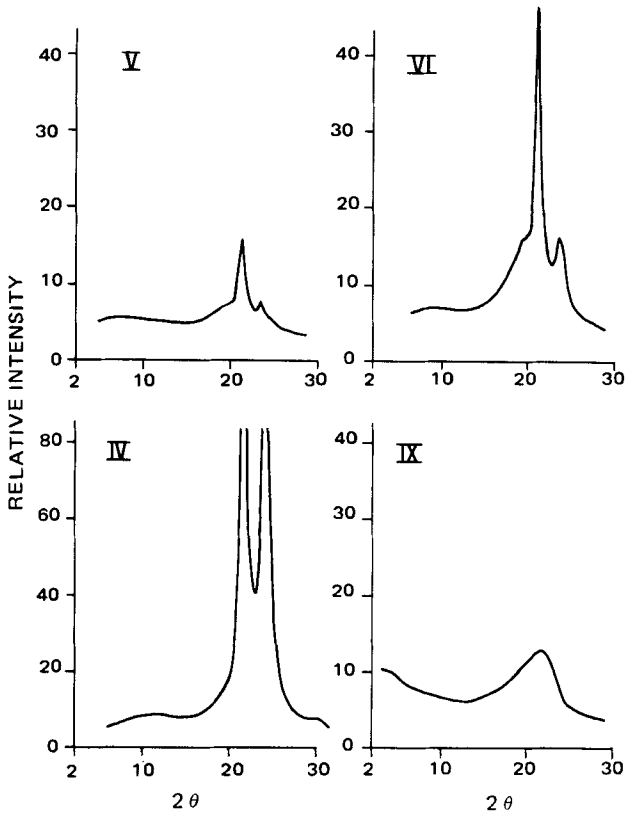

Figure 1—*X-ray diffraction patterns from the heat-seal polymers of packaging materials. Key: V, low density polyethylene; VI, low density polyethylene; IV, high density polyethylene; and IX, ionomer.*

DISCUSSION

Decomposition—In previous studies (1–4, 7–9), it was assumed that chemical decomposition does not contribute significantly to the potency loss of nitroglycerin tablets. The present data demonstrate that potency loss through decomposition may be significant, at least when povidone is present. Povidone apparently functions as a catalyst for nitroglycerin hydrolysis. Although the decomposition rate (Table VI) was slow at 26°, ~0.4%/month, the decomposition rate increased sharply with increasing temperature. Clearly, one may not assume that the addition of a nominally inert additive, such as povidone, has no effect on the chemical stability of nitroglycerin.

Package Sorption of Nitroglycerin—It is not immediately obvious whether nitroglycerin is adsorbed on the heat-seal film's surface or whether nitroglycerin is dissolved in the polymer. The slow rate of nitroglycerin removal from the packaging (Table V) suggests that most nitroglycerin is dissolved in the polymer. The data for Package VII are completely consistent with the diffusion theory based on assumption of a homogeneous solution of nitroglycerin in the polymer.

The diffusion theory is less satisfactory for Package V. However, the experimental rate is slower than the rate calculated from diffusion theory at small times. Thus, the data are not consistent with a surface adsorption model but rather suggest a diffusion model where, in Package V, the

Table IV—Potency Loss of Tablets and Package Sorption of Nitroglycerin at 37° [a]

Package[b] (Heat-Seal Thickness)	Package Assay[c] 1 month, μg/cm²	2 months μg/cm²	2 months wt. %	Potency Loss[d] 1 month, μg/cm²	Potency Loss[d] 2 months, μg/cm²
II (3.8 μm)	13	14	2.8	19	25
III (3.2 μm)	14	19	4.6	14	21
V (19 μm)	16	16	0.92	11	14
VI (76 μm)	16	16	0.23	22	22
VII (69 μm)	3.0	3.2	0.049	16	29
VIII	17	18	—	17	19
IX (26 μm)	3.8	4.3	0.17	7	7
IV (53 μm) 26°		(4 months) 0.3	0.005		(4 months) 5

[a] Thirty tablets were sealed in a package with 141 cm² package area exposed to the tablets (4.7 cm²/tablet). All tablets were 0.4 mg initial potency and contained 0.36 mg of povidone as a stabilizer. Initial vapor pressure of nitroglycerin (37°) was 12.3×10^{-4} Torr (4). [b] See Footnote 2 in the text. [c] Estimated uncertainty, ±10% relative error in micrograms per square centimeter data. [d] Estimated uncertainty, ±2 μg/cm². Calculated from the difference between tablet assays on strip-packaged tablets and on tablets in the control package (~300 tablets in glass with tin-lined screw cap).

Table V—Rate of Nitroglycerin Removal from Packaging in a Well-Stirred Infinite Water Medium at 25°

Hours	Nitroglycerin Content of Package, % of Initial: Experimental	Diffusion Theory, Eq. 1
	Package VII, $D = 2.02 \times 10^{-10}$ cm²/sec	
0.50	78.7	80.2
1.66	64.9	63.7
3.67	51.4	46.0
5.75	31.8	34.0
21.7	3.2	3.0
	Package V, $D = 2.54 \times 10^{-11}$ cm²/sec	
3.64	81.4	65.1
5.05	77.4	58.5
7.30	66.3	50.0
22.5	19.4	18.6
27.0	12.5	13.8
31.4	9.6	10.4
46.7	3.9	3.8
55.2	2.8	2.2

diffusion constant of nitroglycerin increases with time at small times due to water absorption by the polymer. Presumably, equilibration with water is so rapid with the more hydrophilic ionomer (Package VII) that the polymer is water saturated throughout the period of nitroglycerin diffusion.

With the assumption that nitroglycerin is dissolved in the polymer, nitroglycerin sorption by various films is best compared in terms of weight percent nitroglycerin in the film. The data in Tables III and IV demonstrate that the heat-seal films studied varied greatly in their affinity for nitroglycerin. The sorption of nitroglycerin was less when the nitroglycerin source was a stabilized tablet (Table IV) than when pure nitroglycerin was exposed to the polymer (Table III). This observation is consistent with the significantly lower vapor pressure of nitroglycerin in the stabilized tablets (4). However, even for stabilized tablets, loss of nitroglycerin to the packaging was excessively high for some types of packaging.

The order of decreasing affinity for nitroglycerin was: vinyls ≫ low density polyethylene > ionomers > high density polyethylene. The low solubility of nitroglycerin in high density polyethylene is undoubtedly due to the high crystallinity of this polymer film (Fig. 1). The solubilities of nitroglycerin in Packages V and VI, both low density polyethylene, were not identical. The lower solubility in Package VI may have resulted from the higher degree of crystallinity of the polyethylene in this package (Fig. 1).

Crystallinity is not the only important factor affecting the sorption of nitroglycerin by a polymer film. Chemical structure of the polymer is also important. For example, the ionomers have very low crystallinities, but nitroglycerin solubility in these films is low. The chemical structure of an ionomer differs from polyethylene in that the ionomer contains

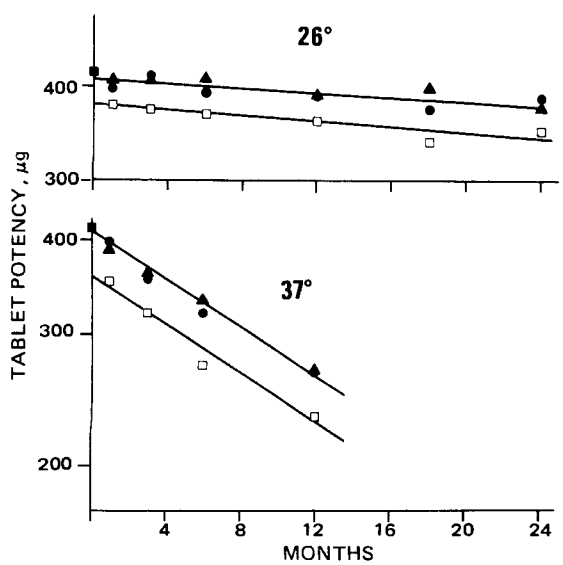

Figure 2—*Stability of nitroglycerin tablets in various packages. Key:* ■, *initial assay;* ▲, *control package;* ●, *conventional package; and* □, *unit-dose package, foil–ionomer (IX).*

Table VI—Stability of Nitroglycerin Tablets in Unit-Dose Packages: Comparison of Unit-Dose Package IX with Conventional Packaging[a]

Nominal Tablet Potency, µg/Storage Temperature	Package	N_0[b], µg/35.6 mg Tablet	k_1 ($\pm\sigma$)[b], month^{-1}	Mean Content Uniformity, σ, mg/mg
300/26°	Control	323	0.004 ± 0.002	—
	Conventional	318	0.005 ± 0.002	5.3
	IX	297	0.005 ± 0.002	3.3
400/26°	Control	411	0.003 ± 0.001	—
	Conventional	402	0.002 ± 0.001	6.3
	IX	376	0.004 ± 0.002	4.2
600/26°	Control	610	0.004 ± 0.002	—
	Conventional	590	0.001 ± 0.001	6.8
	IX	554	0.003 ± 0.002	4.0
300/37°	Control	324	0.030 ± 0.002	—
	Conventional	313	0.041 ± 0.013	7.7
	IX	284	0.040 ± 0.008	5.2
400/37°	Control	408	0.036 ± 0.002	—
	Conventional	407	0.037 ± 0.003	5.9
	IX	356	0.037 ± 0.005	5.0
600/37°	Control	617	0.020 ± 0.003	—
	Conventional	616	0.039 ± 0.005	8.2
	IX	511	0.022 ± 0.007	5.3

[a] 4.7 cm² of the unit-dose package was exposed to each tablet. The conventional package was 100 tablets in a glass bottle with rayon stuffing and a low density polyethylene-lined screw top closure. The control package was ~300 tablets in a glass bottle without stuffing and a tin foil-lined screw top closure. [b] The parameters N_0 and k_1 are defined by $\ln N = \ln N_0 - k_1 t$, where N is the mean tablet potency at time t, $t \geq 1$ month.

structurally bound anions and their corresponding counterions. Perhaps the electrostatic field of the ions is sufficient to salt out nitroglycerin in much the same way that electrolytes decrease the aqueous solubility of many nonpolar solutes.

Package Permeability—Diffusion of nitroglycerin through the package is not a source of potency loss whenever the barrier component of the package is essentially impermeable to nitroglycerin. For packages containing aluminum foil, one would not expect significant permeability to nitroglycerin. Thus, the potency loss should not exceed the nitroglycerin content of the package. With the possible exception of Package II, the data in Table IV support this conclusion. Even for films where the nitroglycerin solubility is very low, permeation of the film apparently can be significant. Permeability was quite high for ionomer (VII) film, while high density polyethylene film exhibited small, but probably significant, permeability to nitroglycerin even at 26°.

Unit-Dose Nitroglycerin—To achieve stability in a unit-dose package comparable to the stability in conventional packaging, the heat-seal film employed must have a low affinity for nitroglycerin and the barrier should be impermeable to nitroglycerin. The data in Tables III and IV indicate that, of the packaging studied, Package IX would be the best choice for unit-dose nitroglycerin. Although having a low affinity for nitroglycerin, Package IV (high density polyethylene) would probably not be suitable for a shelflife of several years. Permeability of the magnitude suggested by the data would lead to a potency loss of ~30% over 2 years at 26°.

Figure 2 and Table V summarize the results of a 2-year stability study with unit-dose nitroglycerin in Package IX. The control package was ~300 tablets (full bottle) in a glass bottle closed with a tin-lined screw cap. Because of the large number of tablets, the impermeability of the container, and the lack of package material that could absorb nitroglycerin, tablets in the control package could lose potency only through chemical decomposition. Potency losses in the unit-dose or conventional

packages in excess of that for the control package would indicate sorption by the packaging and/or permeation of the package by nitroglycerin.

The potency–time curves for the control package and the conventional package are not significantly different. Except for a drop in potency shortly after packaging due to absorption (8% at 26°), the potency–time curves for the unit-dose package are indistinguishable from those for the control package. Therefore, permeation of the package by nitroglycerin is not significant.

The mean content uniformity (Table VI) appears to be slightly better for the unit-dose package than for the conventional package. Although the tablets studied were stabilized, a small amount of intertablet migration (~2% increase in standard deviation) apparently occurred as the tablets were aged in conventional containers. Since intertablet migration was prevented in the unit-dose package, the content uniformity remained essentially unchanged upon aging.

In summary, acceptable stability for up to 2 years[6] at 26° was demonstrated for unit-dose nitroglycerin in Package IX. The tablets employed in this research were stabilized tablets; conventional tablets would probably lose excessive nitroglycerin through absorption.

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[6] Since the potency does decrease slightly with time due to decomposition, the exact time period during which the tablets will meet USP standards will depend upon the tablet potency before packaging. The excess over label claim was generally small for the tablets studied. More recent lots of Lilly nitroglycerin tablets are formulated to provide a larger excess over label claim at the time of manufacture.

Disposition of Sulfonamides in Food-Producing Animals V: Disposition of Sulfathiazole in Tissue, Urine, and Plasma of Sheep following Intravenous Administration

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Abstract □ The plasma, urine, and tissue sulfathiazole concentrations were determined at various times following intravenous administration to 12 sheep. The plasma and urine data were consistent with a one-compartment pharmacokinetic model, with an elimination half-life of 1.1 hr and a volume of distribution of 0.39 liter/kg. Sulfathiazole was eliminated by excretion of unchanged drug in urine (67%) and by formation of two metabolites. The data obtained from eight tissue sites were consistent with the one-compartment pharmacokinetic model presented and confirmed that tissue residues of sulfathiazole can be calculated from serum and urine drug concentrations.

Keyphrases □ Sulfonamides—disposition of sulfathiazole in tissue, urine, and plasma of sheep following intravenous administration □ Sulfathiazole—disposition in tissue, urine, and plasma of sheep following intravenous administration, pharmacokinetic model □ Pharmacokinetics—sulfathiazole in sheep following intravenous administration□ Disposition, biological—sulfathiazole in tissue, urine, and plasma of sheep following intravenous administration, pharmacokinetic model □ Antibacterials—sulfathiazole, disposition in tissue, urine, and plasma of sheep following intravenous administration, pharmacokinetic model

When food-producing animals are treated with antibacterial drugs, significant drug concentrations may remain for some time in food tissues. Human consumption of meat containing drug residues may subsequently cause the development of hypersensitivity to drugs used therapeutically or the preferential selection of bacterial strains resistant to those drugs (1).

BACKGROUND

Normally, drug residues in the food tissues of animals are controlled by cessation of treatment at some minimum specified time, *i.e.*, the withdrawal time, before slaughter, allowing the drug to "washout" from the food tissues. However, field surveys reporting the number of carcasses with illegal concentrations of antibacterial drugs suggest that a sufficient withdrawal time often is not allowed (2).

The current method for controlling the appearance of drug-contaminated meat on the market consists of randomly checking carcasses at the slaughterhouse. This method is inefficient because drug assays of tissue are generally expensive and time consuming and the detection of contaminated carcasses may cause the condemnation of complete carcass lots. If a method could be developed to detect animals whose meat contained more than the tolerance limit of a drug before slaughter, it would be possible to delay slaughtering until the drug is below tolerated levels, thereby saving the carcass from needless destruction. Furthermore, if the detection method analyzed blood or urine instead of tissue specimens, it should be possible to reduce the cost and time involved in assay and thereby increase the efficiency of surveillance.