Salicylate Release Characteristics of Selected Polyethylene Glycol Suppositories

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Abstract □ Salicylate suppositories were prepared using polyethylene glycol 1540 and polyethylene glycol 6000 in various proportions. The *in vitro* release of salicylates from each suppository combination was studied using a closed system apparatus designed to circulate fluid about the suppository at 37 ± 0.2°. At scheduled time intervals, samples of the circulating fluid were assayed spectrophotometrically for salicylate content. Suppositories were also removed from the apparatus, their length and diameter were measured with a vernier caliper, and the change in their surface area was calculated. These surface area changes were then correlated with the salicylate release data. Release of salicylate from the polyethylene glycol suppositories simulated zero-order kinetics, and the time for 50% release of salicylate ($t_{1/2}$) from each polyethylene glycol combination did not differ significantly for salicylic acid or its sodium salt. Salicylate release differed markedly for bases composed solely of polyethylene glycol 1540 or 6000; however, when suppositories contained a mixture of the two polyethylene glycols, the rate of release of salicylate approximated that observed for a base composed solely of polyethylene glycol 6000.

Keyphrases □ Suppositories, polyethylene glycol—salicylate release characteristics □ Polyethylene glycol suppositories—salicylate release characteristics □ Salicylate release characteristics—polyethylene glycol suppositories □ Release characteristics, salicylate—polyethylene glycol suppositories

The polyethylene glycols are water-soluble polymers of ethylene glycol; they are widely used in pharmaceuticals as solvents, as tablet binders and coatings, as cosmetic bases, and as ointment and suppository vehicles. When used as suppository vehicles, they release incorporated medicament by dissolving in the rectal fluids. Several investigators compared the liquefaction (1) and disintegration times (2, 3) and the absorption of drugs from polyethylene glycol bases with other suppository bases such as theobroma oil and glycerinated gelatin (4–10). However, studies on the effects of varying polyethylene glycol base composition on release kinetics have not been reported. Therefore, the purpose of this study was to investigate the drug release characteristics of various polyethylene glycol suppository bases.

EXPERIMENTAL

Preparation of Suppositories—The suppositories were formulated to contain 60 mg. of salicylic acid or 70 mg. of sodium salicylate by melting the polyethylene glycols[1] at 64 ± 2° on a hot plate and then dissolving the salicylates[2] into the melt. The molten mass was poured into a polytetrafluoroethylene-coated (11) mold[3] and allowed to solidify at 23 ± 3°. The suppositories were removed from the mold and stored in well-closed containers at 8°. Prior to use, all suppositories were allowed to stand for 4–6 hr. at room temperature.

Five lots, of 20 suppositories each, were prepared for each formulation (Table I). Each suppository was cylindrical in shape, measured 17.8 mm. in length and 8 mm. in diameter, and weighed approximately 1 g.

All chemicals used were USP grade.

Dissolution Apparatus—The dissolution apparatus consisted of a flow chamber, constant flow pump, and solution reservoir. The flow chamber was constructed from a glass tube with an inside diameter of 2.2 cm. and a length of 7.5 cm. A stainless steel screen, resting on a fiber washer, was used to support the suppository inside the chamber. Each end of the chamber was fitted with a Büchner filter holder. The upper filter holder was modified to accommodate a calibrated thermometer having a range of from −2 to 68°, graduated in intervals of 0.2°. A vial filler[4] was used to circulate distilled water from a sampling reservoir and past the suppository in the flow chamber at a rate of 1 ml./sec.

The volume of the circulating fluid was kept constant at 500 ml. by adding an equal volume of water each time a sample was withdrawn. The fluid was maintained at 37 ± 0.2°, and evaporation from the system was prevented by placing a Mylar closure around the opening of the sampling flask.

Salicylate Release Determination—Suppositories from the various lots were chosen at random and placed individually in the flow chamber of the suppository dissolution apparatus. Half-milliliter samples of the circulating fluid were withdrawn at 100-sec. intervals and assayed for salicylate content. Reference solutions for the assay of the salicylate released were prepared by adding 0.5 ml. of dilute salicylate solution to 4.5 ml. of 0.1 *N* HCl. The absorbance of each reference solution was read at 304 nm. on a spectrophotometer[5].

Suppository Surface Area Determination—Suppositories were removed from the flow chamber of the dissolution apparatus, and the length and diameter of the suppositories were measured using a vernier caliper. The measurements obtained were then used to calculate the surface area, A, of each suppository using the equation:

$$A = \frac{\pi D^2}{2} + \pi DL \qquad \text{(Eq. 1)}$$

where π is 3.142, D is the diameter of the suppository, and L is the length of the suppository in millimeters.

RESULTS AND DISCUSSION

In general, the release of salicylates from the polyethylene glycol bases shows deviation from linearity for the first 6 mg. and for the last 12 mg. from each base (Figs. 1–4). The deviation from linearity for the last 12 mg. of drug released, that is, for the last 20% of the data, may be explained in terms of crystal formation by the polyethylene glycol matrix during cooling. Although the suppositories retained a cylindrical shape remarkably well, a core of harder material was observed during the latter stages of dissolution. The appearance of this slower dissolving core correlated approximately with the last 20% of the dissolution period. This harder core most likely arises from a slower cooling of the inner core producing more crystallinity to the mass than the quicker cooling of the outer areas of the cylinder and the resulting lower degree of crystallinity in the polyethylene glycol. The greater the degree of crystallinity, the slower is the dissolution. The degree of crystallinity of these polymers is known to be related to their thermal history, particularly the time element[6].

[1] Union Carbide Corp., New York, NY 10017
[2] Mallinckrodt Chemical Works, St. Louis, MO 63147
[3] The mold, constructed from aluminum plate and having a capacity of 30 cavities, 0.9 ml. each, was polytetrafluoroethylene coated by Tetrafluor, Division of Amerco Inc., Inglewood, CA 90301

[4] The model A B Filamatic vial filler, manufactured by National Instruments Co., Baltimore, Md., was equipped with a 5-ml. syringe.
[5] A Beckman model DUR recording quartz spectrophotometer equipped with a Gilford modification.
[6] The authors are grateful to the reviewer for suggesting crystal formation as an explanation for the slower dissolving core.

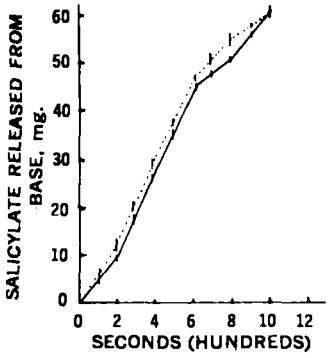

Figure 1—In vitro *release o salicylates from a suppository base consisting of polyethylene glycol 1540 (100%). Key: ——, salicylic acid, 60 mg., in base; and . . ., sodium salicylate, 70 mg., in base. Each point represents the mean value of five suppositories (vertical bars ± SE).*

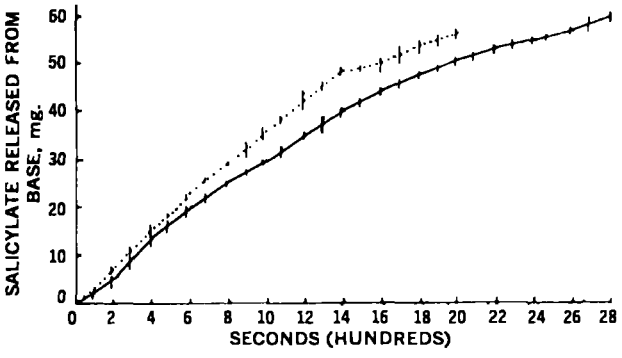

Figure 2—In vitro *release of salicylates from a suppository base consisting of polyethylene glycol 6000 (100%). Key: ——, salicylic acid, 60 mg., in base; and . . ., sodium salicylate, 70 mg., in base. Each point represents the mean value of five suppositories (vertical bars ± SE).*

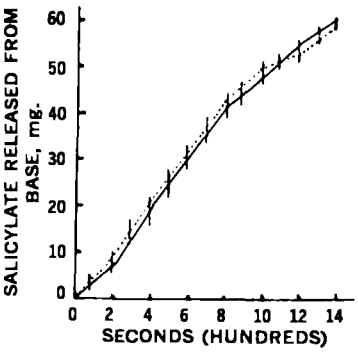

Figure 3—In vitro *release of salicylates from a suppository base consisting of polyethylene glycol 1540 (80%) and polyethylene glycol 6000 (20%). Key: ——, salicylic acid, 60 mg., in base; and . . ., sodium salicylate, 70 mg., in base. Each point represents the mean value of five suppositories (vertical bars ± SE).*

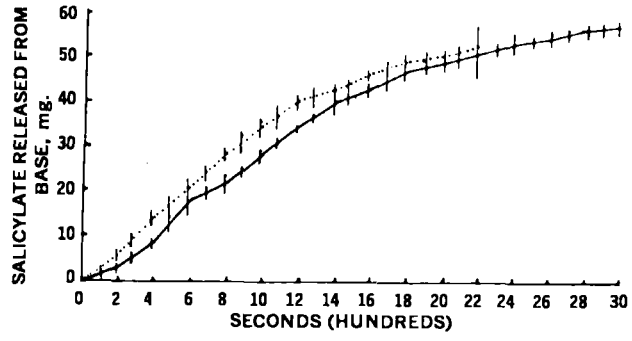

Figure 4—In vitro *release of salicylates from a suppository base consisting of polyethylene glycol 1540 (20%) and polyethylene glycol 6000 (80%). Key: ——, salicylic acid, 60 mg., in base; and . . ., sodium salicylate, 70 mg., in base. Each point represents the mean value of five suppositories (vertical bars ± SE).*

From the data presented, it would seem that the drug itself has little effect on the rate of dissolution. Rather, it is the character of the polyethylene glycol matrix that is most influential. However, it is known that salicylates form complexes with the polyethylene glycols (12–14); this phenomenon probably occurs and may have some minor influence.

The deviation from linearity for the first 10% of salicylate release is attributed to incomplete mixing of the circulating test solution and correlates with the time required for fresh solution to be pumped from the reservoir past the suppository.

Plots of the linear portion of the salicylate release data are corrected to pass through the origin using the equation:

$$Sr' = k''t \qquad \text{(Eq. 2)}$$

where Sr' represents the corrected value for the milligrams of salicylate released at time t, and k'' is the slope of the linear portion of the plotted data. Plots of the corrected salicylate release data are shown in Figs. 5 and 6.

Although it was apparent that the release of salicylate from polyethylene glycol bases simulated zero-order kinetics, the existent deviation from linearity suggested the necessity of further studies, regarding the change in the surface area of the suppositories with time. Therefore, suppositories were removed from the dissolution apparatus at selected time intervals, and the length and diameter of each suppository were measured and its area was calculated as previously described (see *Experimental: Suppository Surface Area Determination*) using Eq. 1. Plots of the calculated area *versus* time are shown in Fig. 7.

In addition, the rate constants for the change in surface area of the suppository with respect to time were calculated by differentiating Eq. 1 to give:

$$\frac{dA}{dt} = \frac{d}{dt}\left(\pi \frac{D^2}{2}\right) + \frac{d}{dt}(\pi DL) \qquad \text{(Eq. 3)}$$

which reduces to:

$$\frac{dA}{dt} = \pi D\frac{dD}{dt} + \pi \frac{d(DL)}{dt} \qquad \text{(Eq. 4)}$$

which for a small change in time may be expressed as shown in Eq. 5:

$$\frac{\Delta A}{\Delta t} = \pi D\frac{\Delta D}{\Delta t} + \pi \frac{\Delta(DL)}{\Delta t} \qquad \text{(Eq. 5)}$$

Table I—Suppository Formulations

Number	Formula: Component	g.	PEG[a] Expressed as Percent of Base	Assayed Salicylate Content[b], mg./Suppository
1	Polyethylene glycol 1540	18.80	100	63
	Salicylic acid	1.20	—	
2	Polyethylene glycol 1540	18.61	100	62
	Sodium salicylate	1.39	—	
3	Polyethylene glycol 6000	18.80	100	63
	Salicylic acid	1.20	—	
4	Polyethylene glycol 6000	18.61	100	61
	Sodium salicylate	1.39	—	
5	Polyethylene glycol 1540	15.04	80	61
	Polyethylene glycol 6000	3.76	20	
	Salicylic acid	1.20	—	
6	Polyethylene glycol 1540	14.89	80	59
	Polyethylene glycol 6000	3.72	20	
	Sodium salicylate	1.39	—	
7	Polyethylene glycol 1540	3.76	20	59
	Polyethylene glycol 6000	15.04	80	
	Salicylic acid	1.20	—	
8	Polyethylene glycol 1540	3.72	20	55
	Polyethylene glycol 6000	14.89	80	
	Sodium salicylate	1.39	—	

[a] Abbreviation for polyethylene glycol. [b] See *Experimental: Salicylate Release Determination.*

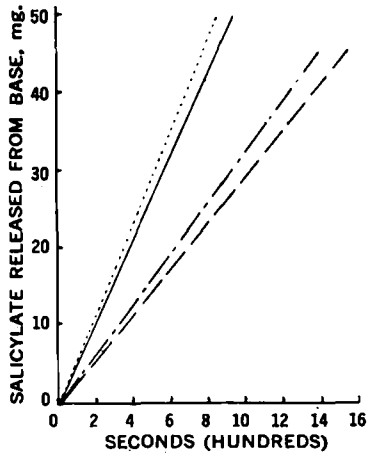

Figure 5—*Plots of corrected data for* in vitro *release of salicylates from various suppository bases. Key:* ——, *salicylic acid, 60 mg., in polyethylene glycol 1540 (80%) and polyethylene glycol 6000 (20%) (Formulation No. 5);* . . ., *sodium salicylate, 70 mg., in polyethylene glycol 1540 (80%) and polyethylene glycol 6000 (20%) (Formulation No. 6);* — —, *salicylic acid, 60 mg., in polyethylene glycol 1540 (20%) and polyethylene glycol 6000 (80%) (Formulation No. 7); and* — · —, *sodium salicylate, 70 mg., in polyethylene glycol 1540 (20%) and polyethylene glycol 6000 (80%) (Formulation No. 8). The average value of salicylate released from five suppositories at each time interval was used to determine the slope of each plot.*

Taking $D = D_1$ at $t = t_1$ and $D = D_2$ at $t = t_2$:

$$\Delta A = A_2 - A_1 \qquad \text{(Eq. 6)}$$

and:

$$\frac{\Delta A}{\Delta t} = \frac{\pi D(D_2 - D_1) + \pi[(DL)_2 - (DL)_1]}{t_2 - t_1} \qquad \text{(Eq. 7)}$$

where:

$$D = \frac{D_1 + D_2}{2} \qquad \text{(Eq. 8)}$$

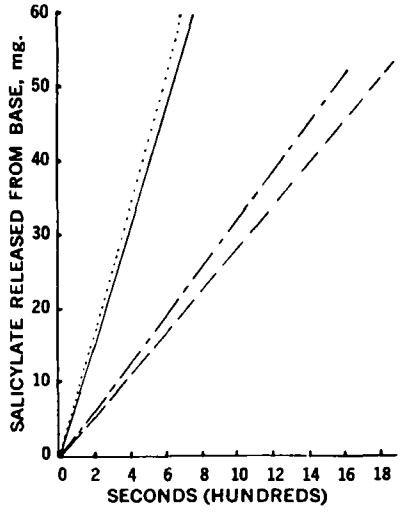

Figure 6—*Plots of corrected data for* in vitro *release of salicylates from various suppository bases. Key:* ——, *salicylic acid, 60 mg., in polyethylene glycol 1540 (100%) (Formulation No. 1);* . . ., *sodium salicylate, 70 mg., in polyethylene glycol 1540 (100%) (Formulation No. 2);* — —, *salicylic acid, 60 mg., in polyethylene glycol 6000 (100%) (Formulation No. 3); and* — · —, *sodium salicylate, 70 mg., in polyethylene glycol 6000 (100%) (Formulation No. 4). The average value of salicylate released from five suppositories at each time interval was used to determine the slope of each plot.*

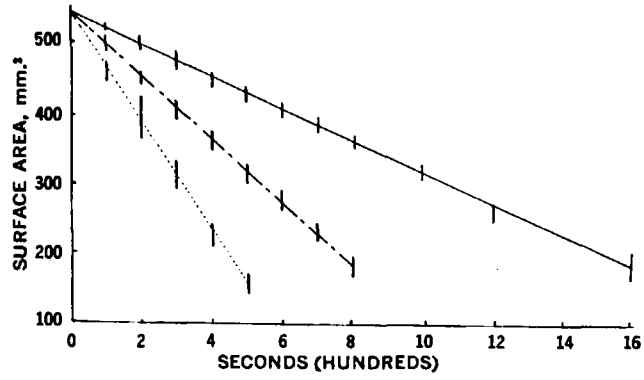

Figure 7—*Change in surface area of various suppositories with respect to time. Key:* . . ., *sodium salicylate, 70 mg., in polyethylene glycol 1540 (100%) (Formulation 2);* — · —, *sodium salicylate, 70 mg., in polyethylene glycol 1540 (80%) and polyethylene glycol 6000 (20%) (Formulation No. 6); and* ——, *salicylic acid, 60 mg., in polyethylene glycol 6000 (100%) (Formulation No. 3). Each point represents the mean value of five suppositories (vertical bars ± SE).*

If A decreases uniformly with time, one can say:

$$k = \frac{dA}{dt} \qquad \text{(Eq. 9)}$$

where k is the rate constant for a pseudo-zero-order reaction. For a small change in time, Eq. 9 may be expressed as:

$$k = \frac{\Delta A}{\Delta t} \qquad \text{(Eq. 10)}$$

Substituting Eq. 10 in Eq. 7, one has:

$$k = \frac{\pi D(D_2 - D_1) + \pi[(DL)_2 - (DL)_1]}{t_2 - t_1} \qquad \text{(Eq. 11)}$$

Taking a typical set of experimental results, one can calculate the rate constant, k, for the change in surface area of the suppository with respect to time. For example, consider the means (Fig. 7) for the suppository base containing polyethylene glycol 1540 (80%) and polyethylene glycol 6000 (20%), where:

$$D_1 = 8.0 \text{ mm.}$$
$$D_2 = 3.8 \text{ mm.}$$
$$L_1 = 17.8 \text{ mm.}$$
$$L_2 = 9.6 \text{ mm.}$$
$$t_1 = 0.0 \text{ sec.}$$
$$t_2 = 800.0 \text{ sec.}$$

Substituting these values into Eq. 11, one has:

$$k = \frac{3.142\left(\frac{8.0 + 3.8}{2}\right)(3.8 - 8.0)}{800 - 0} + \frac{3.142 \times [(3.8 \times 9.6) - (8.0 \times 17.8)]}{800 - 0} \qquad \text{(Eq. 12a)}$$

or:

$$k = -0.513 \qquad \text{(Eq. 12b)}$$

The value calculated for k (−0.513) approximates the value obtained by graphical analysis of the data (Fig. 3) and indicates that the change in surface area simulates zero-order kinetics. Therefore, one can assume that the release of salicylates from the polyethylene glycol suppositories also simulates zero-order kinetics. This assumption is in accord with findings reported by Wagner (15).

Table II—Average[a] Half-Lives and Rate Constants for Release of Salicylate from Various Polyethylene Glycol Suppository Formulations

Number	Suppository Formulation[b]	Average Half-Lives ($t_{1/2}$) ± *SE*, sec.	Average Rate Constants (k') ± *SE*, mg./sec.
1	Salicylic acid Polyethylene glycol 1540 (100%)	426 ± 31	0.07483 ± 0.00356
2	Sodium salicylate Polyethylene glycol 1540 (100%)	385 ± 9	0.08119 ± 0.00191
3	Salicylic acid Polyethylene glycol 6000 (100%)	1118 ± 5	0.02827 ± 0.00041
4	Sodium salicylate Polyethylene glycol 6000 (100%)	834 ± 14	0.03320 ± 0.00041
5	Salicylic acid Polyethylene glycol 1540 (80%) Polyethylene glycol 6000 (20%)	586 ± 11	0.05244 ± 0.00074
6	Sodium salicylate Polyethylene glycol 1540 (80%) Polyethylene glycol 6000 (20%)	546 ± 17	0.05411 ± 0.00161
7	Salicylic acid Polyethylene glycol 1540 (20%) Polyethylene glycol 6000 (80%)	1090 ± 12	0.02966 ± 0.00063
8	Sodium salicylate Polyethylene glycol 1540 (20%) Polyethylene glycol 6000 (80%)	805 ± 7	0.03446 ± 0.00112

[a] Represents the average of five suppositories. [b] Each suppository was formulated to contain either 60 mg. of salicylic acid or 70 mg. of sodium salicylate.

The time for 50% release of salicylate from each suppository, $t_{1/2}$, was calculated as follows:

$$t_{1/2} = \frac{Sro}{2k'} \qquad \text{(Eq. 13)}$$

where *Sro* is the total milligrams of salicylate released from the suppository (Table I), and k' is the release rate constant expressed in milligrams per second. The release rate constant, k', was also calculated using the expression:

$$k' = \frac{Sr}{t} \qquad \text{(Eq. 14)}$$

where t is the time when 80% of the salicylate, *Sr*, is released.

Taking a typical set of experimental results, that is, where t = 1800 sec. and *Sr* = 51 mg. (see Fig. 6, Formulation No. 3), one has:

$$k' = \frac{51}{1800} = 0.0283 \text{ mg./sec.} \qquad \text{(Eq. 15)}$$

and:

$$t_{1/2} = \frac{63}{(2)(0.0283)} = 1113 \text{ sec.} \qquad \text{(Eq. 16)}$$

Plots of the corrected salicylate release data (Figs. 5 and 6) and the half-lives for salicylate release from each suppository base (Table II) indicate that sodium salicylate is released at a slightly faster rate than is salicylic acid. The data also show that the composition of the polyethylene glycol base can affect markedly the time for 50% salicylate release. For example, the half-life of salicylic acid in polyethylene glycol 1540 is 426 sec., whereas in polyethylene glycol 6000 it is 1118 sec.

The appreciable differences between the half-lives for salicylates in the various polyethylene glycol bases may be predicted from a knowledge of the physical-chemical properties of the polyethylene glycols. For example, polyethylene glycol 1540 is approximately 1.5 times more soluble in water than polyethylene glycol 6000 (16).

The data also show that when mixtures of the polyethylene glycols are used in the suppository bases (Figs. 5 and 6), the rate of release of salicylate tends to approximate that observed for the higher molecular weight polyethylene glycol component. For example, the base consisting of 80% polyethylene glycol 6000 has a salicylate release half-life (Table II) almost identical with that observed for the base composed solely of polyethylene glycol 6000. In contrast, the base containing 80% polyethylene glycol 1540 has a salicylate release half-life that differs appreciably from that for the base consisting solely of polyethylene glycol 1540.

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