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IN VITRO AND IN VIVO RELEASE OF SALICYLIC ACID FROM POVIDONE/POLYDIMETHYLSILOXANE MATRICES

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ABSTRACT

Povidone (PVP)/Polydimethylsiloxane (PDMS) matrices were evaluated as drug delivery devices. PVP was utilized as a hydrophilic component to alter drug release. Salicylic acid was employed as a model drug substance.

Discs were prepared by placing the blended ingredients into a mold and allowing PDMS to cross-link at room temperature. The experimental formulations were evaluated for salicylic release via in vitro and in vivo experiments. In vitro experiments were conducted by USP Method II. In vivo release was determined by monitoring salicylate depletion after subdermal implantation. In vitro and in vivo release rate of salicylic acid was found to be proportional to PVP concentration. All release rate curves displayed $t^{1/2}$ relationships for at least 75% of the total release period. Mouse survival was related to salicylic acid release rate.

INTRODUCTION

Silicone polymers have been used in drug delivery devices since the early 1960's. Folkman and Long (1,2) were the first to demonstrate the utility of silicone implants in drug therapy. These investigators encapsulated thyroid hormone in silicone and implanted the capsules in the myocardial tissue of dogs with heart block. The thyroid hormone was released at a steady rate producing a local hyperthyroid effect that increased pacemaker activity. Silicone has since been used in a variety of ways to control drug release.

In 1979, McGinity (3) reported the use of water soluble additives in PDMS matrices to enhance drug release. His goal was to develop a drug delivery system for inducing morphine dependence in rats. McGinity used gelatin, sodium lauryl sulfate, sodium alginate and lactose as water soluble components in PDMS matrices to enhance the release of morphine sulfate. The presence of 10% gelatin, sodium lauryl sulfate or lactose in the silicone matrix increased morphine sulfate release in 1 week from 9% to 20%. Sodium alginate had the greatest overall effect. Morphine sulfate released after 1 week was 50% in silicone matrices with 10% sodium alginate. Since McGinity's report a number of investigators have published on enhanced drug release from silicone matrices.

Carelli and Dicolo (4) screened a series of water soluble additives to determine their ability to promote water absorption into silicone matrices. The additives they tested were ethylene glycol, glycerin PEG 200, 400 and 600, polysorbate 80 and lactose. Glycerin was the most active promoter of water sorption by PDMS. PDMS discs with 12% w/w glycerin swelled, reaching 2.8 times their original weight after 800 hours of exposure to 0.1M pH 7.4 phosphate buffer. Subsequently, these investigators determined the effect of water soluble components on the release of sulfanilimide from PDMS matrices (5).

In this study, it was determined that glycerin, PEG 200 and 400, sodium alginate and sodium chloride enhanced sulfanilimide release from PDMS matrices. For all additives, except sodium chloride plots of Q vs $t^{1/2}$ were linear. Similar results were obtained when the therapeutic agent under investigation was prednisolone (6). Hsieh and Chien (7) performed a further investigation into the effects of glycerin studying the release of indomethacin from PDMS matrices. These investigators used PDMS discs with an indomethacin loading dose of 1% containing from 0 to 30% glycerol and examined in vitro and in vivo release. The time for approximately 50% indomethacin to be released in discs with 0% glycerin was 30 days. From the matrices containing 30% glycerin, 50% of the indomethacin was released in 6 days. In vitro release correlated with an in vivo release study performed in mice. Linear Q vs $t^{1/2}$ plots were observed.

Hsieh (8) also showed that water soluble carriers could enhance the release of therapeutic macromolecules from PDMS matrices. In release experiments with Bovine Serium Albumin it was shown that at a 35% loading dose and a water soluble carrier concentration of 20% glycerin, ethylene glycol propylene glycol or PEG 400 could be used to enhance the release of BSA from PDMS elastomers. Similar results were obtained with chymotrypsin.

It was the purpose of this investigation to evaluate the use of PVP as a hydrophilic additive to PDMS matrices for the purpose of enhancing drug release. PVP has certain advantages over the previously mentioned additives. Its safety and tolerance from all routes of administration is well documented. It is available in a variety of molecular weights which may provide versatility in altering release rates.

The dissolution rates of many drugs have been altered by incorporation into PVP solid dispersions. This concept may be utilized in PDMS matrices. Finally, PVP is a relatively high molecular weight hydrophilic polymer that exists in the solid state.

As such it would not be expected to diffuse readily from PDMS matrices. This may prolong its ability to induce water sorption into PDMS matrices and subsequently extend the time period available for enhanced release.

EXPERIMENTAL

Materials

Silastic Medical Grade Elastomer 382 and Catalyst M (Dow Corning) was used to prepare PDMS matrices. Povidone (Plasdone K30) was obtained from GAF Corp. Reagent grade (Fisher-Scientific) sodium hydroxide, methyl alcohol, and potassium phosphate monobasic were utilized. Salicylic acid, USP was obtained form Aldrich Chemical Co.

For the in vivo studies DC-1 mice were anesthetized with sodium pentobarbital solution (Vi Pento, Steris Labs). Wounds were closed with Michel Clips (Fisher Scientific).

Equipment

A polycarbonate mold was designed and constructed in conjunction with Schering-Plough Research Engineering. The mold consisted of two polycarbonate slabs (11.4 cm x 11.4 cm x 2.4 cm) that when fastened together produced an internal circular chamber that was 10 cm in diameter and 1mm in depth. In vitro release tests were performed with the Distek Model 2000 Dissolution System (Distek Inc.). A Spectronic 2000 Spectrophotometer System (Bausch and Lomb) was used for spectrophotometric analysis.

Preparation of PDMS Discs

Povidone and salicylic acid were separated into different particle size cuts by using the Rotap Sieve Shaker for 10 minutes.

The 60-100 mesh cut of salicylic acid and PVP K30, was used for all experiments. To prepare discs, Silastic was added to a polyethylene weighing "boat". A blend of PVP and salicylic acid was prepared in a mortar and pestle. The PVP and salicylic acid mixture was blended with the Silastic using a spatula and the polymer mixture placed in a desiccator under vacuum for 10 minutes. One drop of Catalyst M per gram of mixture was then added and the resulting mixture was placed in the mold. Curing was allowed to proceed from 24 hours to 48 hours before initiation of testing. Suitably sized discs were cut out with a cork borer.

In Vitro Release of Salicylic Acid from PDMS Discs

In vitro release of salicylic acid was performed in the USP dissolution apparatus with USP Baskets at 50 RPM. The elution media was (1000 ml) of 0.1M potassium phosphate buffer (37°C) at pH 7.4.

Sampling was performed automatically with the programmable Distech Sampling Apparatus. By means of a peristaltic pump, samples were removed and passed through a 20 micron cellulose filter (Distech) at predetermined time periods. Six discs from each lot were tested. In vitro release was monitored from 1.5 hours to 120 hours.

In vitro release samples were assayed spectrophotometrically (λmax=295nm). Standard solutions were tested for each day. Absorbance readings from 0-2.0 were read directly. If absorbance readings were greater that 2.0, the necessary dilutions were performed.

Extraction of Residual Salicylic Acid from PDMS Discs (0.1M).

PDMS discs containing salicylic acid were sub-divided into small pieces placed into 30 ml of methanol and rotated for 24 hours to extract residual salicylic acid. The extraction media was analyzed spectrophotometrically for saliclyic acid.

Extraction of approximately 97 to 99% of the salicylic acid in PDMS discs was possible even when the discs were first exposed to aqueous media.

Implantation and Removal of PDMS Discs in Mice

Procedure was similar to that described by Hsieh (7). CD-1 mice weighing from 25-30 g were anesthetized with a single 40 mg/kg dose of sodium pentobarbital administered I.P.. An approximately 40 cm x 40 cm patch of skin on the dorsal surface was swabbed with 70% ispropopyl alcohol and a subcutaneous pocket was made with surgical scissors. A disc was inserted in each pocket and the wound closed with a Michel wound clip. At predetermined time periods, the mice were sacrificed by asphyxiation with carbon dioxide. Wounds were opened and the discs were removed. Discs were patted dry with filter paper and placed into vials for subsequent extraction and analysis of salicylic acid.

In Vivo Release Experiment - Protocol

Forty-eight CD-1 mice were divided into 4 blocks of 12 mice. The four blocks represented the test intervals of 6, 12, 24, and 48 hours. Each block of 12 mice was further divided into 3 groups of 4. In each group of 4 mice, a 100 mg disc containing 20% salicylic acid, and either 0%, 15% or 30% PVP K30 was implanted as previously described.

The mice were then placed in cages and given water and pelletized feed ad libitum. Each cage was numbered and coded for formulation and the day and date of implantation.

At the completion of each predetermined time interval the designated block of mice was sacrificed and the discs recovered. Each disc was analyzed for salicylic acid as previously described. The amount of salicylic acid in each disc was subtracted from the theoretical starting amount in order to determine the amount released during the time interval.

RESULTS AND DISCUSSION

As shown in Figure 1, strong correlation existed between salicylic acid release rates from PDMS discs implanted subdermally in mice and in vitro release rates.

Table 1 displays a summary of in vitro release rate data for discs containing 0%, 15% and 30% PVP K30 (Figure 2). Table 2 displays the corresponding in vivo data. In both in vitro and in vivo tests the order of release rate was 30% > 15% > 0% PVP K30. A comparison of in vitro and in vivo release rate data can be seen in Table 3. Reported release rate constants are the slopes of the best fit lines of Q mg/released/cm^2 vs $t^{1/2}$ plots calculated by linear regression (Figure 3). Although correlation was excellent between in vitro and in vivo release of salicylic acid, in vivo release was consistently higher. This may possibly be due to the lower surface tension of interstitial fluid in the subdermal cavity than in the in vitro elution medium.

As the release rate of salicylic acid increased so did the mortality rate. This effect was so pronounced that for the mice receiving 30% PVP K30 there were no survivors at the 24 hour and 48 hour time points. As displayed in Table 4 for each time period the percentage of surviving mice was ranked 0% > 15% > 30% PVP K30 (Figure 4). The dose of salicylic acid in this study was 0.7 mg/kg. The oral LD_{50} of salicylic acid in rabbits is 1.3 mg/kg(9). If we assume the toxic effects of salicylic acid to be similar in both species, the proximity of the LD_{50} to the administered dose in this study my provide some explanation for the observed mortality.

Since the mortality does not appear to be random it is likely due to toxic effects from rapid absorption of salicylic acid. Absorption rate is predicted to be greater from a subdermal site than from the G.I. tract. In addition it is not unreasonable to expect that at high concentrations salicylic acid (a keratolytic agent) will act as its own absorption promoter.

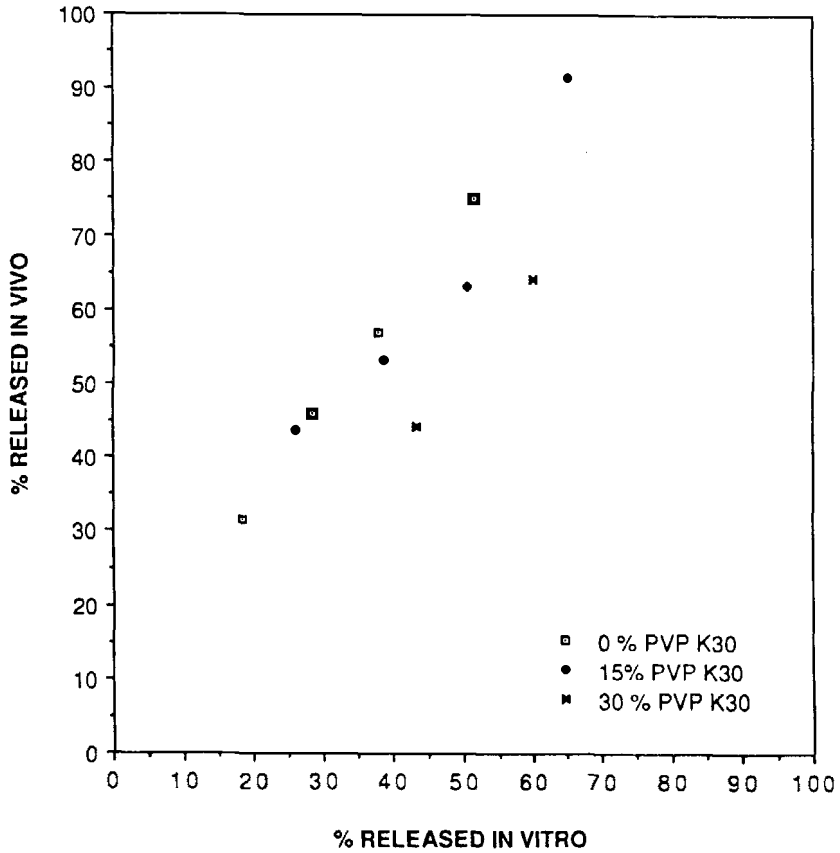

FIGURE 1

CORRELATION BETWEEN IN VITRO AND IN VIVO RELEASE OF SALICYLIC ACID FROM PDMS DISCS

TABLE 1

100 MG DISCS FOR IN VITRO/IN VIVO

RELEASE EXPERIMENTS - 20% SALICYLIC ACID

IN VITRO RELEASE

Time, hrs.	% RELEASE ± S*		
	0% PVP K30	15% PVP K30	30% PVP K30
1.5	----	13.2 ± 1.2	20.8 ± 2.7
3	13.6 ± 4.0	18.7 ± 0.9	29.8 ± 3.5
6	18.5 ± 4.1	25.9 ± 1.2	43.2 ± 4.4
9	24.3 ± 1.5	33.8 ± 2.5	52.6 ± 6.2
12	28.3 ± 5.0	38.7 ± 2.0	60.1 ± 6.4
18	32.9 ± 4.8	44.9 ± 3.7	72.5 ± 7.4
24	37.7 ± 5.1	50.4 ± 2.6	81.7 ± 7.1
36	47.8 ± 4.8	61.2 ± 2.2	86..5 ± 6.4
48	51.4 ± 5.3	65.4 ± 2.8	92.4 ± 4.0
60	56.7 ± 5.4	71.7 ± 2.5	99.3 ± 1.9
72	60.7 ± 7.2	76.1 ± 2.5	100.1 ± 0.9
96	67.4 ± 4.0	85.1 ± 3.9	100.1 ± 0.4

* Standard Deviation

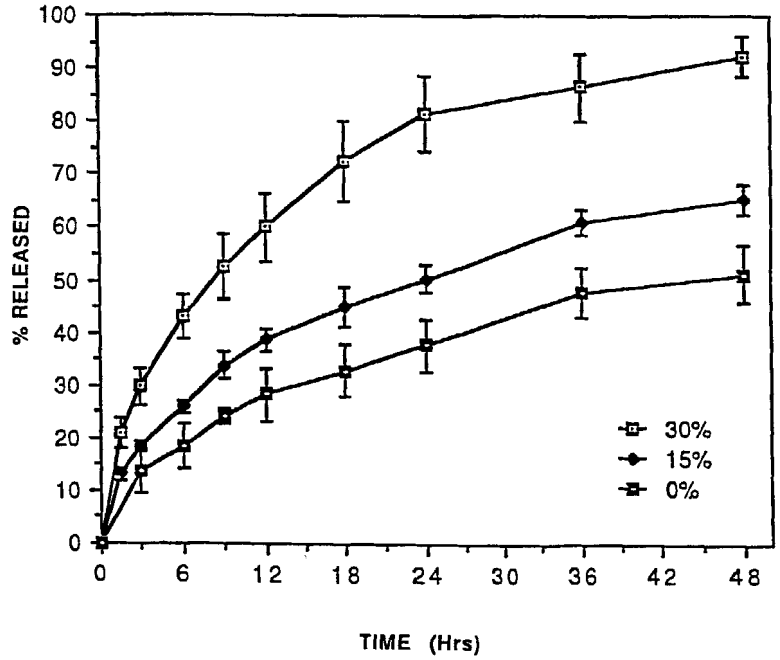

FIGURE 2

IN VITRO RELEASE - 100 MG PDMS DISCS WITH 20% SALICYLIC ACID

EFFECT OF PVP K30 CONCENTRATION

TABLE 2

100 MG DISCS FOR IN VITRO/IN VIVO

RELEASE EXPERIMENT - 20% SALICYLIC ACID

IN VIVO RELEASE

	% RELEASE ± S*		
TIME, HRS.	0% PVP K30	15% PVP K30	30% PVP K30
6	31.7 ± 3.6	43.9 ± 1.7	44.2 ± 3.2
12	45.9 ± 4.7	53.2 ± 0.5	64.3 ± 3.8
24	56.9 ± 0.7	63.3 ± 4.9	
48	75.0 ± 2.6	91.5 ± 0.4	

* Standard deviation

TABLE 3

COMPARISON OF IN VITRO AND IN VIVO RELEASE RATE

OF SALICYLIC ACID (20%) IN PDMS DISCS

	% RELEASED					
	0% PVP K30		15% PVP K30		30% PVP K30	
TIME, (HRS)	IN VITRO	IN VIVO	IN VITRO	IN VIVO	IN VITRO	IN VIVO
6	18.5	31.7	25.9	43.9	43.2	44.2
12	28.3	45.9	38.7	53.2	60.1	64.3
24	37.7	56.9	50.4	63.3	—	—
48	51.4	75.0	65.4	91.5	—	—

$K\left(\frac{mg/cm^2}{hrs^{1/2}}\right)$

	0% PVP K30	15% PVP K30	30% PVP K30
IN VITRO	0.92	1.19	2.17
IN VIVO	1.23	1.37	2.28

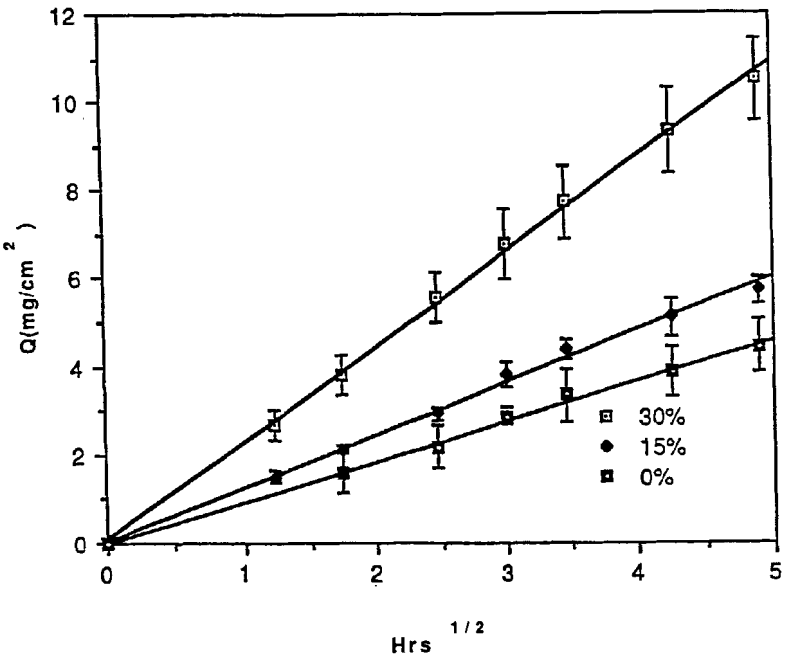

FIGURE 3

IN VITRO RELEASE - Q vs $t^{1/2}$

100 MG PDMS DISCS WITH 20% SALICYLIC ACID

EFFECT OF PVP K30 CONCENTRATION

TABLE 4

SURVIVAL RATES OF MICE

IN IN VIVO RELEASE EXPERIMENT

	SURVIVING MICE (PERCENTAGE)		
TIMEPOINT	0% PVP K30	15% PVP K30	30% PVP K30
6	13/15 (86%)	11/15 (73%)	7/16 (44%)
12	10/11 (91%)	8/11 (73%)	3/13 (25%)
24	7/8 (88%)	5/8 (63%)	0/8 (0%)
48	4/4 (100%)	3/4 (75%)	0/4 (0%)

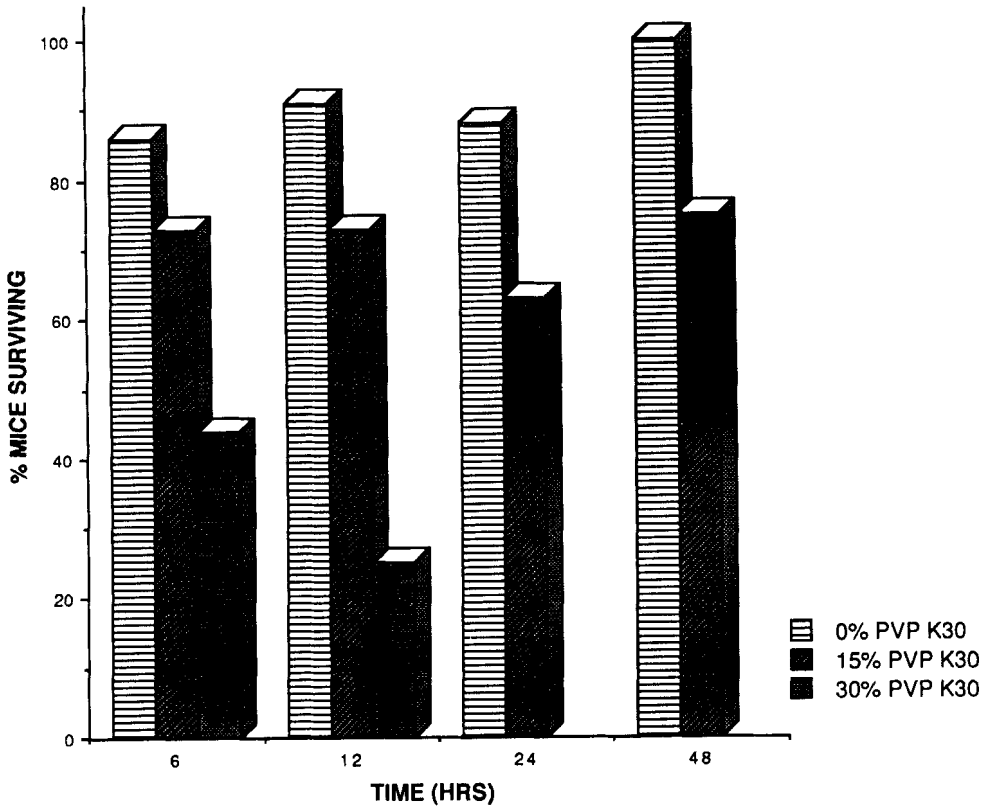

FIGURE 4

EFFECT OF PVP K30 CONCENTRATION

ON MOUSE SURVIVAL AFTER IMPLANTATION OF PDMS DISCS

Overdoses of salicylic acid can be lethal. In man death is eventually caused by cardiovascular and respiratory collapse (10).

PDMS discs containing 0%, 15% and 30% PVP also behaved differently in terms of the weight they gained or lost (excluding weight loss due to drug release) during the in vivo study. This data is shown in Table 5.

PDMS discs with both 0% and 15% PVP K30 had net weight gains over 48 hours. The 30% PVP K30 disc displayed a net loss in weight during the 12 hours it was implanted. This net loss in weight for the 30% PVP K30 matrix was probably due to physical erosion caused

TABLE 5

% WEIGHT GAIN (+) OR LOSS (-) OF PDMS DISCS

DURING IN VIVO RELEASE EXPERIMENT

TIME, (HRS)	% WEIGHT GAIN (+) OR LOSS(-)		
	0% PVP K30	15% PVP K30	30% PVP K30
6	-0.10	+2.69	-3.70
12	+0.10	+3.72	-4.50
24	+0.46	+88.03	
48	+2.25	+15.30	

by the high hydrophilic load. This erosion can be clearly seen upon visible inspection. In view of this, it is likely that erosion also did occured in vivo. When PVP is incorporated into PDMS discs, surface PVP probably dissolves and is released by the matrix but the fact that weight gain still increases even when a significant amount of salicylic acid has been depleted points to the conclusion that a significant portion of PVP remains in the PDMS disc enhancing water uptake and salicylic acid release throughout the test period. This is consistent with the fact that PVP K30 although a hydrophilic substance is still a polymer with a M.W. of 40,000 and will not easily diffuse through PDMS. The fact that PVP will not readily diffuse through PDMS as opposed to smaller molecule such as sodium chloride or glycerin makes PVP more attractive as a hydrophilic agent with which to enhance drug release from PDMS matrices.

In summation, this study demonstrated that PVP can be used to control release of salicylic acid from PDMS discs. In addition a strong correlation was observed between in vitro and in vivo

release rates. PVP/PDMS matrices may be useful in controlling drug release in moldable dosage forms.

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