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FORMULATION OF PENETRATION ENHANCERS IN POLYMERS

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ABSTRACT

Two commercial polymer matrices were prepared : the hydrophilic macromolecular polyvinyl alcohol-povidone type and the hydrophobic microseal silastic silicone type. Different blends of the penetration enhancers Azone, 2-Pyrol and M-Pyrol in glycerine were incorporated with the drug, levodopa. The in-vitro dissolution of drug from these matrices and its diffusion through a semi-permeable membrane were measured. Results show that povidone polymers released 10 times more levodopa than did silicone polymers. The penetration enhancers significantly increased the rate of release of drug.

INTRODUCTION

Polymer matrices make good drug reservoirs for sustained release medication. The polyvinyl alcohol-povidone

gel and the silicone polymer are two such matrices employed in transdermal systems and subdermal implants, respectively. Drugs that have been used are nitroglycerin [1], clonidine [1], scopolamine [2], estradiol [3] and indomethacin [4]. Other common polymers are carbopol 934 [5], polyvinyl acetate [6], polyethylene [6], ethylene-vinyl acetate [6] and polyHEMA [7].

Penetration enhancers are substances that temporarily reduce the impermeability of the skin, hence promoting the passage of drug through it. Various enhancers have been recognised, like dimethylsulfoxide, dimethylformamide, dimethylacetamide, pyrrolidones and azacycloalkan-2-ones [8]. The latter two were employed in this project. The pyrrolidones used were M-Pyrol®(N-methyl-2-pyrrolidone) and 2-Pyrol®(2-pyrrolidone). They are water soluble, viscous solvents that solubilize most drugs [9]. Azone® (1-dodecylazacycloheptan-2-one) is an oily, water insoluble liquid with a recommended use of 2 to 10%. It has been successfully employed for the percutaneous absorption of antibiotics, antifungals and steroids [10].

Our aim was to demonstrate that penetration enhancers, when used in sufficient concentrations, could alter the formulation properties and increase the rate of drug release. Our selection of levodopa in this project was based on its solubility in an aqueous sink and its ease of analysis.

MATERIALS AND METHODS

Preparation of macromolecular polymer matrices: Glycerine and water are heated to 70°C in a 100 ml beaker. Polyvinyl

TABLE I

Formulas for Macropolymer Matrices

Ingredient	Percent Concentration					
	IA	IB	IC	ID	IE	IF
Polyvinyl alcohol	15	15	15	15	15	15
polyvinyl pyrrolidone[a]	8	8	8	--	--	--
polyvinyl pyrrolidone[b]	--	--	--	8	8	8
Glycerine	30	30	30	30	30	30
purified water	46	26	41	46	26	41
2-pyrrolidone	--	10	--	--	10	--
N-methyl-2-pyrrolidone	--	10	--	--	10	--
Azone	--	--	5	--	--	5
Levodopa	1	1	1	1	1	1

[a]Type K29-32 [b]Type K26-28

Polyvinyl alcohol (Aldrich Chemical Company, Milwaukee, WI.)
Pyrrolidones (GAF Corporation, Linden, NJ.)
Azone (Nelson Research, Irvine, CA.)
Levodopa (Sigma Chemical Company, St. Louis, MO.)
Glycerine (Humco Laboratory, Texarcana, TX.)

alcohol and polyvinyl pyrrolidone are added gradually and mixed with a steel spatula. On obtaining a uniform mass, the heat is removed, and levodopa (as a 120 mesh fine powder) and the penetration enhancers are added to the warm mass. Mixing is carried out for a further 10 min. This mixture is then poured into tared weighing boats lined with aluminum foil. The boats are filled to volume, placed in a desiccator, and allowed to gel under vacuum for 2 hr. The boats were square with an area of 13.69 cm^2 , a depth of 0.47 cm and held 6.5 ml of matrix (approximately 6.0 to 7.0 gm). Six formulas were made by this procedure (Table I).

TABLE II

Formulas for Microseal Polymer Matrices

Ingredient	Percent Concentration					
	IIA	IIB	IIC	IID	IIE	IIF
Elastomer + curing agent[a]	88	88	88	--	--	--
Elastomer + curing agent[b]	--	--	--	88	88	88
Glycerine	12	4	7	12	4	7
2-pyrrolidone	--	4	--	--	4	--
N-methyl-2-pyrrolidone	--	4	--	--	4	--
Azone	--	--	5	--	--	5
Levodopa	10% of the total matrix weight					

[a]Type MDX4-4210 (polydimethyl siloxane with a platinum catalyst) [b]Type 382 (polydimethyl siloxane with a stannous octoate catalyst)

Silicone elastomers (Dow Corning Corporation, Midland, MI.)

Preparation of microseal polymer matrices: The elastomer and glycerine are weighed into a 50 ml beaker. The drug and penetration enhancer are added and stirred with a steel spatula for 10 min. The curing agent is next weighed in and mixed for complete homogeneity. Filling and drying of the boats are carried out as previously described. The boats are stored for at least 3 days at room temperature to ensure complete vulcanization. The boats held approximately 6.5 to 7.0 gm of matrix. Table II lists the six formulas prepared by this procedure.

Release Experiment: The apparatus used in this experiment is similar to that used previously in a study to estimate

drug release from a topical powder[11]. The receptor phase was 300 ml of a 0.1M disodium citrate buffer (pH 5). Two tests were conducted to measure levodopa release.

1. Dissolution test: A 52 μm mesh (SpectraMesh; Spectrum Medical Industries, CA) supports the boat as it is inverted on the surface of the sink medium. Aliquots of buffer are removed at different time intervals for drug analysis.
2. Diffusion test: A 0.002 to 0.014 μm pore size semi-permeable cellulose membrane (SpectraPor2; Spectrum Medical Industries, CA) was used to cover the boat and act as a barrier between the polymer and the sink medium. Aliquots of the medium are removed as before for drug analysis.

Drug Analysis: The concentration of drug in each solution was measured by UV-spectrophotometry at 280 nm (Perkin-Elmer Hitachi 200 UV-VIS spectrophotometer). A standard calibration curve was prepared using a series of known concentrations of drug in pH 5 buffer.

Solubility of Drug in Cosolvents: Mixtures of water, glycerine and the penetration enhancers were prepared in the same ratios as in Tables I and II. Excess of levodopa (100 mg) was added to each of these solutions (10 ml). They were shaken overnight at room temperature to allow for saturation, and filtered using disposable Gelman filter syringes with 0.2 μm paper cartridges. A known volume of

filtrate (0.25 ml) was added to 3 ml of 0.1N hydrochloric acid (pH 1.2), centrifuged and the aqueous solution taken for analysis. The solubility of levodopa in matrix cosolvents was determined.

Solubility of Drug in Polymers: A piece of aluminum foil was placed on a 2" x 4" glass slide. A 1" x 2" rectangle was cut out from this foil, leaving behind a shallow mold. Polymer matrices without drug were prepared and poured into this mold. A second slide was placed over the matrix and set aside for curing. Small pieces of the uniform matrix were cut out, weighed and placed on the bottom of 150-ml beakers containing 100 ml of known concentrations of levodopa (50 and 200 μg per ml) in 0.1 M hydrochloric acid. Aliquots of this solution were taken up to 48 hr and analysed for levodopa concentration. The cream-like matrices had to be spread as thin layers on the bottom of tared beakers.

RESULTS AND DISCUSION

Solubility of Drug in Cosolvents: The results of levodopa solubility in matrix cosolvents are listed in Table III. Higher solubility values were observed in formulations containing penetration enhancers.

Solubility of Drug in Polymers: Previous studies report a method to determine the solubility of a steroid in silicone polymers that contained no cosolvents[12]. As our polymers

TABLE III

Solubility and Consistency Results in each formulation.

Formula	Consistency	Solubility (µg/ml)
IA	+++	4898.83
IB	++	8033.71
IC	++	4779.57
ID	+++	4898.83
IE	+	8033.71
IF	+	4779.57
IIA	+++	1845.73
IIB	+	2786.19
IIC	+	12054.93
IID	+++	1845.73
IIE	+++	2786.19
IIF	++	12054.93

Key:

+++ = solid firm matrix, leaves no impression when pressed
++ = solid firm matrix, leaves impression when pressed
+ = semi-solid and cream-like.

contained different cosolvents, our procedure had to differ. Results obtained depicted that negligible amounts of levodopa dissolved in the matrix after 48 hr. It was also observed that the cosolvents leached out in to the drug solution during each trial. Hence this procedure was ineffective.

Comparison of polyvinyl alcohol and silicone polymers:

Release of levodopa from the 12 formulations is shown in figures 1 - 4. The povidone matrices released 70 % of the

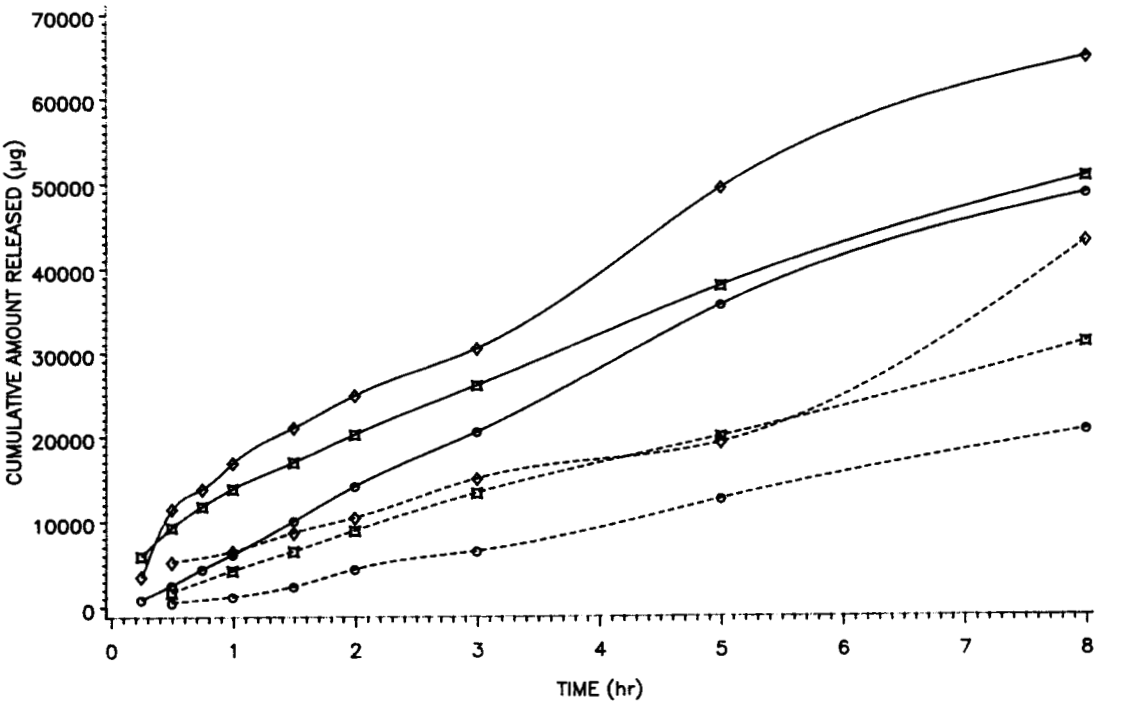

Figure 1: Levodopa release from polyvinyl alcohol–povidone (K29–32) matrices
Key: (o) IA, (□) IB and (◇) IC with mesh (————) and membrane (– – –)

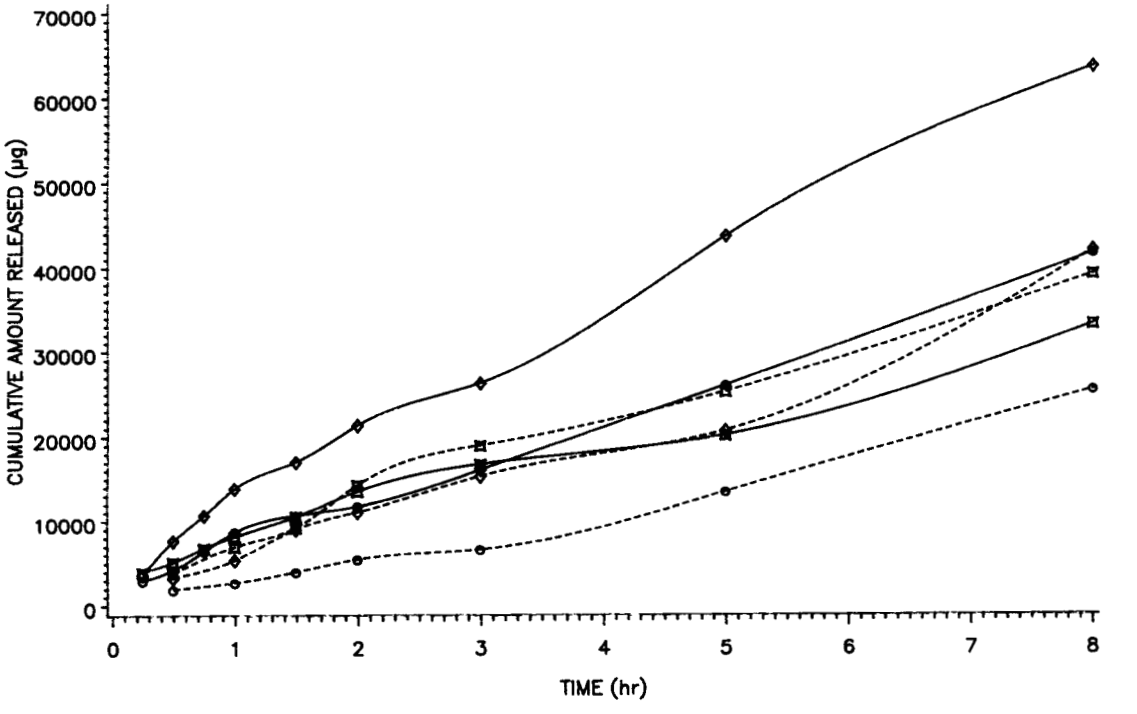

Figure 2: Levodopa release from polyvinyl alcohol–povidone (K26–28) matrices
Key: (o) ID, (□) IE and (◇) IF with mesh (————) and membrane (– – – –)

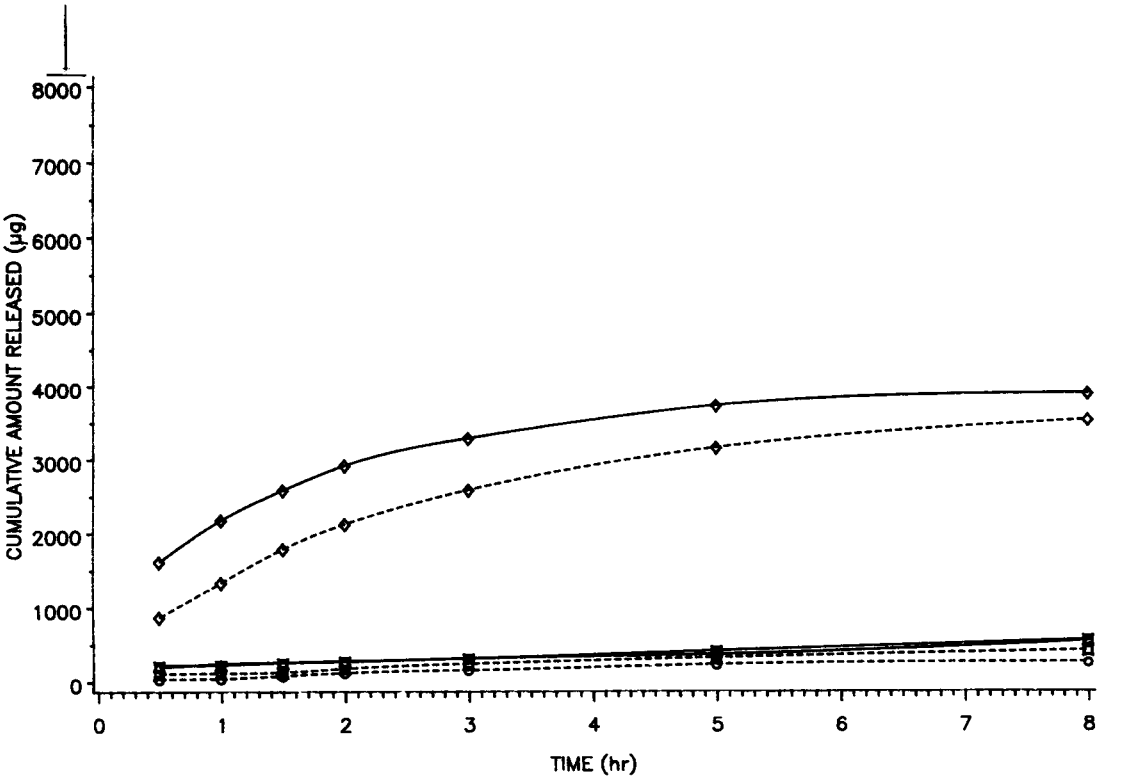

Figure 3: Levodopa release from silicone (Silastic MDX4–4210) matrices
Key: (o) IIA, (¤) IIB and (◊) IIC with mesh (————) and membrane (– – –)

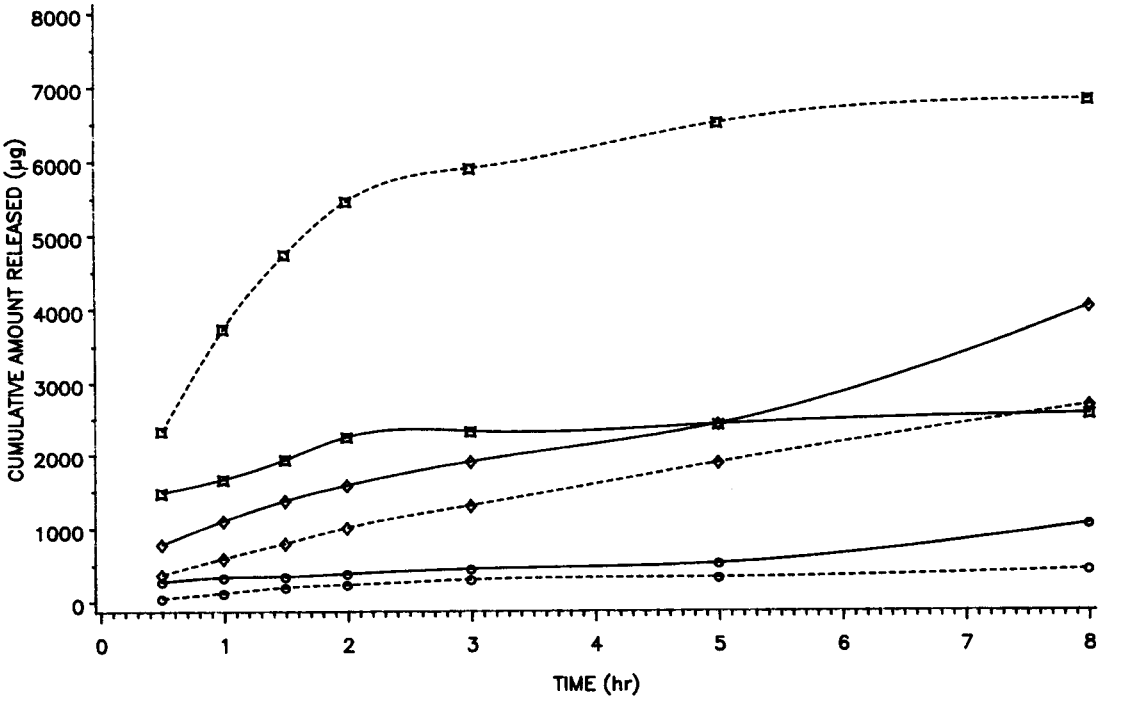

Figure 4: Levodopa release from silicone (Silastic 382 matrices
Key: (o) IID, (¤) IIE and (◊) IIF with mesh (————) and membrane (– – –)

initial drug content in 8 hr, as seen in figures 1 and 2. The silicone matrices released less than 2 % of levodopa in 24 hr. On comparing formulas IIA and IID, it is noted that the Silastic® MDX4-4210 silicone released approximately 1 mg more of drug than the Silastic® 382 polymer.

The large difference in release rates between the povidones and the silicones is expected, the polyvinyl alcohol polymer being hydrophilic and sponge-like while the silicones are water immiscible. Comparison of the K26-28 povidone with the K29-32 povidone showed no significant difference in release patterns, probably due to their low percentage in the formula. Consistency differences were noted between formulas IE, IF and formulas IB, IC as shown in Table III.

Effect of the penetration enhancers: There was significant improvement in drug dissolution and diffusion in the formulations containing the penetration enhancers. Both penetration enhancers appear to have softened the matrix, increased gelling and vulcanization time, and improved drug diffusivity. A comparison of the two indicates that formulas IC, IF, IIC and IIF, which contained Azone had better release rates. The oily nature of Azone does not permit a homogeneous consistency, hence drug release from the polymers was faster.

The use of a semi-permeable membrane has been previously carried out to determine drug release [5]. The

lowering of drug release across the membrane is noticed in all polymers, except in IE and IIB. Drug release in this case is assumed to follow Fick's Law of diffusion, where a film containing a high amount of drug and water soluble penetration enhancers (M-Pyrol and 2-Pyrol) forms between the matrix and the membrane. Thus, a concentration gradient is created between this film and the sink.

CONCLUSION

The incorporation of penetration enhancers in sustained release polymers shows definite improvement in drug permeation across a barrier. Levodopa is released at a sufficiently high rate from povidones, approximately 10.7 $mg/cm^2/24$ hr from formula IA and 14.1 $mg/cm^2/24$ hr from IC. The release from the silicones is approximately 0.2 $mg/cm^2/24$ hr from IIA and 0.4 $mg/cm^2/24$ hr from IIC. The best polymer in this case is the polyvinyl alcohol-povidone combination. Both penetration enhancers are shown to be effective for this hydrophilic drug. Formulations with hydrophobic drugs are under investigation.

Acknowledgements

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