DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 7(5), 497-523 (1981)

A Comparative Study of the In Vitro and In Vivo Release of Dexamethasone from a Spray-On Bandage and Timed Release Aerosol

by

M. Luongo**, J.J. Sciarra*, C.O. Ward***, V. DePaul Lynch**, and W. Feinstein****

- ABSTRACT -

The formulation of several dexamethasone topical delayed release aerosol preparations was studied. Ethylcellulose and tributyl citrate were the film-forming agent and plasticizer, respectively, for the spray-on bandage formulation. The aerosol timed release preparation contained dexamethasone microcapsules suspended in a fluorocarbon aerosol propellant by isopropyl myristate and fumed silica. Both preparations were evaluated using an in vitro method which measured the release of dexamethasone hourly for eight hours. In vitro studies showed that each of the formulations delayed the release of dexamethasone. In the in vivo tests aerosols were

* To whom inquiries should be directed.
** Present address: St. John's University, Jamaica, N.Y.
*** Present address: Gulf Science and Technology Company Medical and Health Resources Division, Toxicology Department, Pittsburgh, Pa.
**** Present address: Whitehall Laboratories Division, American Home Products Corp., New York, N.Y.

sprayed on the unabraded back area of rabbits and the increased 17 - hydroxycorticosteriod urine levels at 24, 48, and 72 hours indicated dexamethasone absorption. In vivo studies indicated that absorption did not occur with the timed release preparation containing dexamethasone microcapsules. However, dexamethasone from the spray-on bandage preparation was absorbed over 72 hours. A commercially marketed topical dexamethasone cream was used for comparison in evaluating the two experimental formulations; however, in vivo studies showed that no absorption occurred with this preparation.

In recent years, a great deal of work has been directed towards the application of medicated polymeric films or tissue adhesives onto the skin to treat minor dermatological problems or serious skin wounds. Among the factors to be considered are: incorporation of a specific active ingredient, the mode of application and the dosage form. Lange and Fang (1,2) developed spray-on bandages using water soluble resins and water as the solvent. Fischl (3) evaluated the effectiveness of a cyanoacrylate monomer in closing skin incisions without affecting wound healing. Bhaskar and Cutright (4) showed that butyl cyanoacrylate could be successfully used as a surface dressing while reducing the degree of inflammation. Sciarra and Gidwani (5,6) reported on the release of gentian violet from selected polymer and plasticizer combinations and established various polymer-plasticizer combinations which could be applied as an aerosol spray. Other studies (7,8) have shown that ethylcellulose and a thermoplastic polyamide resin have potential use in spray-on bandage formulations.

The results indicated that the anti-infectives were released from the films and the spray-on bandages reduced the degree of infection about the wound.

The process of microencapsulation has been applied to various industrial and medical uses. Microcapsules can be prepared so that the encapsulated material will be released slowly. There are various methods of microencapsulation including coacervation, phase separation, interfacial polymerization, an electrostatic method, and vacuum metalization and they have been successfully used with selected drugs (9-13).

The purpose of this study was to develop and evaluate different aerosol formulations containing a therapeutic agent which can be slowly released. In vitro and in vivo systems were used to evaluate the release and absorption of the drug in the test animals.

EXPERIMENTAL

Formulation of the Spray-On Bandage: Formulations were prepared containing 1.0 g dexamethasone[1], 2.5 g ethylcellulose[2], 0.25 g tributyl citrate[3], 5.0 g isopropyl myristate and 6.25 g absolute ethyl alcohol. Heat was used to aid in the solution of ethylcellulose. This provided a continuous and highly flexible film without any cracks or fissures. A blank was also prepared.

---

[1]Micromilled, Napp Chemicals Inc., Lodi, N.J.

[2]Ethylcellulose N-10, Hercules Powder Co., Wilmington, Del.

[3]Citroflex - 4, Chas. Pfizer and Co., New York, N.Y.

Preparation of Calibration Curve: The maximum wavelength for dexamethasone was determined using a double beam spectrophotometer[1] and 1 cm silica cells. Stock solutions of dexamethasone containing 1.0 and 10 mcg/ml were prepared using ethanol as the solvent and their absorbance was determined. A maximum wavelength of 239 nm was obtained. Other stock solutions of dexamethasone were then prepared in concentrations ranging between 1 and 10 mcg/ml and 10 and 70 mcg/ml. The absorbance of these solutions was then plotted against the known concentration of the dexamethasone solution.

Initial Drug Concentration in Model Film: Fifteen grams of the model film was prepared as indicated, to which was added 4.2 g of ethanol. This was poured into a 14 cm diameter petri dish which contained clean filtered mercury. The cast films were allowed to dry at room temperature for 3 days and a film having no cracks or fissures and of uniform thickness was produced. A disc was cut from the film using a calibrated copper cylinder measuring 4.5 cm in diameter. The disc was weighed, dissolved in ethanol, and brought to a final volume of 100 ml and stirred for one hour. The absorbance of the sample was measured against the blank at 239 mm. The dexamethasone content of the film was obtained from the calibration curve. The blank films were treated similarly.

[1]Coleman Hitachi Double Bean Spectrophotometer, Model 124 Coleman Instruments Div., Maywood, Ill.

In Vitro Release Rate: Additional film discs containing dexamethasone were prepared, weighed and glued[1] onto the smooth surface of a glass stopper and allowed to set overnight. The stopper, attached to a plastic rod, was inverted into a 400 ml beaker containing exactly 200 ml of dissolution medium (Sorensen's Buffer Mixture[2] adjusted to pH5.60). The water surrounding the 400 ml beaker was maintained at $37^{o} \pm 0.1^{o}$ as seen in Figure 1.

At one hour intervals for 8 hours, 10 ml samples were removed and assayed spectrophotometrically at 239 nm. For each sample removed, a freshly pipetted 10 ml portion of receiving medium, maintained at 37^{o}, was added to the medium already in the beaker. A cumulative correction factor was used to account for the hourly removed samples in relation to the total amount dissolved (14). The equation for this factor follows:

$$C_n = C_n \text{ (measured)} + \frac{10}{200} \times \sum_{s=1}^{n-1} C_s \text{ (measured)}$$

where C_n (measured) is the concentration obtained through the use of the spectrophotometer, C_n is the concentration of the n^{th} reading expected in the medium if previous samples were not removed, 10/200 is the dilution factor and C_s (measured) is the uncorrected concentration of n^{th} - 1 determinations.

---

[1]Smooth-on Inc., Gillette, N.J.

[2]Potassium Phosphate Monobasic and Sodium Phosphate Dibasic, Dihydrate.

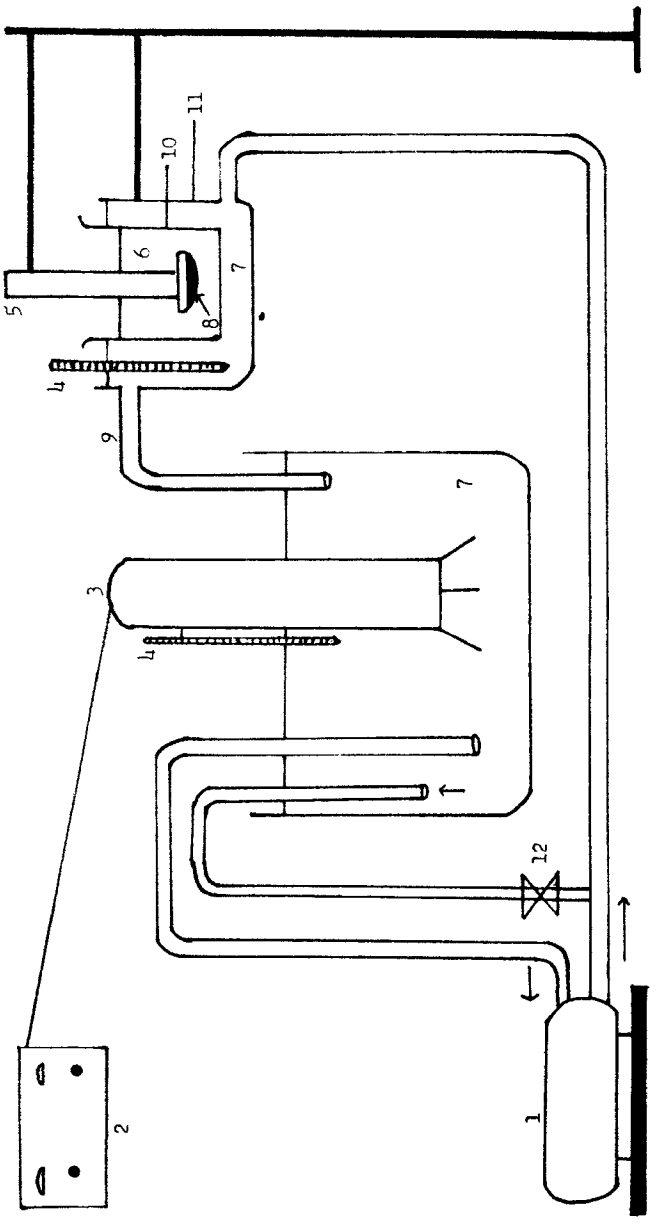

Fig. 1 - Schematic diagram of apparatus used for in vitro studies.

1. motor
2. thermostat for water pump
3. heater and circulating pump
4. thermometer
5. plastic rod with glass stopper
6. receiving medium
7. circulating water
8. drug film
9. overflow return
10. 400 ml beaker
11. plastic container
12. bypass

Preparation of the Aerosol and Delivery Rate Determination: The concentrate was added to a tin-plate 180 ml aerosol container and sealed with an aerosol valve[1]. Dichlorodifluoromethane/dichlorotetrafluoroethane (40:60) was added. The concentrate accounted for 15% by weight while the propellant blend accounted for 85% by weight of the total product.

The containers were stored at 25 ± 1° to allow the contents to attain equilibrium before use. Each container was accurately weighed and placed into the discharge rate apparatus (15). The timer was set for 10 sec and the product was automatically discharged. The container was removed from the apparatus and reweighed. Three determinations were made on each container and the results were averaged to determine the amount of material discharged through the valve in grams per second.

Preparation of the Microencapsulated Dexamethasone: A 10% by weight solution of ethylcellulose was prepared by adding 25 g of ethylcellulose 10 cps to 225 g of toluene. A

[1]Precision Valve Co., Yonkers, New York, 5.08 x 0.05 cm (2 x 0.020 in.) orifice, radius core (nylon) stem, Buna N (regular durometer) gasket, type 302 stainless steel spring, 0.2 cm (0.08 in) nylon body, flat dimpled tin plate, epon-coated mounting cup, standard dip tube, and 0.05 cm (0.02 in) actuator.

laboratory mixer[1] at a speed of 60 to 70 rpm was used and the ethylcellulose was slowly added to the vortex of the toluene. The solution was allowed to stand overnight, or until it became clear, in a sealed container. Fifty to 60 ml of petroleum ether[2] was added dropwise from a 100 ml pipette to the ethylcellulose solution contained in a 1000 ml beaker until a persistent turbidity was produced. Seven and one-half grams of dexamethasone was added to this mixture and mixed. Alternative additions of petroleum ether and talc were then made, using a total of 200 ml and 50 g, respectively. Coated particles were separated from the liquid by filtration. The filtrate was washed several times with additional petroleum ether and the particles were separated and allowed to dry at ambient room temperature on filter paper. Coarse to fine particles were obtained, assayed and by the direct total assay procedure found to contain approximately 7 to 12% of dexamethasone.

Classification of Particle Size: The microcapsules were separated into varying particle sizes[3]. The distribution was determined with the aid of No. 60, 80, 100, 200, 270 and 325 mesh sieves. All batches of microcapsules were separated according to their respective particle sizes until a sufficient amount of each sieve size was obtained.

---

[1] Lab-Stir Apparatus.

[2] Boiling range of 30-60°

[3] Cenco-Meinzer Sieve Shaker, Central Scientific Co., Chicago, Ill.

Determination of Dexamethasone in the Microcapsules: The standard was prepared by adding 50 mg of dexamethasone reference standard to a 250 ml volumetric flask followed by enough absolute ethyl alcohol to achieve the final volume. A 3 ml aliquot of this solution was pipetted into a 100 ml volumetric flask, brought to volume with absolute ethyl alcohol and mixed.

Approximately 1 g of dexamethasone microcapsules was ground to a fine powder after which an amount equivalent to 4 mg of dexamethasone was weighed and transferred to a 100 ml volumetric flask. Approximately 70 ml of absolute ethyl alcohol was added and the flask was shaken for 30 minutes before being brought to final volume with ethanol. A 15 ml aliquot was pipetted into a 100 ml volumetric flask and brought to final volume with ethanol and mixed.

Five ml aliquots of each sample solution, 20 ml of the standard solution and 20 ml of ethanol (serving as the reagent blank) was pipetted into separate 50 ml centrifuge tubes. Two ml each of blue tetrazolium solution (16) and tetramethylammonium hydroxide solution (17) was added to each tube which was then stoppered. After standing in a dark place for 90 minutes the absorbance of the sample and standard was read against the blank at 525 nm. The amount of dexamethasone was determined by the following equation (13):

$$\frac{S}{S_a} \times \frac{C}{1000} \times \frac{100}{W} \times D.F. = \text{mg of dexamethasone/g}$$

where S = absorbance of sample at 525 nm, S_a = absorbance of standard at 525 nm, C = concentration of standard in mcg/ml, W = sample weight in g, and D.F. = dilution factor.

In Vitro Release Rate Studies: Dexamethasone microcapsules (1 g) were added to 100 ml of Sorensen's Buffer[1], pH 5.6, 37°, and placed onto a gyratory shaker. Ten ml samples were withdrawn hourly for 8 hours and after 24, 48 and 72 hours. The absorbance of the samples was read against a blank at 239 nm. Fresh 10 ml portions of the dissolution medium were added to replace the withdrawn samples and a cumulative correction factor was used to correct for the dilution of the solution.

Preparation of the Microencapsulated Dexamethasone Timed Release Aerosol and Delivery Rate Determination: Fifteen grams of dexamethasone microcapsules was mixed with 0.5 g fumed silica and 5.0 g isopropyl myristate and added to a tin-plate aerosol container, fitted with an aerosol valve (as previously described), crimped and pressurized with 79.5 g of dichlorodifluoromethane/dichlorotetrafluoroethane (40:60). Delivery Rate determinations and preparation of the blank were carried out as previously stated.

Preparation of the Dexamethasone Topical Cream: Additional dexamethasone sodium phosphate was added to a commercially marketed cream containing 0.1% dexamethasone sodium phosphate[2] so that each gram of cream would have a final dexamethasone concentration of 35.9 mg so as to have the

[1] Potassium Phosphate Monobasic and Sodium Phosphate Dibasic, Dihydrate.

[2] Decadron Sodium Phosphate Topical Cream - Merck Sharpe and Dohme, West Point, PA.

same concentration as a two second spray emitted from the spray-on bandage preparation and the microencapsulated dexamethasone aerosol.

Preparation of a Hydrocortisone Calibration Curve: Fifty mg of hydrocortisone was weighed, transferred to a 50 ml volumetric flask and brought to final volume with ethanol. Various aliquots were taken and diluted with ethanol to obtain solutions with a concentration of 1 to 10 mcg/ml. Ten ml of each solution and 10 ml of ethanol were pipetted into separate 50 ml centrifuge tubes. One ml each of blue tetrazolium solution and tetramethylammonium hydroxide was added to each tube. After allowing the tubes to stand in a dark place for 90 minutes, the absorbance of the standard was read against the blank at 525 nm. The absorbance was then plotted against the known concentration of the hydrocortisone solution.

In Vivo Testing: Adult male New Zealand white rabbits weighing between 3.40 to 4.17 kg were used. They were allowed food and water ad libitum and housed in separate metabolism cages. The backs were shaved prior to the start of the tests. The aerosol to be tested was sprayed onto the animal's back covering an area adjacent to the spinal column approximately 6.3 x 6.3 cm square (2½ by 2 ½ in.). Each aerosol was sprayed at a distance of 15.2 to 20.3 cm (6-8 in.) for two seconds. Once the back area was dried it was occluded by wrapping[1]. The control group was treated in the same manner except that no

[1]Saran Wrap, Dow Chemical., Midland, Michigan

aerosol prepration was applied. In the case of the dexamethasone cream, 1 g was rubbed into the back area in order to deliver a specified amount of dexamethasone.

Urine samples were collected 24 hours before the start of the experiment and at 24, 48 and 72 hours after each treatment. The urine volume was measured and each sample was frozen for future analysis.

The group of animals tested included the control group and those groups treated with the dexamethasone spray-on bandage and its corresponding blank, the dexamethasone microencapsulated spray and its corresponding blank and the dexamethasone topical cream.

The same five (5) rabbits were used in these studies. A minimum of 10 days was allowed as a rest period before the rabbits were used for subsequent tests.

Procedure for Assaying the Rabbit Urine Samples for 17-Hydroxycorticosteroid Content: Ten ml of each urine sample was pipitted into separate 50 ml centrifuge tubes. Ten ml of purified water adjusted to pH 5.0 with acetic acid was pipetted into another centrifuge tube and was used as the blank. Four ml of beef liver glucuronidase solution[1] was added to each sample and blank. The tubes were mixed, stoppered and incubated overnight at 30°. Upon reaching room temperature, 10 ml of carbon tetrachloride was added, shaken for 5 minutes and then centrifuged for 5 minutes. After transferring the aqueous

[1]Beta-Glucuronidase solution (5000 Fishman united/ml), Sigma Chemical Co., St. Louis, Mo.

phase to a 40 ml centrifuge tube, the extraction was repeated with another 10 ml of carbon tetrachloride. Twelve ml of the aqueous phase was transferred to a 125 ml separator, extracted using 50 ml of methylene chloride and then allowed to settle for 30 minutes. The organic phase was transferred to a 125 ml Erlenmeyer flask to which 30 pellets of sodium hydroxide was added. The flasks were shaken for 5 minutes, allowed to settle and the solution filtered through Whatman No 4 filter paper into a 50 ml centrifuge tube. Twenty ml of the filtrate was then pipetted into a 40 ml centrifuge tube and evaporated to dryness on a 30^{o} steam bath, using vacuum to aid in evaporation. The residue was dissolved in 10 ml of ethanol. The sample solutions and blank were treated with 1 ml each of blue tetrazolium solution and tetramethylammonium hydroxide solution, mixed and allowed to stand in a dark place for 90 minutes. The absorbance of the samples was read against the blank at 525 nm.

RESULTS AND DISCUSSION

The spray-on bandage formulation produced a flexible model drug film which allowed for the uniform distribution of the drug. Table I shows the continuous release of dexamethasone from the film over an eight hour period. Table II indicates the delivery rate of dexamethasone from the aerosol container. Approximately 1.5 g/sec of formulation is delivered so that a two second spray delivers approximately 0.03 grams of dexamethasone to the desired site.

TABLE I

IN VITRO RELEASE OF DEXAMETHASONE FROM

SPRAY-ON BANDAGE*

Time Hours	Uncorrected Concentration (mcg/ml)	"A" Corrected concentration (mcg/ml)	A/15.904 (mcg/cm^2)	A_o **-A (mcg/ml)	Log A_o -A
1	9.42	9.42	0.59	37.07	1.57
2	14.69	15.16	0.95	31.33	1.49
3	19.05	20.25	1.11	26.24	1.42
4	22.98	25.14	1.58	21.35	1.33
5.	25.23	28.54	1.79	17.95	1.25
6.	27.73	32.30	2.03	14.19	1.14
7.	30.19	36.14	2.27	10.35	0.99
8.	32.86	40.32	2.54	6.17	0.68

*Represents the average of 5 determinations.

**A_o= inital concentration of 4.5 cm disc = 46.49 mcg/ml
A/15.904 = concentration of drug released at time "t".
A_o-A = concentration of drug remaining in film at time "t".

TABLE II

DELIVERY RATE AND AMOUNT

OF DEXAMETHASONE IN SPRAY-ON BANDAGE*

Dexamethasone	Delivery rate g/sec	Dexamethasone % in film	Weight of Product g/2 sec	Weight of non-volatile film g	Dexamethasone in the remaining film g
Can 1	1.5	11.4	3.00	0.26	0.03
*Can 2	1.6	11.4	3.15	0.28	0.03

*used for the in-vivo tests

The amount of dexamethasone contained in the microencapsulated preparation is given in Table III. After the microencapsulated dexamethasone particles had been prepared and particle sized, the release of dexamethasone from the microcapsules was determined. Table IV shows sieve size No. 100 microcapsules containing approximately 3.2% of dexamethasone released the dexamethasone gradually over 8 hours. Once the delayed drug release pattern was demonstrated for the microcapsules, the aerosol to be used for the in vivo testing was prepared. Table V indicates a delivery rate of about 1.8 g/sec for the aerosol used in the in vivo study.

Six different categories were used for the in vivo studies including the control group, the group treated with the spray-on bandage product, the group treated with the spray-on bandage "blank" product, the group treated with the microencapsulated dexamethasone spray, the group treated with microencapsulated dexamethasone "blank" spray and the group treated with dexamethasone topical cream. Figure 2 illustrates the difference resulting when the mean value for the 17-hydroxycorticosteroid levels is plotted versus time.

After treatment with the dexamethasone preparations, there were scattered increases in the urine level of 17-hydroxycorticosteroids, indicating absorption of the drug; however, a decreased urinary excretion level of this steroid was also obtained after treatment with the dexamethasone preparation. The lack of consistency may be attributed to any of the following: the absorbed

TABLE III

DIRECT TOTAL ASSAY VALUES FOR DEXAMETHASONE MICROCAPSULES

Microcapsules Prepared to Contain Approximately 3-4% Dexamethasone		Microcapsules Prepared to Contain Approximately 7 to 12% Dexamethasone		
Collected on Sieve	Amount Collected mg/g	Amount Collected - mg/g		Average Value mg/g
		Determination 1	Determination 2	
#60	39.7	120.2	116.5	118.3
#80	34.7	107.8	118.9	113.3
#100*	32.2	103.0	97.9	100.4
#200	32.2	85.8	92.9	89.4
#270**	29.7	75.6	71.9	73.7
#325**	34.7	76.8	68.1	72.4

*Used for the In Vitro Test

**Used for the In Vitro Tests on a 50:50 Ratio.

TABLE IV

IN VITRO RELEASE RATES OF DEXAMETHASONE MICROCAPSULES*

Time Hours	Corrected Concentration - mcg/ml				
	Determination 1	Determination 2	Determination 3	Determination 4	Averaged Value for the Corrected Concentration mcg/ml
1	13.0	13.5	14.0	16.0	14.1
2	19.3	20.9	20.9	23.1	21.0
3	26.1	25.8	25.9	28.9	26.6
4	30.4	30.6	30.6	33.8	31.3
5	36.9	35.1	35.1	38.0	36.3
6	39.8	38.8	38.8	41.9	39.8
7	43.2	42.6	43.1	45.9	43.7
8	46.7	46.5	47.1	50.0	47.5
24	55.0	55.5	60.0	56.8	56.8
48	71.0	70.5	72.5	71.4	71.3
72	82.1	81.6	82.2	81.9	82.0

*sieve size #100 and containing approximately 3.2% dexamethasone.

TABLE V

DELIVERY RATE AND AMOUNT OF DEXAMETHASONE MICROCAPSULES IN SPRAY-ON BANDAGE*

Microencapsulated Dexamethasone	Delivery rate g/sec	Dexamethasone % in concentrate	Weight of product g/ 2 sec.	Weight of non-volatile residue remaining g	Weight of microcapsules remaining in residue g	Dexamethasone in the microcapsules left in the residue mg.
Can 1**	1.8	73.2	3.68	0.754	0.551	40.3
Can 2	1.9	73.2	3.89	0.797	0.583	42.6

*microcapsules used contain approximately 7.3% dexamethasone

**used for the *in vivo* tests

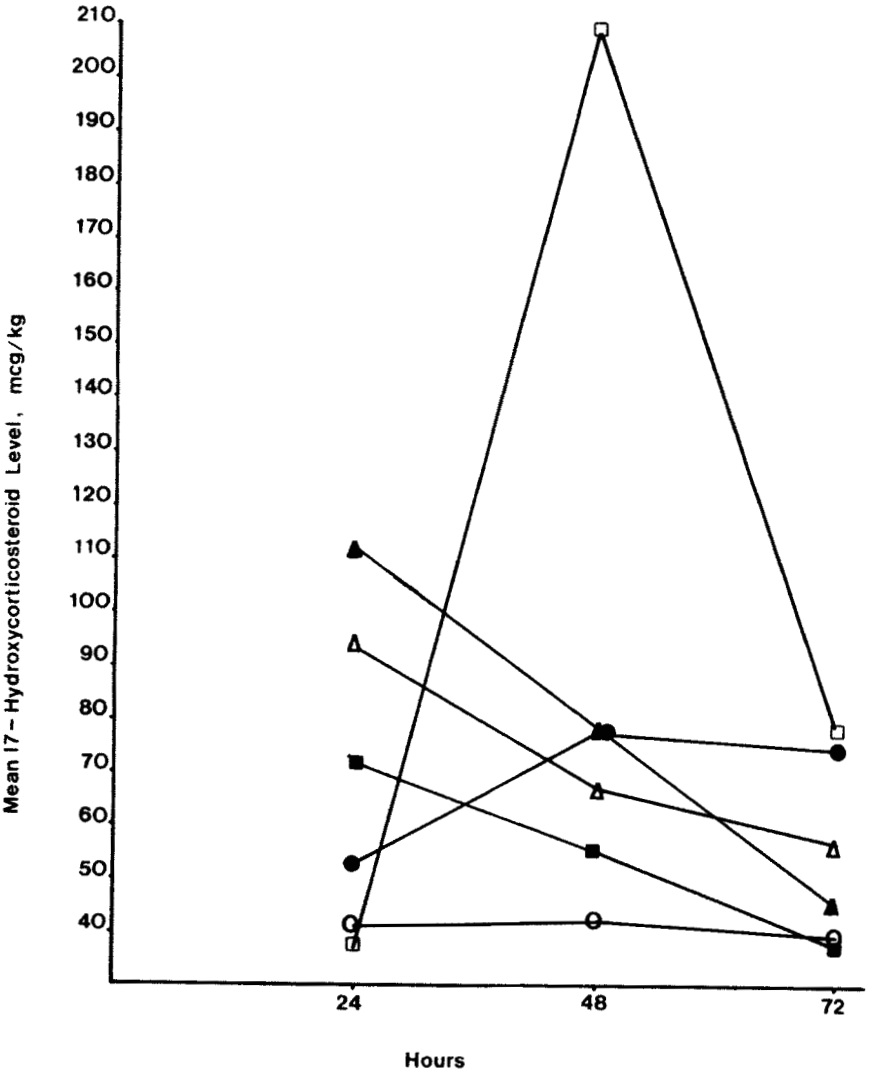

FIGURE 2

Mean 17 - Hydroxycorticosteroid Levels in Rabbit Urine.

KEY: □, Spray-on bandage; ▲, Spray-on bandage/blank; ●, Control; △, Microencapsulated dexamethasone; ■, Dexamethasone cream; O, Microencapsulated/blank

dexamethasone could cause a partial shutdown of adrenal activity (18); the animal could have a low state of activity with decreased skin circulation and drug absorption (19); a decrease could reflect a lower output of urine (20); or the values could reflect systemic absorption and not the actual skin absorption (19).

In order to determine if absorption did occur, a probability of $p = < 0.05$ was chosen to be the statistically significant cutoff value when students' "t" Test for paired data was evaluated (Table VI). No change in the 17-hydroxycorticosteroid levels was seen during the 72 hour period in the control group of rabbits.

Table VI shows the results of the "t" test when comparisons were made between control rabbits, between treated rabbits and on the difference between the five (5) treatments and the control group. The results listed under "A" concerns the 17-hydroxycorticosteroid concentration (mcg/kg) and is the difference within the group of animals being treated at that particular time. The results listed under "B" deals with the difference on a percentile basis between the values from the experimentally treated group and the control group. In essence, the values listed under "A" deal with the changes within the group while the values listed under "B" deal with the difference between the groups.

After treatment with the dexamethasone spray-on bandage there was no change within the group; however, there was a difference in the 17-hydroxycorticosteroid levels between this treated group and the control group, indicating that absorption did occur after treatment with this aerosol. When treated with the corresponding "blank" of this formulation,

TABLE VI

EVALUATION OF STUDENT "t" TEST, PAIRED DATA

Type of Treatment	0 Hour	24 Hour	48 Hour	72 Hour	Level of Probability P=
Control Group:					
A*	--	NS (P = .51)	NS (P = .65)	NS (P = .70)	> .25
Spray-On Bandage		NS	NS	NS	
A*	--	(P = .70)	(P = .80)	(P = .75)	> .15
B**	--	S (P =.995)	S (P = .95)	S (P = .99)	< .01
Spray-On Bandage Blank:					
A*	--	NS (P = .90)	NS (P = .75)	NS (P = .50)	.05
B**	--	NS (P = .85)	NS (P = .75)	NS (P = .70)	> .10

Microencapsulated Dexamethasone Spray:					
A*	--	S (P = .98)	S (P = .95)	S (P = .95)	< .01
B**	--	NS (P = .90)	NS (P = .90)	NS (P = .85)	.05
Microencapsulated Dexamethasone Blank Spray:					
A*	--	NS (P = .53)	NS (P = .55)	NS (P = .50)	> .40
B**	--	NS (P = .80)	NS (P = .80)	S (P = .95)	< .03
Decadron Topical Cream					
A*	--	NS (P = .90)	NS (P = .80)	NS (P = .60)	.05
B**	--	NS (P = .90)	NS (P = .80)	NS (P = .90)	.05

*Refers to 17-Hydroxycorticosteroid Concentration in mcg/kg

**Refers to % Change Experimental vs. Control Group
NS=Not Significant
S=Significant

no change within the group and no difference in the 17-hydroxycorticosteroid levels between this group and the control group was observed. Absorption did occur after treatment with the spray-on bandage product.

After treatment with the microencapsulated dexamethasone spray, there was a change within the group indicating that the animals did not all react similarly. Closer examination revealed no difference in the 17-hydroxycorticosteroid levels between the treated and the control groups. After a two second spray, 31.5 mg of dexamethasone from the spray-on bandage formula was deposited on the animal's back while a comparable two second spray left 40.3 mg of dexamethasone from the microencapsulated product deposited by the latter, no absorption occurred. Though the *in vitro* testing showed delayed release of dexamethasone from the microcapsules, the *in vivo* tests showed that absorption did not occur. It is possible that drug release was not adequate to produce significant results or that the composition of the aerosol concentrate interfered with the release. There were no changes within the group after treatment with the corresponding "blank" aerosol. For the 24 and 48 hour intervals after treatment with the "blank" product, no difference in the 17-hydroxycorticosteroid levels between this group and the control was noticed, but there were differences at 72 hours. The difference could reflect animal stress which increased ACTH cortisol production (21).

After treatment with the dexamethasone cream, no difference was noted in the 17-hydroxycorticosteroid levels

between the treated and control group. Since the amount of dexamethasone in this cream (35.9 mg/g) is comparable to the average amount of dexamethasone in the other two formulations, it is probable that the spray-on bandage product produced the best results with the in vivo test system.

After examination of all the data, no absorption of dexamethasone from any of the prepared formulations or the commercial cream occurred with the exception of the spray-on bandage aerosol, where absorption was observed.

CONCLUSION

The formulation of two difference topical dexamethasone aerosol preparations were studied for their release of active ingredient. Both in vivo and in vitro studies were conducted and the release of dexamethasone from these formulations was compared.

Ethylcellulose was chosen as the film-former for the in vitro tests. Once the in vitro studies showed that dexamethasone was steadily released from the drug film over a period of hours, an aerosol was prepared in which the concentrate accounted for 15% w/w of the total while propellant 12/114 (40:60) accounted for 85% w/w of the formulation, producing a quick drying film. Dexamethasone microcapsules were prepared and subsequent in vitro studies on the microcapsules showed continuous release over a period of hours. An aerosol containing approximately 7.3% of the active ingredient was prepared using isopropyl myristate and fumed silica in the propellant blend.

The aerosols were sprayed onto the intact skin of rabbits and assays were performed to determine the 17-hydroxycorticosteroid urine levels.

Evaluation of the data obtained from the in vivo studies indicated that the dexamethasone from the spray-on bandage preparation was absorbed over a 72 hour period. No absorption occurred with the timed release preparation, however.

To evaluate the release rate, the preparations were compared to a commercial dexamethasone cream using the same in vivo test model. Evaluation of the data showed that absorption of dexamethasone did not occur. The in vivo testing showed the spray-on bandage was the only formulation which produced drug absorption.

REFERENCES

1. W. Lange and V. Fang, J. Soc. Cosmet. Chem., 16, 563 (1965).
2. W. Lange and V. Fang, ibid., 17, 115 (1966).
3. R. Fischl, Plast. Reconstruct. Surg., 30, 607 (1962).
4. S. Bhaskar and D. Cutright, J. Dent. Res., 48, 294 (1969).
5. J. Sciarra and R. Gidwani, J. Soc. Cosmet. Chem., 21, 667 (1970).
6. J. Sciarra and R. Gidwani, J. Pharm. Sci., 61, 754 (1972).
7. J. Sciarra and S. Patel, J. Soc. Cosmet. Chem., 23, 605 (1972).
8. M. Luongo, J. Sciarra and C. Ward, J. Pharm. Sci., 63, 1376 (1974).
9. L. Luzzi, ibid., 59, 1367 (1970).
10. R. Phares and S. Sperandio, ibid., 53, 515 (1964).

11. L. Luzzi and R. Gerraughty, ibid., 53, 429 (1964).

12. E.L. Rowe, U.S. Patent 3,336,155.

13. W. Feinstein and J. Sciarra, J. Pharm. Sci., 64, 408 (1975).

14. D. Wurster and P. Taylor, ibid., 54, 670 (1965).

15. "CSMA Aerosol Guide", 6th Ed., Chemical Specialties Manufacturers Association, New York, N.Y. 1971, p. 75.

16. "National Formulary", 14th Ed., American Pharmaceutical Association, Washington, D.C., 1975, p. 1033.

17. "The United States Pharmacopeia", 19th Ed., Mack Publishing Company, Easton, Pa., 1975, p. 763.

18. P. Burch and C. Migeon, Arch. Ophthal., 79, 174 (1968).

19. R. Levine, "Pharmacology: Drug Actions and Reactions", Little, Brown and Co., New York, N.Y., 1975, pp. 74-88.

20. J. DiPalma, "Basic Pharmacology in Medicine", McGraw Hill Book Co., New York, N.Y., 1976, p. 333.

21. G. Thorn, "Steroid Therapy - A Clinical Update for the 1970's", Medcom, Upjohn Co., Kalamazoo, Mich., p. 9.

Received January, 1981 from the Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University at University Plaza, Brooklyn, New York 11201

Presented at the American Pharmaceutical Association Annual Meeting, Academy of Pharmaceutical Sciences, Industrial Pharmaceutical Technology Section, Anaheim, CA., April 25, 1979.

Abstracted in part from a dissertation submitted by M. Luongo to the Graduate Faculty, College of Pharmacy and Allied Health Professions, St. John's University, in partial fulfillment of the Doctor of Philosophy degree requirements, January, 1977.