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DISSOLUTION RATES OF PREDNISOLONE TRITURATIONS USING POROUS AND NON-POROUS SILICAS. I. PILOT ORAL ABSORPTION STUDY IN DOGS

A.N. Narurkar and C.I. Jarowski
St. John's University, College of Pharmacy and Allied Professions, Jamaica, New York, 11439

ABSTRACT

Prednisolone:Silica triturations were prepared with 5 grades of silicas by ball-milling and solvent deposition. Drug:Silica ratios ranged from 1:0.11 to 1:19. Dissolution rates in simulated intestinal juice were greatest for the 1:0.11 triturations prepared by solvent-deposition. Oral absorption efficiency of prednisolone in dogs was similar whether administered as porous or non-porous silica triturations.

INTRODUCTION

Silicas are extensively used in the production of a large number of pharmaceutical dosage forms[1]. They have been proposed as carriers for enhancing the dissolution rates of slightly soluble drugs[2-4]. There is, however, very little information on the absorption efficiency of drugs from drug:silica triturations.

This study was initiated to evaluate the effects of three porous and two non-porous silicas on the dissolution rate of prednisolone. The silicas selected differ

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TABLE 1

Structural Parameters of the Various Silicas Used for the Incorporation of Prednisolone

Type	Surface Area (m^2/gm)	Particle Size (microns)	Av. Pore Diameter (A^o)	Bulk Density (lb/ft^3)	Silanol Groups per 100 A^2 Surface Area	R*	pH** 5%(w/w) Aqueous Suspension in Water
S-I (porous)	675	9	20	29	4 - 6	1.46	4.1
S-II (porous)	340	4	150	11	4 - 6	1.46	6.6
S-III (porous)	310	4	200	7	4 - 6	1.46	7.6
S-IV (non-porous)	390	0.007	—	2.3 max	3	1.46	3.5 - 4.2
S-V (non-porous)	380	0.007	—	2.5-3.5	3	1.46	3.6 - 4.3

Note: The above data was obtained from the supplier's information bulletins.

* Refractive index

** Aqueous suspension of the silicas.

from one another in surface area, particle size, pore volume, pore diameter, bulk density, silanol groups and surface pH (Table 1).

The triturations will be prepared by dispersing prednisolone on the surface of the silicas by solvent-deposition and ball-milling techniques. Selected drug: silica triturations exhibiting rapid *in vitro* dissolution will be evaluated in dogs to check their oral absorption efficiency.

EXPERIMENTAL

Materials

The following were obtained from commercial sources: Syloid 63 (S-I, amorphous silica, Davison Chemical Co., Baltimore, Md.), Syloid 72 (S-II), Syloid 244 (S-III), Cab-O-Sil EH-5 (S-IV, non-porous silica, Cabot Corp., Boston, Mass.), Aerosil 380 (S-V, Degussa Inc., Pigments Division, New York, N.Y.), anhydrous prednisolone, USP (Merck & Co., Inc., Rahway, N.J.), methanol, HPLC Grade (U.S. Industrial Chemicals Co., New York, N.Y.), ethanol, SDA-3A, toluene (Burdick & Jackson Laboratories Inc., Muskagon, Mich.), methylene chloride (Eastman Kodak Co., Rochester, N.Y.), sodium hydroxide pellets (A.R. grade, Fischer Scientific Co., Fairlawn, N.J.), sulfuric acid, glacial acetic acid, phenylhydrazine hydrochloride, pH 4 and pH 7 phosphate buffer (Beckman Instrument Co., Inc., Fullerton, California).

Equipment

The following were used: spectrophotometer, model 240 (Gilford Instrument Laboratories, Inc., Oberlin, Ohio), spectrophotometer, model 25 (Beckman Instrument Co., Inc.), analytical balance, model 33 (Mettler Instrument Corp., Hightstown, N.J.), pH meter (Corning Glass Works, Corning, N.Y.), constant temperature bath (Precision Scientific Co., Chicago, Ill.), dissolution

apparatus, USP (Hanson Research Corp., Northridge, Cal.), jarmill, 10.16 cm diameter with 1.27 cm diameter porcelain balls (Abbe Engineering Co., New York, N.Y.), U.S. standard sieve, 60-mesh (Newark Wire Cloth Co., Newark, N.J.), millipore filter paper, 0.45 micron porosity (Millipore Corp., Bedford, Mass.), multiple developing tank (Desega, Heidelberg, West Germany), thin-layer chromatography plates precoated with microcrystalline cellulose (thickness 250 microns, Analtech Inc., Newark, Del.) and a colorimeter (The Perkin-Elmer Corp., Norwalk, Conn.).

Preparation of Prednisolone:Silica Triturations

Prednisolone:Silica triturations were prepared in weight ratios ranging from 1:0.11 to 1:19 by solvent-deposition and ball-milling procedures previously described by Yang *et al*[4]. Among the range of samples prepared were weight ratios calculated to produce monomolecular and bimolecular layers of drug (Table 2).

Spectrophotometric Absorption and Calibration Curves

Calibration curves for prednisolone in simulated intestinal fluid (without pancreatin) and in methyl alcohol at wavelengths of maximum absorbance at 244 nm and 242 nm, respectively, obeyed Beer's Law.

Assay of the Prednisolone:Silica Triturations

The various samples were extracted with methanol. The extracts were centrifuged at 2500 rpm for 5 min. The supernatants were decanted and the residues were further treated in a similar manner three times with 5 ml of methanol. After dilution with methanol, the absorbance was determined spectrophotometrically and the concentration was determined from the calibration curve. Only those samples containing 100 $\pm$ 5% of the required amount of prednisolone were used in the dissolution studies. Replicate assays were conducted.

TABLE 2

Selected Ratios of Prednisolone:Silica Based on Theoretical Surface Areas*

Grades of Silica	Surface Area (m^2/gm)	Pore Diameter (A^o)	Ratio Drug:Silica	Type of Trituration
S-I	675	20	1:1.47	Monomolecular Layer
			1:2.94	Excess Silica
			1:0.74	Bimolecular Layer
S-II	340	150	1:2.92	Monomolecular Layer
			1:1.46	Bimolecular Layer
S-III	310	200	1:3.21	Monomolecular Layer
			1:1.60	Bimolecular Layer
S-IV	390	—	1:2.55	Monomolecular Layer

* Based on the true density of prednisolone (1.30) and its molecular weight (360.5) the weight of prednisolone needed to form a monomolecular layer on the silica surface was calculated as follows:

Number of molecules in 1 $cm^3 = \frac{1.30}{360.5} \times 6.02 \times 10^{23} = 0.0217 \times 10^{23}$

Number of molecules in 1 $cm^2 = (0.0217 \times 10^{23})^{2/3} = 1.68 \times 10^{14}$

Since 1 cm = 10^8 A^o, then 1 $cm^2 = 10^{16}(A^o)^2$

The area covered by 1 prednisolone molecule = $\frac{1}{1.68 \times 10^{14}} = 5.95 \times 10^{-15}$ cm^2

The area in $(A^o)^2 = 59.5$ $(A^o)^2$/molecule. Since 1 $m^2 = 10^{20}$ $(A^o)^2$ the area covered by 1 gram of prednisolone can be calculated to be 994 m^2. If one assumes that all the area is available then 1.47 gm of S-I is needed for the formation of a monomolecular layer.

Assay of Prednisolone in Dog Plasma

The assay procedure followed has been accepted[5].

In Vitro Dissolution Studies

The rates of dissolution in simulated intestinal fluid were determined by the USP basket method at 37 ± 0.5°C. at a stirrer speed of 100 rpm under sink conditions[6]. Aliquots withdrawn for assay were filtered through a millipore filter, diluted appropriately and assayed spectrophotometrically. Replicate experiments were conducted.

Protocol for Oral Administration to Dogs

Two mongrels which had been conditioned 40 - 60 days were used in the initial evaluation. Each dog was treated as its own control. Two beagles were used for the final evaluation. The dogs were fasted for 12 hrs. prior to oral administration, but water was made accessible. Water was removed 2 hrs. before initiation of the study and was withheld throughout. A minimum of 2 weeks was allowed to elapse before using the animals for the second dosing. Blood specimens were collected from the external jugular vein. Hard gelatin capsules containing 60 mg equivalent of prednisolone were put on the posterior portion of the tongue to avoid their being chewed before being swallowed. Blood samples were taken at intervals of 1, 2, 3, 4, and 6 hours. They were placed in heparinized tubes and centrifuged at 2500 rpm for 15 min. The plasma samples were stored in the frozen state until they were assayed.

RESULTS AND DISCUSSION

On the basis of the curves in Figure 1 it is apparent that the ball-milled samples of prednisolone:S-I showed the slowest rates of dissolution. Prednisolone dissolution rates for the samples prepared by solvent-

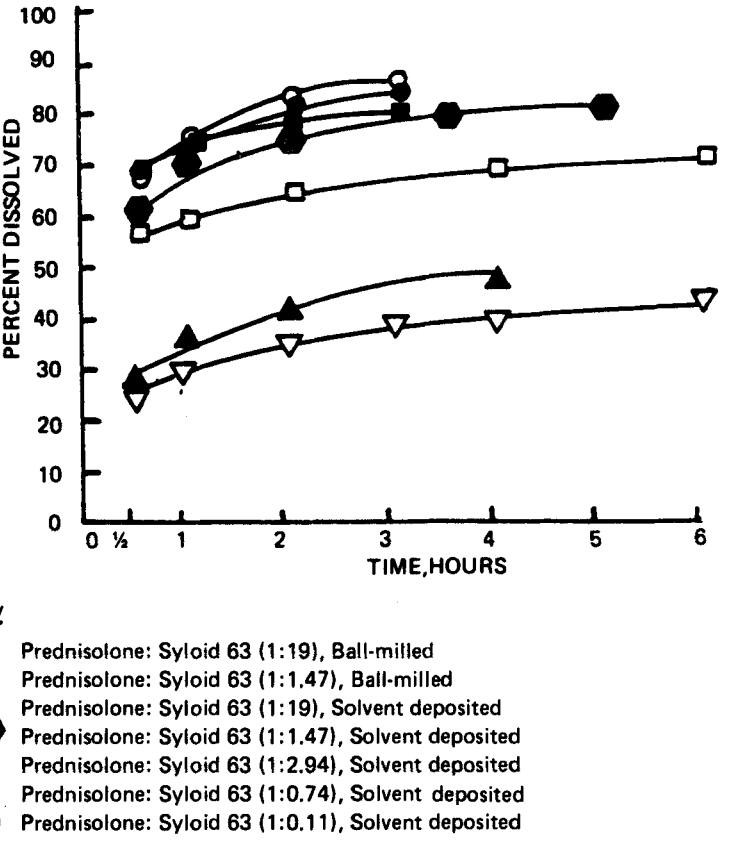

Figure 1: Dissolution rates of solvent deposited and ball-milled Prednisolone:Syloid 63 triturations in simulated intestinal fluid (pH 7.4) at 37°C.

deposition on S-I decreased in the following order: 1:0.11, 1:0.74, 1:1.47, 1:2.94, 1:19. These findings with porous silica triturations are in agreement with Monkhouse and Lach[2] who showed that the dissolution rates of the drugs they studied were minimally improved with concentrations of non-porous silica greater than 10%. These authors theorized that a monomolecular layer was formed when 10% silica was used. Our calculations, however, indicate that a monomolecular layer requires a higher concentration.

TABLE 3

Dissolution Data for Selected Prednisolone:Silica Triturations in Simulated Intestinal Fluid Expressed as the Parameters of Apparent 1st Order Kinetics

Ratio of Prednisolone:Silica for a Monomolecular Layer				Method of Preparation	k ($\times 10^{-1}$/hr)	t_{90} (hours)
S-I	S-III	S-IV	S-II			
1:1.47				ST*	1.8	13.1
1:1.47				BM**	0.9	25.4
	1:3.21			ST	1.1	21.4
	1:3.21			BM	1.7	13.9
		1:2.55		ST	2.4	9.4
		1:2.55		BM	1.5	15.0
			1:2.92	ST	0.9	24.6
			1:2.92	BM	3.2	7.2

* Solvent-deposition.

** Ball-milled.

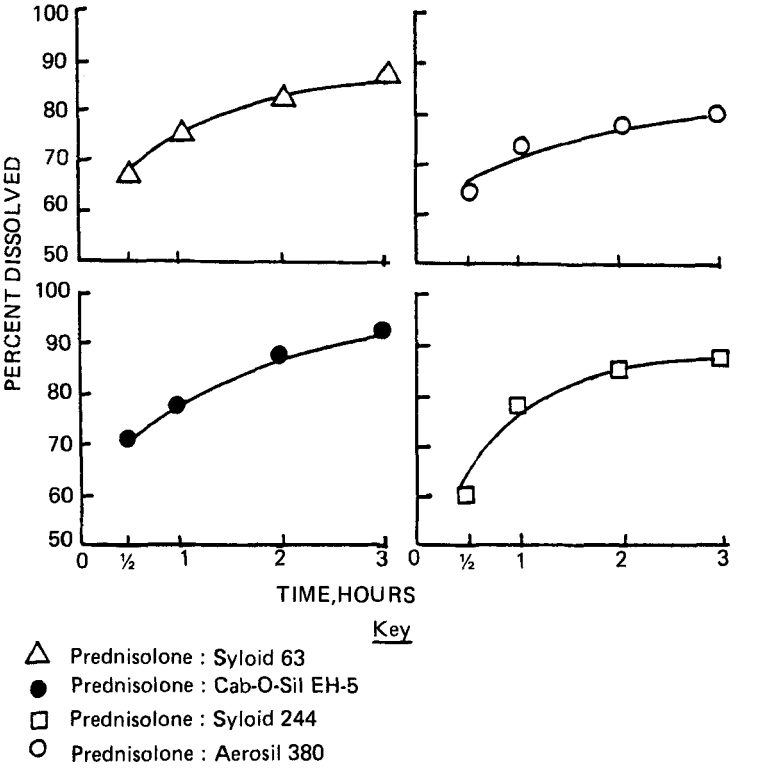

Figure 2: Comparative study of dissolution rates of solvent deposited Prednisolone-Silica triturations (1:0. 11) in simulated intestinal fluid (pH 7.4) at 37°C.

In Table 3 the prednisolone:silica dissolution rate constants and t_{90} values for drug:silica weight ratios calculated to have the prednisolone dispersed as a monomolecular layer. All these samples have t_{90} values much greater than those for triturations containing weight ratios of drug:silica of 1:0.11 (Figure 2).

As can be seen in Figure 2 the dissolution rate of prednisolone was most rapid when it was solvent-deposited on S-IV (92% in 3 hours) or on S-I (87% in 3 hrs.). As a consequence these two candidates were selected for an oral absorption study in dogs as compared with solvent treated bulk prednisolone. The latter exhibited 85% dissolution in 3 hours.

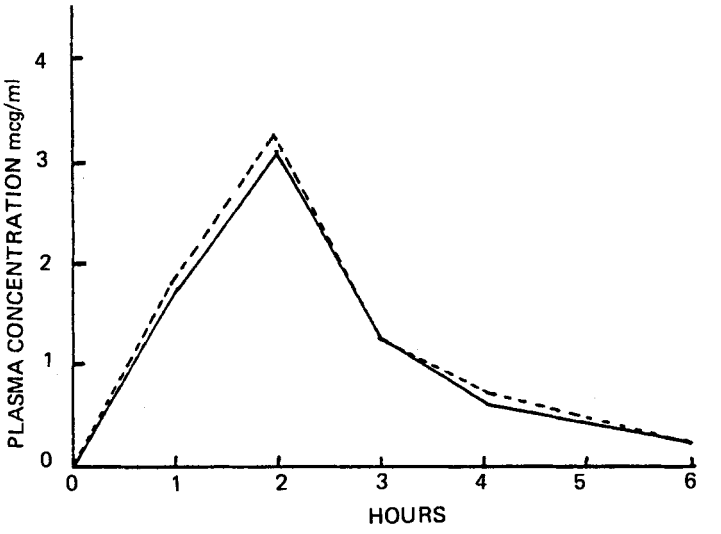

FIGURE 3. Concentration of prednisolone in the plasma of adult beagle dog No. 1 after oral administration of 60 mg of prednisolone equivalent. Key:—— Drug:S-I (1:0.11); --- Drug:S-IV (1:0.11).

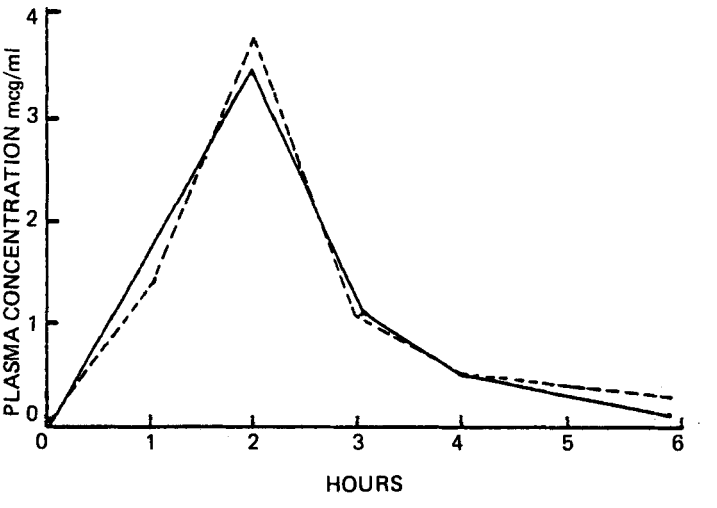

FIGURE 4. Concentration of prednisolone in the plasma of adult beagle dog No. 2 after oral administration of 60 mg of prednisolone equivalent. Key:—— Drug:S-IV (1:0.11); --- Drug:S-I (1:0.11).

TABLE 4

Prednisolone Pharmacokinetic Parameters After Doses of 60 mg Were Administered to Male Mongrel Dogs

Sample	Time Interval	C_{max} (mcg/ml)	t_{max} (hrs)	$t_{1/2}$ (hrs)	A*
Dog No. 1 (15.5 kg)					
Prednisolone:S-I (1:0.11, solvent deposited)	1st Run	3.62	2	2.70	9.9
Prednisolone (solvent treated)	2 weeks	1.80	4	—	5.8
Prednisolone:S-I (1:0.11)	4 weeks	3.00	2	1.81	9.5
Dog No. 2 (13 kg)					
Prednisolone:S-IV (1:0.11, solvent deposited)	1st Run	2.38	2	2.94	7.3
Prednisolone (solvent treated)	2 weeks	1.82	4	—	5.8
Prednisolone:S-IV (1:0.11)	4 weeks	2.22	2	0.95	5.9

A* = area under the Concentration-Time curve (0 to 6 hours, units = mcg hour/ml)

TABLE 5

Prednisolone Pharmacokinetic Parameters After Doses of 60 mg Were Administered to Male Beagle Dogs

Dog No. 1 (9 kg)					
Prednisolone:S-I (1:0.11, solvent deposited)	1st Run	3.50	2	0.97	6.7
Prednisolone:S-IV (1:0.11, solvent deposited)	2 weeks	3.75	2	1.44	7.3
Dog No. 2 (10.6 kg)					
Prednisolone:S-IV (1:0.11, solvent deposited)	1st Run	3.12	2	1.13	7.3
Prednisolone:S-I (1:0.11, solvent deposited)	2 weeks	3.30	2	1.28	7.7

Plasma concentrations versus time are shown in Figures 3 and 4. Pharmacokinetic parameters for the dog plasma data are shown in Tables 4 and 5. It is evident that S-I and S-IV are equally good silicas upon which to solvent-deposit the prednisolone insofar as oral absorption efficiency is concerned.

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