Dissolution Rates of Corticosteroids Utilizing Sugar Glass Dispersions

LOYD V. ALLEN, Jr. ˣ, VICTOR A. YANCHICK *, and DALE D. MANESS *

Abstract □ A method of increasing the dissolution rates of some orally administered corticosteroids was investigated. This method involved glass dispersions using dextrose, galactose, and sucrose as the carriers. These dispersions were prepared by the fusion process and were subjected to a modified NF XIII dissolution rate determination. The results revealed a marked increase in the dissolution rate of the corticosteroids contained in the solid dispersions when compared to the dissolution rate of the plain corticosteroid powder. The increase in dissolution rates was attributed to the presence of the corticosteroid in a very fine state of subdivision and to the increased wettability of the corticosteroid powder.

Keyphrases □ Corticosteroids, various—glass dispersions using sugar carriers, dissolution rates compared to plain powder □ Glass dispersions—various corticosteroids, sugar carriers, dissolution rates compared to plain powder □ Dissolution rates—various corticosteroids, glass dispersions using sugar carriers compared to plain powder □ Sugars—dextrose, galactose, and sucrose as carriers in glass dispersions of various corticosteroids, dissolution rates compared to plain powder □ Solid-state dispersions—various corticosteroids, sugar carriers, dissolution rates compared to plain powder

In 1961, Sekiguchi and Obi (1) introduced a unique approach of utilizing solid dispersions to reduce the particle size of drugs and to increase their dissolution and absorption rates. They proposed the formation of a eutectic mixture of a poorly soluble drug, such as sulfathiazole, with a physiologically inert, easily soluble carrier, such as urea.

The possibility of using a solid solution approach in which a drug is molecularly dispersed in a soluble carrier was subsequently introduced (2, 3). A series of reports (4–7) presented a detailed discussion of the advantages of the solid solution over the eutectic mixture.

A method was reported for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers, *e.g.*, povidone (8). The dissolution rate of griseofulvin was enhanced markedly when dispersed in povidone by the same solvent method (9). The term "solid-state dispersions" was used to refer to these solid dispersions. The mechanisms of increased dissolution rates of drugs solid dispersed in povidone carriers were reviewed (10). Additional studies supported the significance of the solid dispersion technique (11–19).

The concept of glass solutions was introduced recently to increase dissolution rates (14). This concept also was discussed in an extensive review of the pharmaceutical applications of solid dispersions (20). In this investigation, when a melt of a griseofulvin–citric acid mixture, which was highly viscous, was solidified, it was transformed into a glassy state. This glassy state, or glass solution, exhibited a very rapid dissolution rate with griseofulvin. The glass dispersion technique was used successfully with sulfabenzamide (21).

The corticosteroids are considered to be generally poorly water soluble and have demonstrated unpredictable dissolution rates (22–27). Polyethylene glycol solid dispersions were used to increase the dissolution rates of prednisolone acetate and hydrocortisone acetate (15). The purpose of this investigation was to apply the glass dispersion technique to alter the dissolution rates of several orally administered corticosteroids, *e.g.*, betamethasone acetate, cortisone acetate, hydrocortisone acetate, methylprednisolone acetate, prednisolone, and prednisone. Conceptually, this method could result in increased and more predictable dissolution rates, benefiting the therapeutic response.

EXPERIMENTAL

It was desired to use nontoxic, physiologically acceptable carriers that possessed no significant therapeutic effects and had melting points less than or close to the melting points of the corticosteroids used. The latter was considered a requirement since the corticosteroids melt with some decomposition. The use of sucrose and dextrose as glass-forming substances was discussed (14) and, upon investigation, galactose also was found to form a glass upon rapid cooling from a melt. These three sugars also met the other listed criteria.

Preparation of Dispersion Systems—All dispersion systems were prepared by the fusion method as follows. A suitable amount of the drug–carrier mixture [in a ratio containing 6 mg of betamethasone acetate or methylprednisolone acetate added to 200 mg of the carriers (sugars), or 5 mg of each of the other corticosteroids added to 200 mg of the carriers] was weighed and placed in a preformed aluminum foil boat, 7 cm in diameter and 2 cm in depth. The materials were mixed thoroughly and placed on a wire screen positioned on a preheated electric heating plate. Heat was applied with constant stirring until a melt was obtained.

This melt was heated further to the following temperatures: dextrose carriers, 185°; galactose carriers, 169°; and sucrose carriers, 200°. This melt was rapidly solidified by placing the boat containing the melt on a hollowed out portion of a block of dry ice. After solidification, the dispersion system was quickly removed from the dry ice to prevent water condensation and placed in a glass desiccator containing a drying agent where it was stored for 24 hr at 37°.

The solid was pulverized to the desired particle size, and the 60–100-mesh fraction (250–150-μm particle size) was collected by standard sieves[1] placed on a sieve shaker[2] and shaken for 5 min. The powder was then placed in an amber, screw-capped glass vial and stored in a desiccator at 25°. The plain corticosteroids used as the controls possessed a particle size of 250–150 μm (60–100-mesh fraction).

Dissolution Rate Determinations—The dissolution rate determinations were carried out using a modified NF XIII dissolution rate apparatus (23).

An appropriate amount of the dispersion system, containing 6 mg of betamethasone acetate or methylprednisolone acetate or 5 mg of the other corticosteroids, was weighed and placed in the basket of the dissolution apparatus. This amount was used because it allowed absorption within the 0.2–0.8 range on a spectrophotometer[3] (all corticosteroids followed Beer's law throughout the concentration ranges used). A thin circular piece of clear plastic was fitted at the bottom of the dissolution basket to prevent the powder from falling out. The temperature and sample flow rate were established, and the basket was lowered into 1000 ml of the dissolution medium (deionized water) to a point 2 cm from the bottom of the kettle and rotated at a constant speed of 100 rpm. There was a lag time of about 4 sec for the sample to reach the flowcell, and a complete circuit required about 10 sec.

As the dispersion system dissolved, the concentration of the corticosteroid in solution was monitored and recorded with a chart recorder[4].

[1] Sargent-Welch Scientific Co., Skokie, Ill.
[2] W. S. Tyler, Inc., Mentor, Ohio.
[3] Beckman DB, Beckman Instruments, Fullerton, Calif.
[4] Beckman Instruments, Fullerton, Calif.

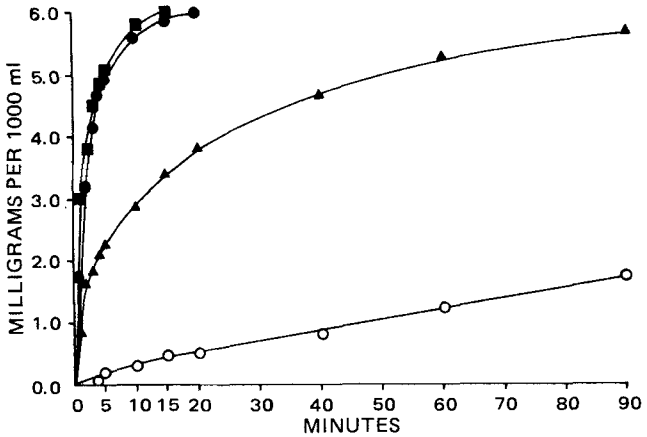

Figure 1—*Dissolution rates of betamethasone acetate. Key:* ○, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

The determinations were made for 90 min and were done at least in duplicate. The wavelengths of maximum absorption used were determined experimentally in aqueous solutions and were: betamethasone acetate, 239 nm; cortisone acetate, 238 nm; hydrocortisone acetate, 243 nm; methylprednisolone acetate, 243 nm; prednisolone, 242 nm; and prednisone, 239 nm. These substances followed Beer's law in the concentration range used.

Short-Term Stability Study—A short-term stability study was performed by storing the powdered dispersion systems at 25° for 30 days and repeating the dissolution rate determinations described.

Corticosteroid Stability Studies—The chemical stability of the corticosteroids during the preparation of the dispersion systems was studied using TLC. Chromatogram sheets[5] were spotted with an aqueous solution of the respective dispersion systems and a methanol solution of the reference corticosteroids. The sheets were allowed to dry at room temperature and placed in a chamber containing chloroform–ether–methanol (6:3:1). The plates were removed, air dried, and visualized under UV light. UV scans of the dispersion systems in deionized water also were obtained before and after preparation of the dispersion systems.

RESULTS

Glass Formation—Dextrose, galactose, and sucrose formed glasses quite readily. Dry ice was used to hasten solidification of all melts so that the systems would not be exposed to atmospheric moisture and contamination longer than necessary. The corticosteroids were not necessarily completely miscible with the carriers in the glass systems because of the generally lower temperatures used in their preparation. Complete melting was not attempted in these cases because of decomposition of the sugars and the corticosteroids at the high temperatures that would be required. All systems were relatively easy to prepare. The glass dispersion systems were hygroscopic and, as such, required storage in a desiccator.

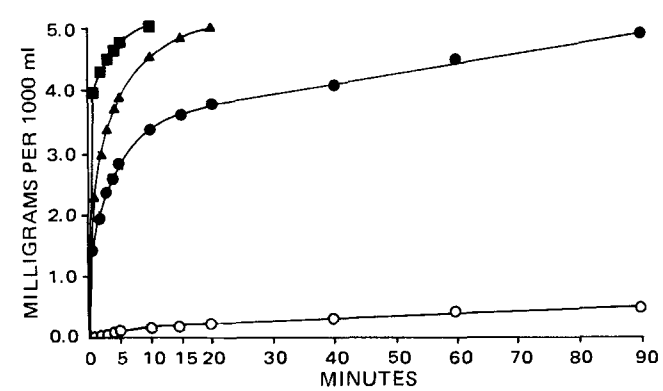

Figure 2—*Dissolution rates of cortisone acetate. Key:* ○, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

[5] Eastman Chromagram Sheets, Eastman Kodak Co., Rochester, N.Y.

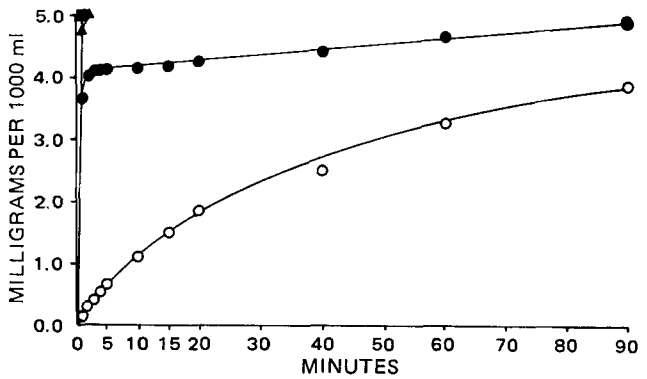

Figure 3—*Dissolution rates of hydrocortisone acetate. Key:* ○, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

Dissolution Rate Determinations—As shown in Figs. 1–6, the dissolution rate determinations revealed marked increases in the dissolution rates of all corticosteroids utilizing all three sugar carriers. The dextrose and sucrose glass dispersions possessed the fastest release characteristics for 50 and 100% dissolution (Table I).

Samples of the glass dispersions prepared at different times reproduced these results. The glass dispersion samples assayed after storage for 30 days showed no decrease in the dissolution rates. These amorphous systems may recrystallize upon aging for a longer time. One would expect that a return to the crystalline state would result in a decrease in the dissolution rate of the system. The time required for these systems to return to the crystalline state has not been determined.

Stability of Components—None of the corticosteroids demonstrated any decomposition products after being subjected to the preparation of the dispersion systems according to the analytical methods used. TLC revealed no additional spots, and there was good correspondence with the reference samples. UV spectra of the dispersion systems in deionized water revealed no decomposition products, and the absorbance values were unchanged.

A light-amber discoloration of the melt and of the cooled glass was observed during the dextrose and sucrose glass formation process, possibly indicating slight decomposition of these sugars. This color change did not appear to interfere with the fast release characteristics of the carrier.

DISCUSSION

The dissolution of these powders occurred in two phases: a very rapid initial phase followed by a slower, more prolonged, second phase. The rapid initial rate was attributed to the release of the corticosteroid present in a state of very fine subdivision. With the glass dispersion, a portion of the corticosteroid probably is solubilized during preparation by the molten carrier. Since this melt quickly solidifies, crystallization would be retarded because of the high viscosity of the melt and the very short time interval required for solidification. When this portion of the dis-

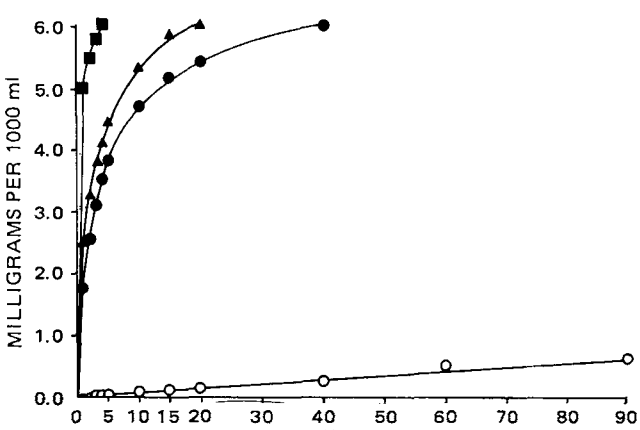

Figure 4—*Dissolution rates of methylprednisolone acetate. Key:* ○, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

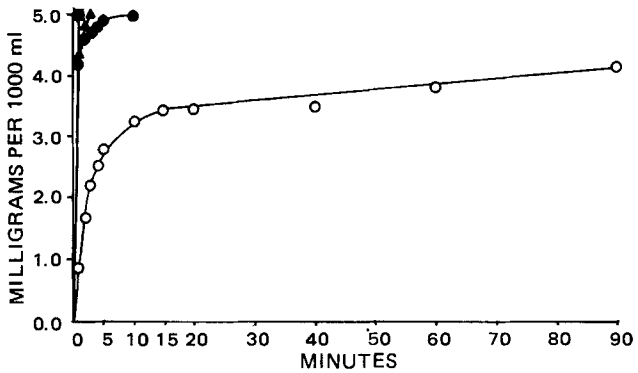

Figure 5—*Dissolution rates of prednisolone. Key:* O, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

persion system is exposed to the aqueous medium, the corticosteroid would immediately be released in its molecular state.

The second phase of dissolution, exhibited by most systems, was the more prolonged phase. The dissolution rates of the second phase of the glass dispersions were somewhat more rapid than that of the plain powder. This difference can be attributed to the increased wettability of the corticosteroid powders. Glass carriers may act similarly to wetting agents, as follows.

It is frequently difficult to disperse a finely divided powder in a liquid because of entrapped or adsorbed air or some other contaminant. When a strong affinity exists between a liquid and a solid, the liquid easily forms a film over the surface of the solid. However, when this affinity is nonexistent or weak, the liquid has difficulty displacing the air or other substances surrounding the solid. The sugars used in this investigation are readily soluble in an aqueous medium. During the preparation of the dispersion system, intimate contact was achieved between the sugar and the corticosteroid particles. The high temperatures involved in the preparation process aided in removing adsorbed and entrapped air. Upon exposure of this system to an aqueous medium, the sugar rapidly dissolved and a complete wetting of the corticosteroid occurred at the same time.

The temperatures reached during the preparation of the melts were greater than the melting points of the sugars but less than the melting points of the corticosteroids. There were two main reasons for reaching this temperature before quenching the melt. First, since this temperature was somewhat less than the melting point of the corticosteroids, decomposition of the corticosteroid did not occur or was negligible. This factor was desirable since the corticosteroids decompose to some degree at their melting points (22). Second, the sugars could not be heated much higher than the preparation temperatures because of decomposition, manifested by an amber discoloration. The temperatures used were a compromise between the melting points of the corticosteroids and the decomposition ranges of the sugars.

These solutions were not glass solutions, since complete melting of both components did not occur and a molecular dispersion of the corticosteroid in the glassy carrier did not result. The portion of the corticosteroid molecularly dispersed in the glass carriers could account in part for the extremely rapid initial release rate. This phase was followed by a slower rate of release of the dispersed particles.

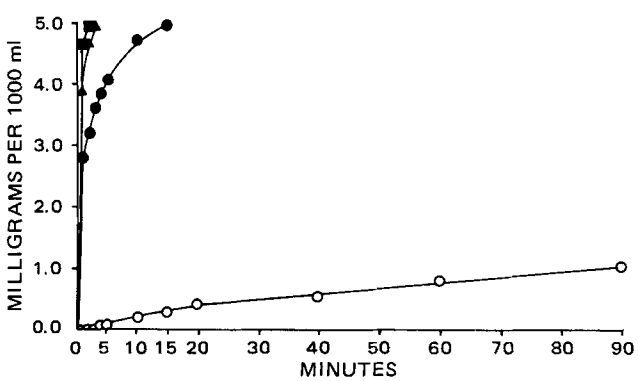

Figure 6—*Dissolution rates of prednisone. Key:* O, *plain;* ▲, *dextrose carrier;* ●, *galactose carrier; and* ■, *sucrose carrier.*

Table I—50 and 100% Dissolution Times (Minutes) for Corticosteroids in Glass Dispersions

Corticosteroid	$t_{50\%}$	$t_{100\%}$
Dextrose carrier		
Betamethasone acetate	<15	>90
Cortisone acetate	<2	20
Hydrocortisone acetate	<1	2
Methylprednisolone acetate	<2	20
Prednisolone	<1	3
Prednisone	<1	3
Galactose carrier		
Betamethasone acetate	<2	20
Cortisone acetate	<4	>90
Hydrocortisone acetate	<1	>90
Methylprednisolone acetate	<3	40
Prednisolone	<1	10
Prednisone	<1	15
Sucrose carrier		
Betamethasone acetate	1	15
Cortisone acetate	<1	10
Hydrocortisone acetate	<1	<1
Methylprednisolone acetate	<1	4
Prednisolone	<1	1
Prednisone	<1	2

In view of present-day considerations of the effect of dissolution rates on drug bioavailability, these glass dispersions offer a unique opportunity of making available an extremely fine state of subdivision of active ingredients and a unique method of increasing the wettability of the active ingredients. The sugars enjoy many advantages over other forms of solid dispersion carriers in addition to their being relatively nontoxic, inexpensive, and physiologically acceptable. They have long been utilized in the preparation of pharmaceutical dosage forms, and the only difference in their past use and the newly proposed use is in the physical state. In the past, they have been used in physical mixtures; now it is suggested that they be used as solid dispersion carriers in a glassy state. These solid dispersions should be considered as potential dosage form modifications for the corticosteroids and for other poorly soluble or insoluble drugs with fairly high melting points where an increase in the dissolution rate is desirable.

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Distribution, Dilution, and Elimination of Polychlorinated Biphenyl Analogs in Growing Swine

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Abstract □ Growing swine were given 15 mg/kg po of purified polychlorinated biphenyl analogs and a commercial mixture. Backfat biopsies for 16–18 weeks exhibited two-compartment elimination kinetics when based on concentration. Total body fat was estimated from potassium-40 abundance, and the calculated total fat load indicated that most of the decline in residue concentrations was due to dilution by growth and expansion of the fat compartment. Redistribution in the fat was apparent for various analogs at different times, and tissue distribution varied significantly among analogs.

Keyphrases □ Biphenyls, polychlorinated—tissue distribution, dilution by growth, and elimination, swine □ Polychlorinated biphenyls—tissue distribution, dilution by growth, and elimination, swine □ Distribution, tissue—various polychlorinated biphenyls, swine □ Elimination—various polychlorinated biphenyls, swine

Stable compounds of low water solubility and high lipid affinity such as chlorinated pesticides and polychlorinated biphenyls comprise a special class of pharmacokinetically distinct xenobiotics. Recent studies involving intravenous and oral administrations of a polychlorinated biphenyl mixture containing 54% chlorine to swine and sheep showed that component peaks were distributed at different rates (1, 2). The smaller isomers of low chlorine content generally distributed at a faster rate than those of higher chlorination and were metabolized to a greater extent (1–4).

The high fat–blood concentration ratios of polychlorinated biphenyls (PCB) make sampling of the fat more meaningful for pharmacokinetic modeling. Because the apparent $t_{1/2}$ for elimination is on the order of weeks when fat concentration alone is presented (5), dilution due to growth is a required parameter for studies of rapidly growing animals such as young swine. In addition, the fat compartment is neither static nor a constant proportion of body weight.

This paper presents methods for evaluating the total amount of three pure polychlorinated biphenyl analogs and a commercial mixture[1] in the fat of growing swine. The "total fat load," L_t, is defined as the weight of chlorinated biphenyl present in the fat compartment. The pharmacokinetic parameters defined from these calculations demonstrate that traditional models must be reconstructed for persistent chemicals in food-producing animals.

EXPERIMENTAL

Fifteen matched weanling pigs of mixed Yorkshire/Hampshire breeding were divided into four experimental and one control group of three animals each. The pigs were fed a wet mash containing 100 ppm of 2,5,2′,5′-tetrachlorobiphenyl (I), 2,4,5,3′,4′-pentachlorobiphenyl (II), 2,4,5,2′,4′,5′-hexachlorobiphenyl (III), and a commercial mixture[1] (IV) for 1 week. The mash was offered every morning and left until totally consumed in quantities sufficient to produce a 2.14-mg/kg/day or 15-mg/kg/week dosing regimen.

Total body fat was estimated by a variation of the potassium-40

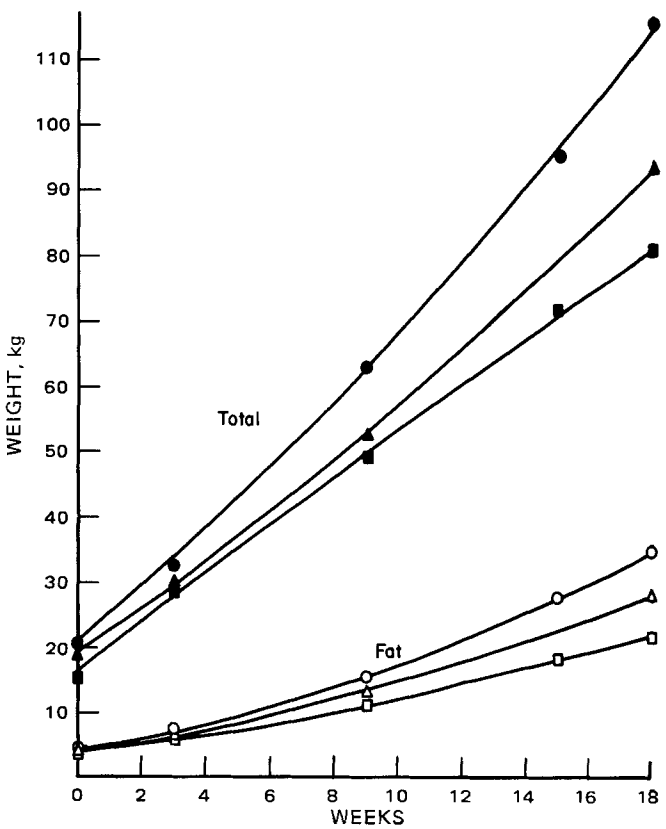

Figure 1—*Comparison of body weight (solid symbols) and body fat (open symbols) in single pigs receiving control (circles), hexachlorobiphenyl (triangles), and 54% chlorine mixture (squares) feed.*

[1] Aroclor 1254, Monsanto electrical grade, lot KB-05-612.