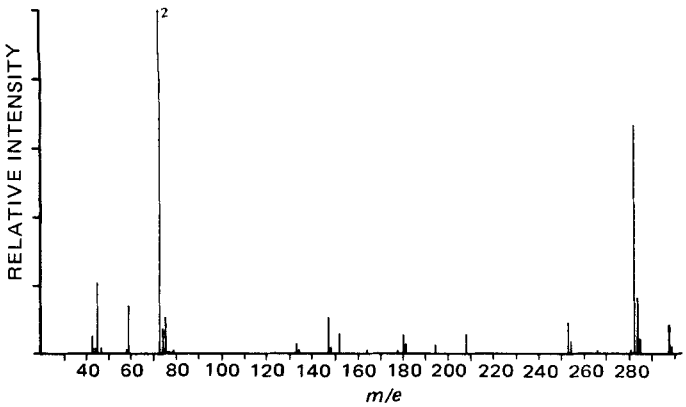

Figure 8—*Mass spectrum of the trimethylsilyl derivative of the degradation product from the oxidation of pirbuterol.*

$< k_C$. The experimental values were consistent with the derived rate equation. Arrhenius plots revealed low activation energies (~10 kcal/mole), which explain why conducting the experiments at 90° did not markedly accelerate the oxidation over that predicted (and observed) at room temperature.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 2, 1976, from *Central Research, Pfizer Inc., Groton, CT 06340.*

Accepted for publication August 5, 1976.

Presented at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, New Orleans meeting, April 1976.

The authors acknowledge L. Van Campen for writing the programs necessary to the calculations and for technical assistance with the manuscript and also C. H. Huang for laboratory assistance.

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Prostaglandin Monolayers II: Monomolecular Film Behavior of Dinoprost C-15 Alkyl Esters

BERNARD E. SIMS [x] and GLENFORD R. DERR

Abstract □ Monomolecular film compression–relaxation behavior was examined for select dinoprost C-15 alkyl esters. Higher homologs of the series such as palmitate and decanoate esters yielded stable expanded monolayers that exhibited minimal relaxation of surface pressure during noncompression. Their limiting molecular areas were consistent with a Hirschfelder model projection in which the prostaglandin moiety assumes a horizontal orientation at the interface with its alkyl ester chain oriented vertical to the surface plane. Shorter chain homologs such as hexanoate, valerate, butyrate, propionate, and acetate also formed expanded monolayers but exhibited increased instability with decreased alkyl chain length, as reflected in their lower surface pressure development during compression and significant relaxation of pressure during noncompression. Such instability can be tied to their increased solubility in the subphase solution and higher desorption rate from the interface.

Keyphrases □ Dinoprost C-15 alkyl esters, various—monomolecular film compression–relaxation behavior compared □ Films, monomolecular—various dinoprost C-15 alkyl esters, compression–relaxation behavior compared □ Prostaglandins—various dinoprost C-15 alkyl esters, monomolecular film compression–relaxation behavior compared

In recent years, much effort has been directed to elucidating the pharmacological and physiological properties of a new class of biological compounds termed prostaglandins (1–3). Very little attention, however, has been directed toward their possible surface-active properties, even though they have been implicated in various roles portending high surface activity (4–9).

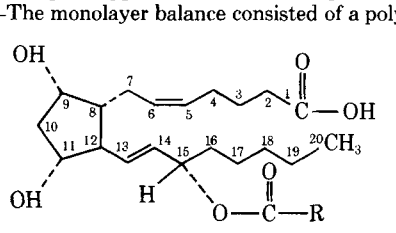
The naturally occurring prostaglandins dinoprost ($F_{2\alpha}$), dinoprostone (E_2), A_1, and B_1 exhibited surface activity in the presence of spread insoluble monomolecular films (10). They in themselves, however, do not tend to form stable monolayers because of their high aqueous solubility. In this article, monolayer film behavior for some long chain alkyl derivatives of dinoprost that do form stable monolayers is reported. This basic and fundamental study should contribute to the limited information available on surface behavior of these ubiquitous and biologically important compounds.

The prostaglandin derivatives selected for monolayer investigation were long chain aliphatic esters of dinoprost attached at the C-15 hydroxyl group (I, R = alkyl). The numbering system generally accepted for prostaglandin-type compounds is with the upper chain carboxylic acid function as the 1-position.

EXPERIMENTAL

Materials—A TLC analysis of the synthesized[1] prostaglandin esters indicated a purity of 99+% for all compounds. Spectroscopic grade hexane–chloroform–methanol (20:2:1) was used as the spreading solvent. Subphase solutions consisted of 0.01 *M* HCl prepared with double-distilled water in an all-glass apparatus with alkaline permanganate.

Equipment—The monolayer balance consisted of a polytef[2]-covered



I

[1] By Dr. Walter Morozowich, The Upjohn Co.

[2] Teflon, du Pont.

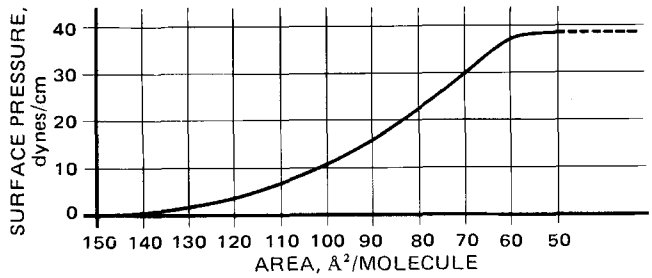


Figure 1—*Monolayer compression–relaxation isotherm generated by dinoprost palmitate ester on 0.01 M HCl subphase at 25° and* v_0 *= 5.17 Å²/molecule-min.*

trough having an area of 315 cm^2 and a width of 10.5 cm. The trough was hollowed out so that water at controlled temperatures could be circulated. This entire unit was enclosed in a large metallic box for protection against dust. The barrier mechanism was driven at controlled rates by means of constant revolutions per minute motors equipped with reversible drive and a positive clutch for an instant stop.

Surface pressure was measured using the Wilhelmy plate method, utilizing a 5-cm roughened platinum plate. Mass changes were measured with an electromagnetic balance[3] and recorded[4]. The balance was housed in a large metallic box above the trough unit and was situated on an elevating stand to facilitate placement of the plate into the subphase. Since vertical movement of the plate was negligible when the self-balancing unit was used (11, 12), it was possible to minimize any errors introduced by possible contact angle change.

General Procedure—Monolayers of the prostaglandins were spread from 1.0-mg/ml solutions of the particular component dissolved in the mixed solvent system. These solutions were added to the surface of the subphase by means of a micrometer syringe[5], which delivered 20–30 μg of material at an initially high area per molecule. After 15 min was allowed for complete spreading and equilibration, the film was subjected to compression at a constant velocity, followed by a period of noncompression to observe relaxation (12–14) and/or dissolution effects.

Each subphase was used only once, and each reported isotherm was reproduced from at least three different spreadings in which areas agreed within ±0.5 Å²/molecule. All experiments were conducted at 25 ± 0.2°.

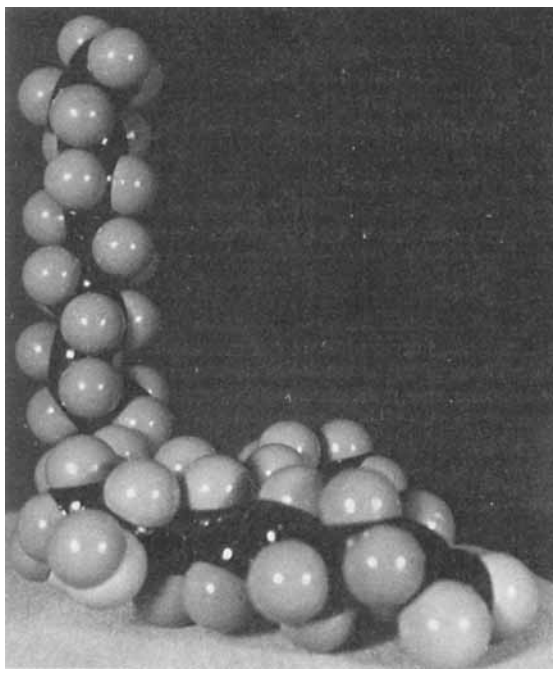


Figure 2—*Hirschfelder molecular model for dinoprost palmitate ester showing vertical orientation of the palmitoyl chain and horizontal orientation of dinoprost moiety in the surface plane (1 cm = 1 Å).*

[3] Cahn RG.
[4] Sargent Welch model SRLG.
[5] Agla, Burroughs-Wellcome.

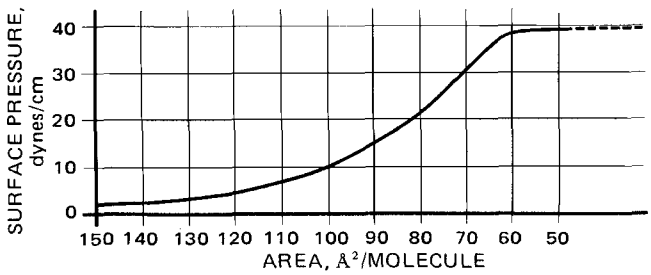


Figure 3—*Monolayer compression–relaxation isotherm generated by dinoprost decanoate ester on 0.01 M HCl subphase at 25° and* v_0 *= 5.17 Å²/molecule-min.*

No significant increment in surface pressure development (>0.2 dyne/cm) was observed upon manual advancement of the barrier over the subphase in the absence of spread film.

RESULTS AND DISCUSSION

The monolayer isotherm obtained for dinoprost palmitate is depicted in Fig. 1. The generally expanded character of the film exhibits surface pressure development at rather high areas per molecule. The isotherm begins to rise rather steeply around 120 Å²/molecule, until collapse is observed at a surface pressure of 40 dynes/cm. During the period of noncompression (dashed lines) immediately following collapse, no relaxation behavior is observed. Such film behavior suggests that lens formation occurs at collapse and that some degree of equilibrium is established between the collapsed bulk phase and monolayer molecules (15).

A limiting area per molecule of 108 Å² can be obtained by extrapolation of the upper linear portion of the curve preceding collapse. This area per molecule agrees very closely with that obtained from a Hirschfelder molecular model projection (Fig. 2). In this molecular configuration, the basic prostaglandin moiety assumes a horizontal orientation within the plane of the surface, with the palmitate chain extended upward and vertical to the surface. The model area projections for such an orientation are approximately 115–98 Å²/molecule. Again, these values appear to be in close agreement with the actual area per molecule of 108 Å² obtained from the π–A isotherm.

A test for this postulated configuration would be to examine another dinoprost C-15 alkyl ester having a significantly different chain length. If the alkyl portion is extended out of the surface, it should not contribute to the limiting area per molecule and both compounds should approximate the same limiting area.

Figure 3 depicts film compression behavior observed for dinoprost decanoate. The π–A compression character is similar to that observed for the palmitate monolayer. The isotherm is expanded at higher areas per molecule and exhibits a relatively rapid surface pressure development at intermediate areas. Collapse occurs at approximately 40 dynes/cm, with no evidence of relaxation during the noncompression period. The limiting area obtained by extrapolation to the area axis yields a value of 103 Å²/molecule. Hence, decreasing the ester chain length by six methylene groups appears to make no major contribution to the observed limiting area per molecule. This finding strongly supports the configuration previously postulated for these prostaglandin esters at the air–solution interface.

In Fig. 4, the monolayer isotherms obtained for dinoprost hexanoate and valerate are presented. Both shorter chained esters produce generally expanded monolayers, as observed with the palmitate and decanoate films. However, the period of noncompression here is characterized by

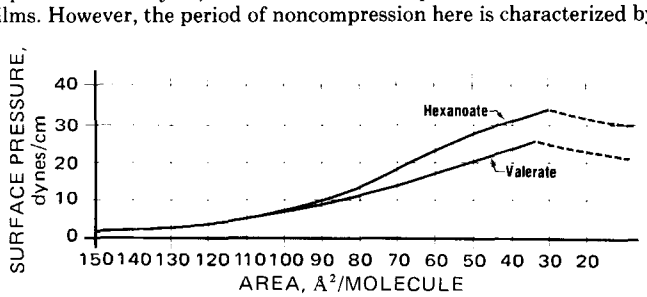


Figure 4—*Monolayer compression–relaxation isotherms generated by dinoprost hexanoate and valerate esters on 0.01 M HCl subphase at 25° and* v_0 *= 5.17 Å²/molecule-min.*

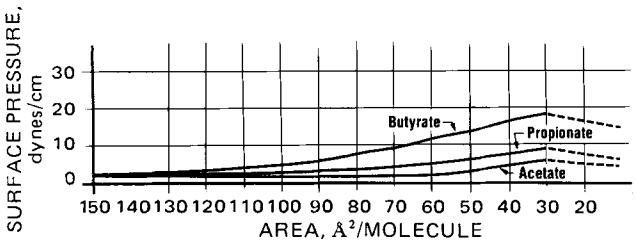


Figure 5—*Monolayer compression–relaxation isotherms generated by dinoprost butyrate, propionate, and acetate esters on 0.01* M *HCl subphase at 25° and* $v_0 = 5.17$ *Å²/molecule-min.*

significant surface pressure reduction, in contrast to the palmitate and decanoate. Another effect of chain length on the stability of these monolayers is seen in the maximum surface pressure developed during compression. The area per molecule at which compression is terminated in Fig. 4 is not a collapse area. Indeed, no collapse is observed for either film. However, under similar conditions of spreading, elapsed time before compression, and compression rate, the hexanoate film is the more stable, as evidenced by the higher surface pressure development throughout the compression sequence. At 32 Å²/molecule, where compression is terminated, the hexanoate film exhibits a maximum pressure of 35 dynes/cm compared to 26.5 dynes/cm for the valerate. The lower pressure of the valerate as well as the surface pressure reduction observed during the noncompression period can be attributed to the shorter chain length and faster dissolution rate from the interface. The hexanoate film is also somewhat soluble in the subphase but to a lesser degree.

Figure 5 presents monolayer behavior for three other members of this alkyl derivative series, butyrate, propionate, and acetate. All three esters tend to accentuate the film behavior previously observed with the hexanoate and valerate films. Monolayer stability is progressively decreased with decreasing alkyl chain length, as evidenced by reductions in surface pressure development during compression. All three compounds exhibit relaxation of surface pressure during noncompression, which appears to be tied directly to their decreased stability as a result of dissolution.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 3, 1976, from *Pharmacy Research, The Upjohn Company, Kalamazoo, MI 49001.*

Accepted for publication August 10, 1976.

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Effect of Primidone Concentration on Glass Transition Temperature and Dissolution of Solid Dispersion Systems Containing Primidone and Citric Acid

M. P. SUMMERS [x] and R. P. ENEVER

Abstract □ The glass transition temperatures of glasses containing various concentrations of primidone in citric acid were measured and found to increase as the primidone concentration increased. Dissolution studies of these systems and particle-size measurements of primidone precipitated during dissolution of devitrified glasses suggest that the increase in the dissolution rate of the devitrified systems is due to both the small size of the precipitated crystals and the excellent wettability of these systems.

Keyphrases □ Primidone—solid dispersion systems with citric acid, effect of concentration on glass transition temperature and dissolution □ Citric acid—solid dispersion systems with primidone, effect of primidone concentration on glass transition temperature and dissolution □ Glass transition temperature—primidone–citric acid solid dispersion systems, effect of primidone concentration □ Dissolution—primidone–citric acid solid dispersion systems, effect of primidone concentration □ Solid dispersion systems—primidone–citric acid, effect of primidone concentration on glass transition temperature and dissolution □ Anticonvulsants—primidone, solid dispersion systems with citric acid, effect of concentration on glass transition temperature and dissolution

The use of citric acid as a water-soluble carrier for sparingly soluble drugs was first investigated by Chiou and Riegelman (1). Recently, a study of a solid dispersion system containing primidone in citric acid was reported (2). The systems were prepared by fusing citric acid with primidone; immediately after preparation, they existed in the vitreous state. Both the viscosity of these glasses and their devitrification rate were dependent on the primidone concentration.

Dissolution studies conducted on the devitrified dispersions showed that they dissolved more rapidly than physical mixtures of primidone and citric acid. It was postulated that there was rapid depletion of citric acid from the solid dispersions, leaving a suspension of primi-