PHYSICAL-CHEMICAL FACTORS AFFECTING THE KINETICS OF DRUG BIOAVAILABILITY

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INTRODUCTION

In recent years the practice of Pharmacy has undergone considerable change. It is now popular to state that the pharmacist must be patient oriented as well as drug product oriented. Patient orientation implies an increased awareness of the pathological state and an increased emphasis on the drug therapy required to alleviate the diseased condition. The educational background required for this activity relies greatly on the biological sciences and demands the application of pathological, pharmacological and therapeutic principles at a high level of sophistication.

Irrespective of the much needed emphasis which is now placed on the biological sciences, this does not, in any way, decrease the importance of such educational course work as mathematics, chemistry, physical chemistry and the other physical sciences in the Pharmacy curriculum. For it is the physical sciences in the academic program which provide the theoretical basis for understanding the problems associated with the drug product and the kinetic process as involved in drug therapy. Kinetics, of course, play a highly important role in modern drug therapy. In pharmacy practice today the pharmacist must be concerned about the kinetics of drug release from the physical-chemical system known as the dosage form and also the kinetics of drug absorption, drug metabolism and drug elimination. A knowledge of these kinetics allows a scientific approach to the adjustment of the dosage regimen as well as the selection of the proper physical-chemical system (dosage form) to be used.

The physical-chemical system, its formula and the manufacturing processes employed, play a much greater role in these kinetic processes than is sometimes recognized. In some cases the rate limiting step in the overall absorption process is the rate of drug release from the dosage form which in turn is controlled by various physical-chemical factors. In other cases the chemical components of the physical system can influence the biological membrane in such a manner that the rate of absorption is affected. Thus, factors inherent in the drug product can influence drug absorption both when the rate limiting step is the rate of release of the drug from the physical system and also when drug transport across the membrane in the biological system is rate limiting.

Optimum therapeutic procedures must, therefore, take into account problems associated with both the physical and the biological system. Thus, the practice of Pharmacy cannot be solely patient oriented but must also treat the problems associated with the drug product as well.

Since another paper in this symposium will deal with the important kinetic processes which occur in drug absorption, metabolism and elimination, this paper will deal primarily with physical influences on the behaviour of drug products. These influences include the chemical composition of the formula, the physical state of the drug, the chemical form of the drug and the processing conditions. Obviously, the number of factors treated here must be limited; however many factors influencing drug release kinetics in oral solids are discussed. Some factors influencing parenteral and dermatological preparations are also included. It must, however, always be remembered that all dosage forms are subject to control by physical-chemical factors.

Physical Influences on Drug Release Kinetics

Compressional Force and Tablet Hardness

The early work of Schulert and Weiner[1] showed that human plasma levels obtained with "hard" tablets were much lower than the levels obtained with "soft" tablets. These data are shown in figure 1. Subsequently, Luzzi, et al[2] and Hirschorn and Kornblum[3] showed the influence of increased tablet hardness and an increase in compressional force in slowing the dissolution rate of the drug in compressed tablets. In similar fashion Varley showed that slow disintegration and slow dissolution[4] rates decreased the plasma levels of tolbutamide and decreased the effectiveness of this drug to lower plasma glucose. More recently Alam and Parrott[5] have shown that storage of Hydroclorthiazid tablets granulated with acacia increased in hardness with a concomittant increase in the disintegration and dissolution rates. These physical parameters remained essentially unchanged, however, when either starch or PVP were employed as the granulating agent.

Particle Size

An increase in compressional force can influence many other factors besides tablet hardness. For example, crystal fracture of the drug may occur which decreases particle size, increases the surface area and increases the dissolution rate. The influence of particle size of the drug on the dissolution and subsequent drug release kinetics has been thoroughly studied in various dosage forms including tablets, capsules and suspensions. For example, many years ago Nelson[6] showed that higher excretion rates in humans were obtained with a 200 mg. dose of tetracycline sodium hexametaphosphate of a 100 micron particle size than with the same dose of larger size particles (figure 2). Similar results were obtained with the drug tolbutamide when various particle sizes were employed[7].

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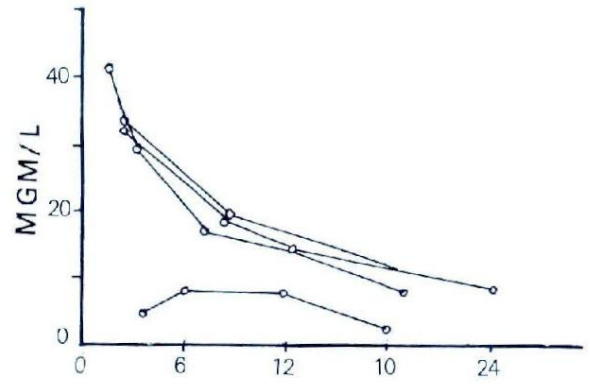

Fig 1

Plasma levels of phenylindanodione following the administration of the same dose (400 mgm.) to the same subject in different forms on different occasions.

□ – – – – □ Capsules of pure ingredient only
∇ – – – – ∇ Intravenous injection
O – – – – O "Soft" tablets
X – – – – X "Hard" tablets

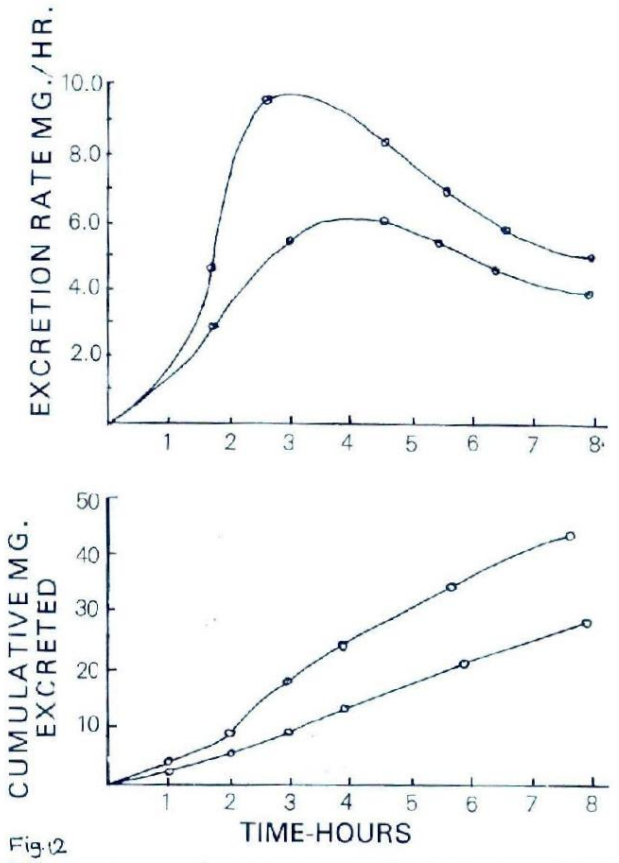

Fig 2

Difference in cumulative amount excreted and excretion rate curves when tetracycline sodium hexametaphosphate complex was taken as pellets and as particles with average diameter of 100 μ. Dose: 200 mg. tetracycline hydrochloride equivalent. Solid circles—100 μ particles and open circles—as pellets

In figure 3 the comparison of the plasma levels of acetaminophen obtained when oral suspensions having drug particles characterized as fine, medium and coarse were administered in 1000 mg./Kg. doses to mice,[8] is shown. Increased absorption rates would also be expected from parenteral suspensions containing an insoluble drug in an aqueous medium when the particle size of the drug is smaller than that taken for comparison. The importance of the type of physical chemical system is readily shown, however, in parenteral suspensions intended for intramuscular injection. If the insoluble drug is suspended in oil, preparations containing larger drug particles will show higher absorption rates than those with smaller particles. The influence of the physical system is thus shown in figure 4 which shows the rabbit serum levels following the administration of various penicillin preparations[9]. This effect is readily explained, theoretically. Assuming uniform drug distribution in the system the erosion of the larger drug particles at the water-oil interface will lead to an increased release of the larger over the smaller particles.

Process Conditions——Solid-State Transformations

Chemical Complexes

It is possible for the process conditions employed in the manufacture of drug products to have a profound influence on the drug release characteristics. For example, it is possible for solid-state transformations to occur during the compression of tablets. In our laboratory complexes have been shown to be both formed and destroyed by tablet compression [10, 11]. A solution prepared complex (A) of paraminobenzoic acid: oxalic acid: water in a 1:1:1 ratio was destroyed by compression as shown by the differential scanning calorimeter thermograms in figure 5 where (A) becomes (B). When a 1:1:2 mixture of PABA: oxalic acid: water was compressed complex (C) was formed. When this complex was recompressed the complex was again destroyed as indicated by (D). When (B) and (D) tablets were ground, water added and the mixtures recompressed the complex again formed as shown in (E) and (G) of figure 6. When tablets (B) and (D) were ground and the material recompressed without the addition of water, no complex was formed as shown by (F) and (H). It must be anticipated that similar solid state transformations can occur when compressed tablets are prepared from drugs as well as the materials used in the above experiment.

Polymorphic Form

Other solid-state transitions can also occur due to the influence of the compressional force applied during tabletting [11, 12]. In figure 7, DSC thermograms show three distinct crystalline forms for succinylsulfathiazole. Figures 8 and 9 show that the hydrated crystalline forms I and II changed when subjected to a compressional force. However, no change occured in the anhydrous crystal form III when subjected to the same compressional conditions (figure 10). In figure 11 it can be observed that these crystal changes also produced changes in the dissolution behaviour, as would be expected. The latter is particularly significant since dissolution in this case influences the rate of drug release. The polymorphic form of a drug has

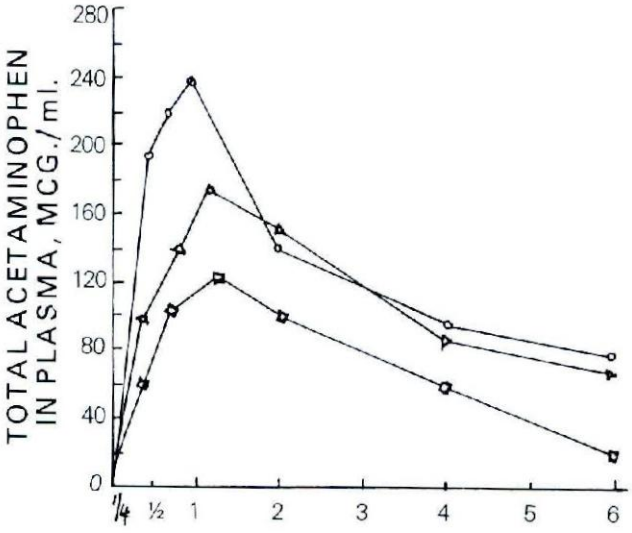

Fig. 3

Plots of plasma concentrations of total acetaminophen (free + conjugated) in mice following oral administration of 1,000 mg./Kg. of fine (O-O), regular (Δ-Δ), and coarse (□-□) particle ATC powders suspended in a 0.5% dispersion of gum tragacanta in water. The plots suggest that, in each case, the absorption of ATC was essentially ended after about 1 hr. The plasma concentrations in the 0- to 2-hr. period are dependent upon the particle sizes of the powders and, presumably, are controlled by their rates of dissolution

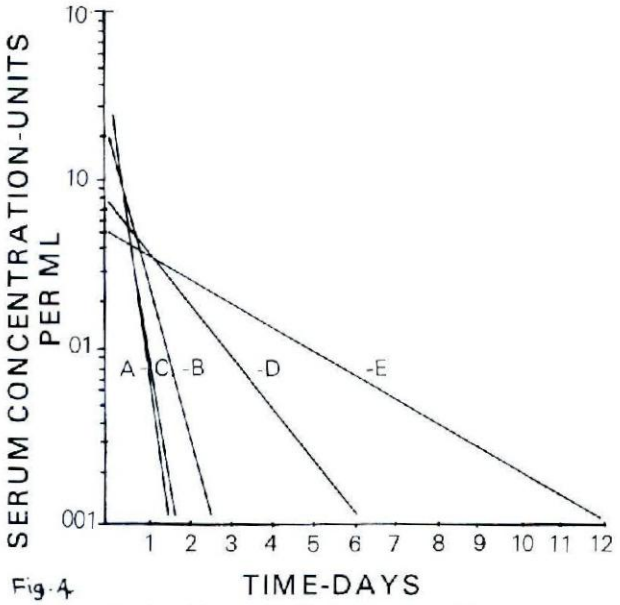

Fig. 4

Penicillin levels in rabbit serum. Single injection—50,000 units per Kg. of suspensions containing 300,000 units per ml.

A, Sodium penicillin G in peanut oil containing beeswax
B, Sodium penicillin G in aluminum stearate gel
C, Procaine penicillin G in peanut oil
D, Procaine penicillin G in aluminum stearate gel, large particles
E, Procaine penicillin G in aluminum stearate gel, small particles

been shown by many to be important in bioavailability considerations. Wurster and Taylor [13, 14] studied the dissolution kinetics of various forms of prednisolone. Aguiar [15, 16] studied the dissolution behaviour of chloramphenicol palmitate polymorphs and their influence on the blood serum levels. Poole [17] compared the serum levels obtained in dogs with anhydrous ampicillin to that obtained with the ampicillin trihydrate polymorph.

Chemical Forms

As commonly known, the chemical form such as the salt, ester, complex, etc. are all capable of altering the equilibrium solubility and dissolution kinetics of a drug. These chemical modifications can thus be utilized to alter the bioavailability of the drug. Morozowich [18] showed that an increased in the dissolution rate of various salts of benzphetamine and etryptamine decreased the LT_{50} in mice.

Chemical Composition of Formula

The various chemicals in a formula all possess the potential to alter the availability of the drug in a product. This may occur by slowing either or both the disintegration rate or the dissolution rate through the use of highly insoluble materials in the formula. Physical adsorption of the drug may also lead to decreased availability. The inhibition of the deaggregation process in chloramphenicol capsules [19] as well as lowered mean plasma levels [20] in humans was found to be caused by these other type ingredients in the formula.

The presence of certain chemicals in the formula may also increase the drug bioavailability in products. Thus, Newmark, et al [21] increased the blood levels of the antibiotic Coumermycin A in both dogs and humans by the addition of N-methylglucamine in a 1:4 ratio with the drug. D'Arcy [22] showed the influence of the formula on the plasma levels obtained with various tablet formulations of prednisolone.

Because many of the physical influences cited decrease drug plasma levels as well as inhibit the dissolution rate many attempts have been made to correlate these two parameters. Bates [23] studied the amount of salicylamide dissolved in a given time versus the amount excreted in one hour following the administration of three dosage forms. Symchowicz [24] found that mean plasma levels correlated well with the dissolution rate for griseofulvin.

Adsorption, Desorption and Membrane Transport

As indicated previously, it is possible for the physical system (dosage form) to bring about physical effects which will also alter the drug transport across the biological membrane. These physical changes may occur in the overall environment or may be direct effects upon the membrane. Crouthamel [25] found the absorption rates for both sulfaethidole and barbital to be increased as the pH of the environment was decreased. Hayton 26 attributed the effect of N, N-di-n-propylproprionamide in enhancing the absorption of prednisolone from the rat intestine to complex formation between the two compounds.

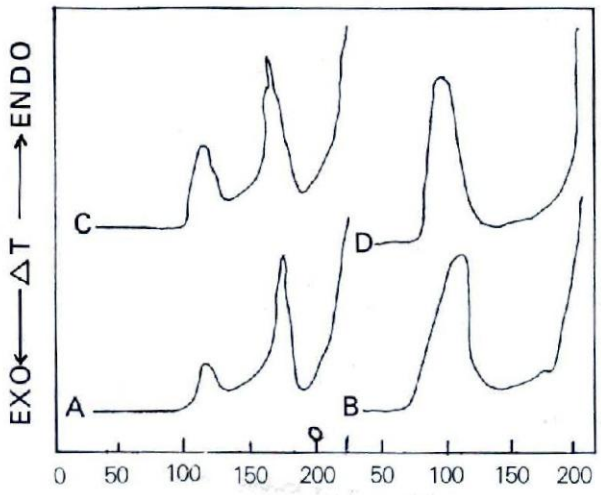

Fig. 5

DSC thermograms showing effect of compressing 1:1:1 complex and recompressing the compressed 1:1:2 mixture (48-hour sample). *A*—1:1:1 complex; *B*—1:1:1 compressed complex; *C*—1:1:2 compressed mixture (48-hour sample); *D*—recompressed 1:1:2 compressed mixture

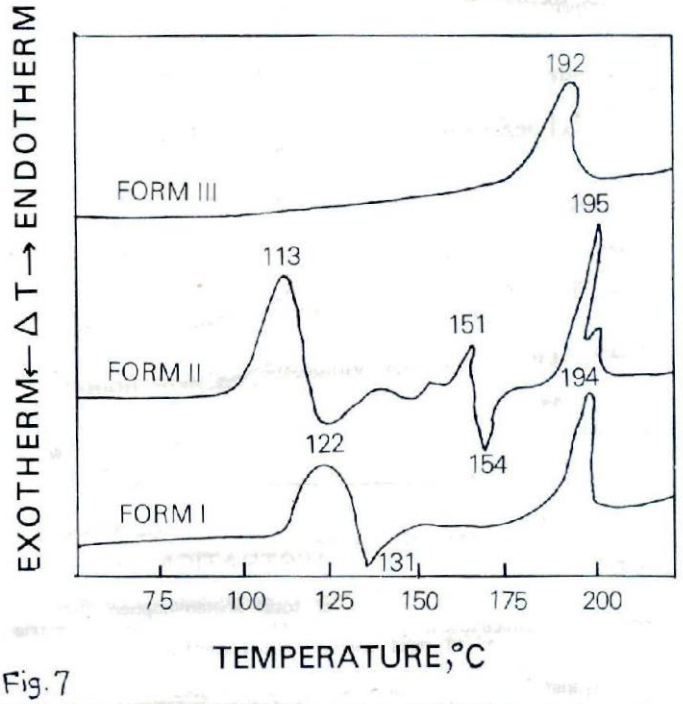

Fig. 7

Representative DSC thermograms of succinylsulfathiazole crystal forms

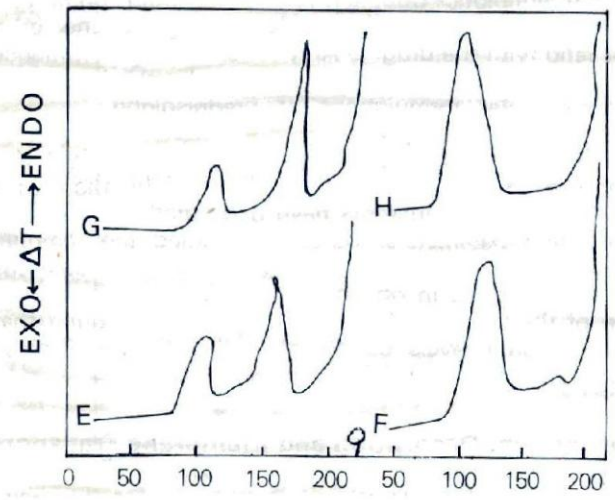

Fig. 6

DSC thermograms showing effect of adding water to compressed samples B and D after grinding, which yield E and G, respectively, after recompression. H and F show effect of recompression of B and D without addition of water

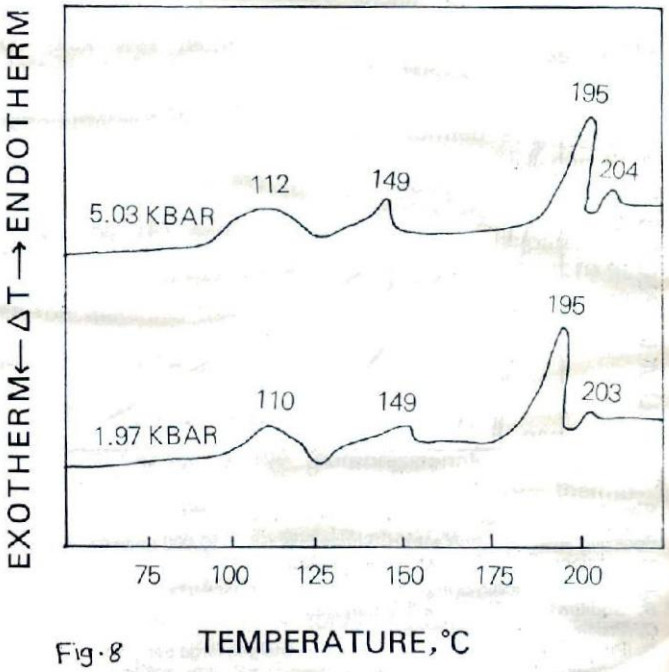

Fig. 8

Effect of compression load on crystal form I thermogram

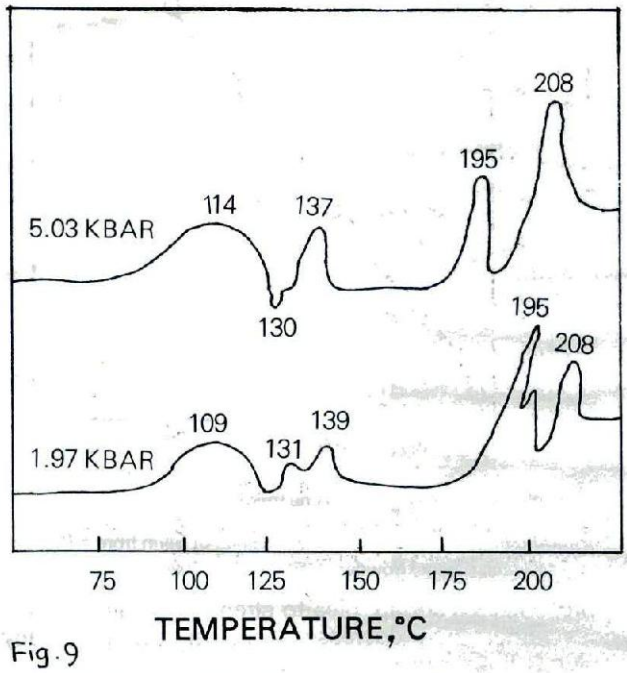

Fig. 9

Effect of compression load on crystal form II thermogram

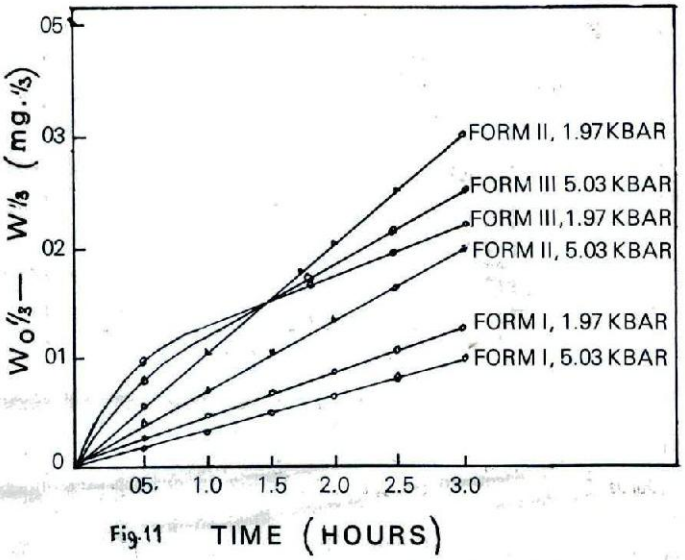

Fig. 11

Effect of compression load on dissolution behaviou of succinylsulfathiazole crystal forms.

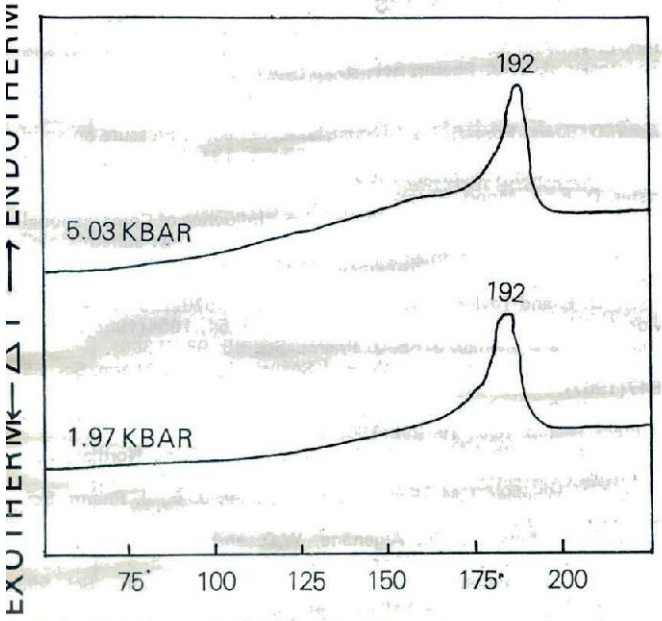

Fig. 10

Effect of compression load on crystal form III thermogram

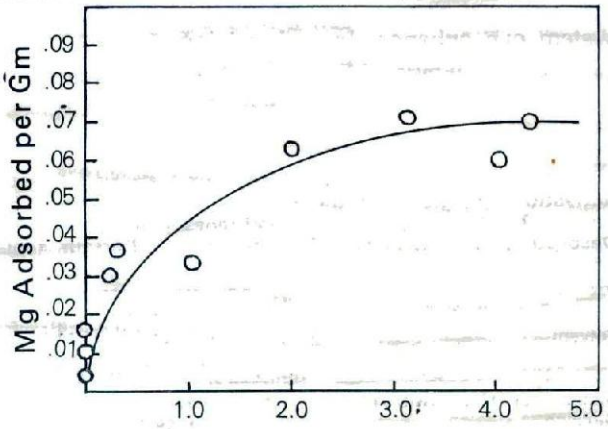

Fig. 12

Adsorption Isotherm for Sarin on *p*-Dioxane Conditioned Keratin (Callus) Powder at 25°C

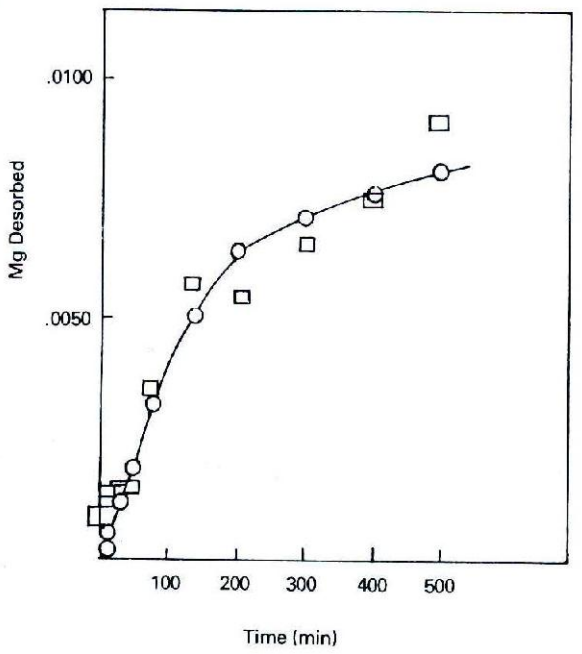

Fig.13 Desorption Isotherm for Sarin from *p*-Dioxane Conditioned Keratin (Callus) Powder at 25°C,O,Computer value, X_3, □, Experimental value, X_2

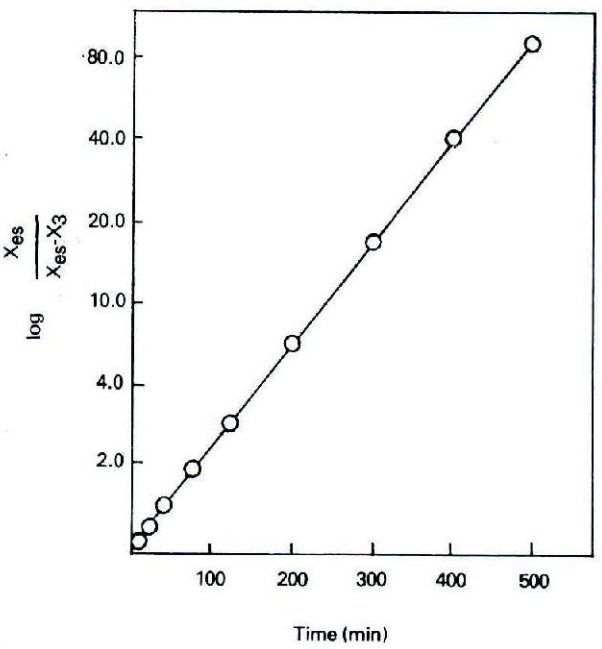

Fig. 14 First Order Plot to Obtain *kd* for Desorption of Sarin from *p*-Dioxane Conditioned Keratin (Callus) Powder at 25°C (*kd* = .0089 min-1)

Wurster and Matheson [11, 27], in percutaneous absorption studies, showed that the conditioning of stratum corneum membranes with certain solvents enhanced the transport Sarin. A theoretical explanation of the latter phenomenon suggests that the solvent decreases the activation energy for the desorption of the drug from the membrane. The energy requirement for the overall transport process is thus also decreased and transport is facilitated. Figures 12 and 13 show the adsorption and desorption isotherms obtained for Sarin on p-Dioxane conditioned keratin powder and figure 14 shows the first order kinetics of the desorption process. From the rate constants obtained as a function of temperature the activation energies for both the transport and desorption processes were calculated and are shown in Table 1. These data tend to support the proposed theory and emphasize how the physical system can enhance drug absorption.

TABLE I

Activation Energies for the I· Transport of Sarin Across Solvent-Treated Human Skin Membranes (callus) and II· The Desorption of Sarin from Solvent-Treated Keratin (callus) Powder

Solvent	Activation energies (Kcal mole^{-1})	
	I Transport	II Desorption
Dimethylsulfoxide (DMSO)	9.05	8.4
Dioxane	20.44	12.7
Methylorthoformate (MOF)	22.35	18.9

From the forgoing discussion it is apparent that the kinetic considerations involved in drug usage must treat the kinetics of drug release from the physical system and the influence of the other chemical components of dosage form on the absorption site as well as the usually employed pharmacokinetics. The author therefore, makes a strong plea to strengthen the physical sciences rather than decrease them in the Pharmacy curriculum.

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