DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(6), 899-914 (1986)

A DIFFUSION MODEL FOR STUDYING THE DRUG RELEASE FROM SEMISOLID DOSAGE FORMS I. METHODOLOGY USING AGAR GEL AS DIFFUSION MEDIUM

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ABSTRACT

Several ointment bases containing three sulfonamides widely different in their physicochemical properties were evaluated for their drug release properties using agar gel as the drug acceptor phase. The drug release/diffusion model was created by making an empty cylindrical core in the center of agar gel plate which was filled with ointment containing the drugs. The results showed that a linear correlation existed when the amount of drug released from each ointment was plotted against the logarithmic time. The solubility of drugs in the base and partition properties into the agar medium played the major role for the release of drugs. The effect of temperature on the diffusion into the acceptor phase was also recorded.

INTRODUCTION

The rate of release of drugs from ointments, creams, and other topical preparations is one of the most important criteria that governs their medicinal efficiency. When any of these preparations is applied

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to the skin, or left in contact with such a stationary layer as nasal or epidermal membrane, drug absorption occurs primarily by a passive diffusion process, and the amount of drug diffused into the skin layers is a function of the drug released from those preparations.

Methods for measuring the release of drugs from a semisolid were reviewed[1]. Many of these methods[2-4] involve measurement of drug transport through model membranes, separating the donor and acceptor phases. In these procedures drug molecules cross the membrane, either by going through holes or pores in the barrier or by traversing the substance of the barrier itself, to an acceptor compartment containing aqueous liquid where a mechanical agitation is continuously provided[5]. However, when topical preparations are applied on the skin, the situation is different. Here, diffusion of drugs occurs passively through the skin as a result of the kinetic energy of the molecules, but the condition is kept fairly static during the diffusion process. It would be of value, therefore, to develop an in-vitro system which can measure the release rate of drugs from ointments under static condition, and at the same time divulge the distribution of the diffused drug throughout the barrier itself. Such systems should expound the efficiency of preparations containing drugs intended for percutaneous absorption.

The purpose of this investigation was to develop a method for evaluating semisolid preparations for topical use as to their drug release rate and diffusivity through hydrogel medium. In this study, the release rates of three sulfonamides, widely varied in their solubility, were measured after dispersing the drugs in petrolatum, O/W cream base and in polyethylene glycol ointment base.

EXPERIMENTAL

Reagents - Sulfacetamide, Sulfabenzamide and Sulfathiazole were used as received[6]. White petrolatum[7] and polyethylene glycols (400 & 4000)[8] were used for preparing an oleaginous base and water soluble ointment base (USP), respectively. The main components of the emulsion base (O/W) were propylene glycol, fatty alcohols and glyceryl monostearate as emulsifying agent. The agar[9] used for preparing the diffusion medium was of a purified grade suitable for preparing microbiological culture media.

Methodology - Preparation of the Drug-Diffusion Medium - A known amount of agar was dissolved in boiling distilled water to prepare 2 per cent (W/V) solution. Fifty ml of the hot agar solution was poured into standard disposable plastic petri dishes (100 x 15 mm)[10] which were filled with the medium to a depth of 8 mm. After the agar plates were completely congealed at room temperature, an empty cylindrical core was created in the center of each plate by piercing a thin walled metal tube of an external diameter of 8.9 mm.

Preparation of the Ointments and Cream - Ointments were prepared by the fusion or spatulation method. The PEG ointment base was prepared according to the method described in USP XX. All of these preparations contained 4 per cent (W/W) each of the three sulfonamides. At this concentration, the three sulfonamides were completely soluble in the PEG base or in the propylene glycol used in the emulsion base. The ointment preparations were run through a three-roller mill[11] to remove air bubbles and to assure good homogenization.

The ointment was added, using disposable syringes, into the empty core of the agar plate to be completely filled to the surface. Care was

taken to avoid capturing of air bubbles at the boundary surface between the ointment and the agar. A stainless steel spatula was used to smooth the surface of the ointment in the core. The plates were then incubated at $37^{o}C \pm 0.5$ in a hot air oven for different time intervals. To study the effect of the temperature on the diffusion rate, polyethylene glycol ointment plates were also incubated at $4^{o}C$ in a refrigerator and at room temperature ($22^{o}C \pm 1$). Each experiment was repeated three times and the mean values are presented here.

Drug Release and Diffusion Rate Study - To study the release rate of each of the sulfonamides from different ointment bases, agar plates which were incubated for 3, 6, 9, 12, 18 and 24 hours were removed from the petri dish and dissolved in 250 ml distilled water by the aid of heat. One ml of this solution was taken for the assay of the drugs using the HPLC procedure described in the analytical section. The total amount of each of the sulfonamides which was released from the ointments at each of the specified time intervals was plotted against the logarithmic time (ln t).

The radial distribution of the sulfonamides in the agar gel was also measured by analyzing samples taken from each agar plate at different distances from the core. Samples were removed using a thin walled metal tube of an external diameter of 3.6 mm. The distance between the center of the plate and the mid-point of each sample taken at different distances was measured using a two pointed compass.

Analytical Method - The sulfonamides were assayed in each sample by a HPLC method. The mobile phase consisted of 0.01 M $(NH_4)_2$ H PO_4 solution and methanol in 7:3 ratio by volume and adjusted to pH 7.2 ± 0.05 with 1 M phosphoric acid solution. The HPLC pump[12] was run at the

rate of 1 ml/min using μ-Phenyl BondaPack column[13] (25 cm X 4.6 mm i.d.). Sulfapyridine[14] was used as the internal standard and the peaks were detected by a UV detector[10] at 254 nm.

A standard calibration plot was prepared for each of the sulfonamides in the concentration range of 1-10 μg/ml. The sulfapyridine concentration was fixed at 5 μg/ml. Stock solutions and subsequent dilutions to obtain standard solutions were made using the mobile phase as a solvent. The solutions were then chromatographed, and plots relating peak height ratio of the sulfonamides to the internal standard versus drug concentrations were obtained.

Sample solutions were prepared by dissolving agar samples taken from the plates in 10 ml volumetric flask using the mobile phase containing sulfapyridine (500 μg/ml). The samples were prefiltered through 0.4 μm Millipore filter. It was found that agar did not interfere with the assay of the sulfonamides.

RESULTS AND DISCUSSION

The release of drug from semisolid topical preparations can often be controlled by altering the composition of the vehicle. In this study the amount and release rate of three sulfonamides from various ointment bases into agar gel were measured at several temperatures. Figure 1-3 compare the release rates of the three sulfonamides from three different ointment bases, petrolatum, O/W emulsion cream, and polyethylene glycol ointment, USP, containing the same amount of sulfacetamide, sulfabenzamide and sulfathiazole at 37°C. Despite different experimental conditions used in the study, it was found that a linear relationship existed, when the amount of drug released was plotted against the logarithmic time. Table 1 shows the correlation

TABLE I
Release Rate and Prediffusion Time of Three Sulfonamides from Different Ointment Bases

Ointment Base	Sulfacetamide Rate of Release mg/ln t	Sulfacetamide r^2	Sulfacetamide P.D. (min)	Sulfabenzamide Rate of Release mg/ln t	Sulfabenzamide r^2	Sulfabenzamide P.D. (min)	Sulfathiazole Rate of Release mg/ln t	Sulfathiazole r^2	Sulfathiazole P.D. (min)
Petrolatum	0.72	1.00	90	0.80	.999	91	0.58	0.999	91
O/W Emulsion	2.07	0.981	62.5	0.85	0.981	65	0.85	0.978	68
PEG Base	3.83	0.999	21.8	2.85	0.989	42	3.18	0.991	17

r^2 = Correlation coefficient

P.D. = Prediffusion time

coefficients of the regression lines and the rate of release of the three sulfonamides from the different ointment bases used in this study. The release rates were obtained by determining the slopes of the plots shown in Figures 1-3. According to Table 1, the rate of release of sulfacetamide from the PEG ointment base is much faster (5.3 times) than that from the petrolatum base, and is approximately 1.8 times faster than its rate of release from the cream base. The release rate of sulfacetamide from the cream base is about 2.9 times that of the petrolatum base. Similarly, for sulfabenzamide the release rate from the PEG base is approximately 3.6 times faster than that of petrolatum and 3.3 times faster than that of the cream. The release rate of this drug from the cream base is only slightly faster than that from the oleaginous base. On the other hand, sulfathiazole was released from the PEG base at a rate 4.6 times that of petrolatum and about 3 times that of the cream. The relative release rates of the three sulfonamides from the different ointment bases are summarized in Table II.

Since the initial drug concentrations in the ointments were kept constant, three other factors could have affected the release of the drugs from the ointment bases. First is the solubility of the drugs in the ointment phase. Second is the solubility of the drug in the gel phase which affects the partition properties of the sulfonamides between the ointment and the agar medium. Thirdly, the intermolecular forces of attraction between the drug molecules and the diffusion medium which might control the diffusion rate and, hence, the release of the drug from the ointment. Table II also shows the solubility of the three sulfonamides in water. Sulfacetamide which has the highest solubility as compared to the other sulfonamides used in this experiment showed the

TABLE II

Relative Release Rates of Sulfonamides from Different Ointment Bases into Agar Gel

Sulfonamide	Solubility[a] g/mL in H_2O	PEG / Cream	PEG / Petrolatum	Cream / Petrolatum
Sulfacetamide	1/150 (20°C)	1.8	5.3	2.9
Sulfabenzamide	1/3225(30°C)	3.6	3.3	1.1
Sulfathiazole	1/1700(30°C)	3.0	4.6	1.5

[a] Merck Index

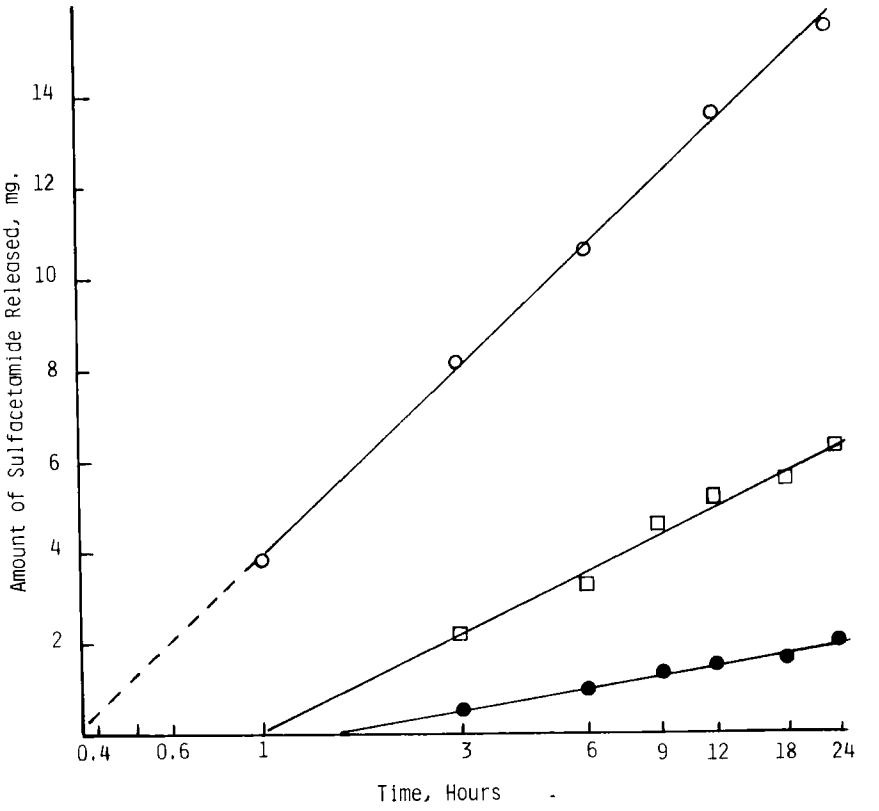

Fig. 1 - Rate of release of Sulfacetamide from different ointment bases into agar gel.

Key: •——•, petrolatum base, □——□, emulsion base, o——o, polyethylene glycol base.

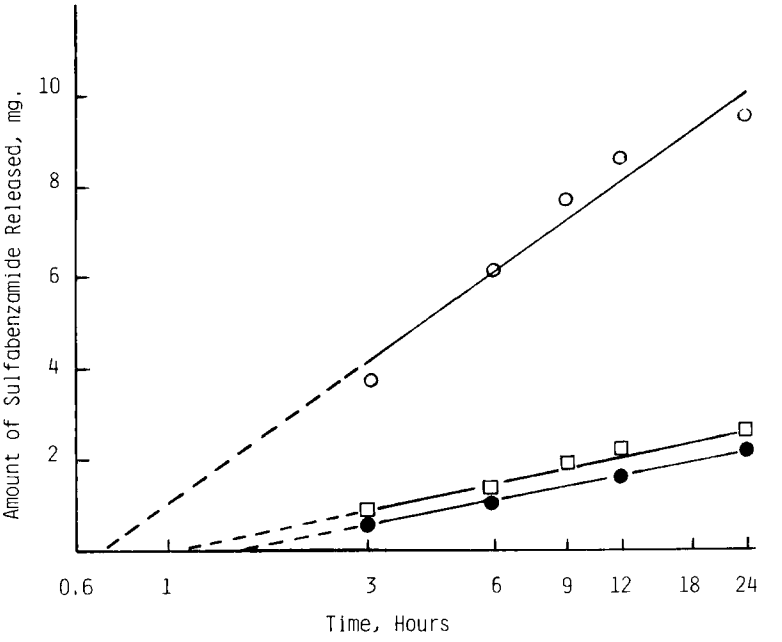

Fig. 2 - Rate of release of Sulfabenzamide, from different ointment bases, into agar gel.
Key: •——•, petrolatum base, □——□, emulsion base, o——o, polyethylene glycol base

highest rate of release from any of the three bases. The results can be attributed to the hydrophilic nature of the acceptor phase.

When topical preparations are applied to the skin or other layers in the body, a lag time usually precedes the diffusion of the drug through the membrane. One possible reason for the time lag found in this study may be due to a situation where the diffusion coefficient of the drug in the acceptor phase is smaller than that of the donor phase. In this study, a prediffusion time was measured by extrapolating the lines in Figures 1-3 to intercept the x-axis. Table I shows the prediffusion times for each of the three sulfonamides from the different ointment bases. The PEG base being a water soluble base did not take as

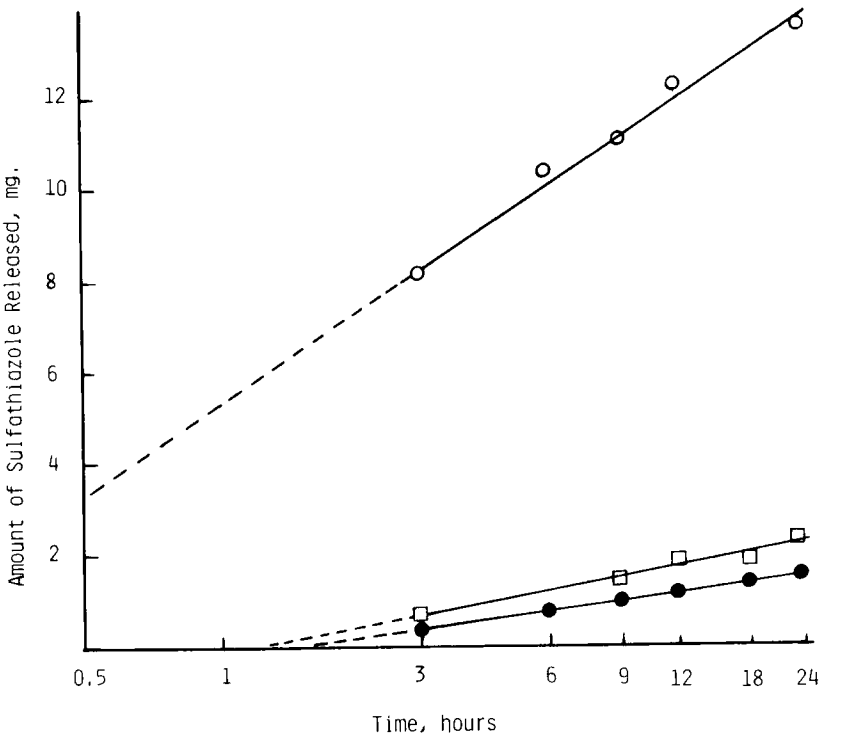

Fig. 3 - Rate of release of Sulfathiazole, from different ointment bases, into agar gel.
Key: •——•, petrolatum base, □——□, emulsion base, o——o, polyethylene glycol base

much time as the emulsion or the oleaginous base to release the drug into the agar phase. Petrolatum, however, took about 1.5 hours before the sulfonamides were released from the ointment. These results also demonstrated the effects of drug solubility and partition properties or the release and diffusion of the drugs into the acceptor phase.

To study the effect of temperature on the release rate of the three sulfonamides into the agar gel, experiment was run with the polyethylene glycol ointment containing the equal amount of the drugs at different temperatures. Figure 4 shows the effect of temperature on the diffusion

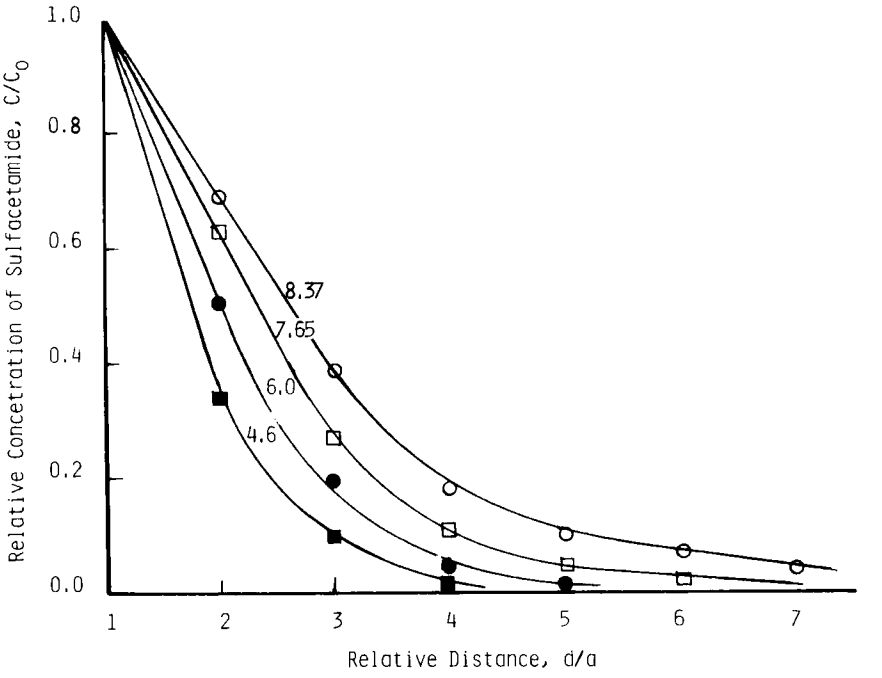

Fig. 4 - Distribution of Sulfacetamide in agar plate as diffused from PEG Ointment, at 37°C, over different periods of time.
Key: ■—■, 6 hr; •—•, 12 hr; □—□, 18 hr; o—o, 24 hr.
The number above each curve represents the extent of diffusion.

$$d/a = \frac{\text{distance from the center of the sample to plate center}}{\text{radius of the ointment core}}$$

C = concentration of the drug in the sample, at d.

C_0 = concentration of the drug at the border between the ointment core and the agar gel, i.e., at a.

of the three sulfanomides at 4°C, 22°C and 37°C. At the higher temperatures a large decrease in the lag time accompanied by an increased rate of drug release was observed. Table III lists the release rates of the three sulfonamides from polyethylene glycol base and their prediffusion times at three different temperatures. According to the data it is anticipated that at the time of drug application the temperature of the

TABLE III
Effect of Temperature on the Prediffusion Time and
Rate of Release of Sulfonamide from PEG Ointment into 2% (w/v) Agar Gel

Sulfonamide	Rate of Release* at			Prediffusion Time (min) at		
	5°C	22°C	37°C	5°C	22°C	37°C
Sulfacetamide	2.72	3.00	3.83	34	22.5	21.8
Sulfabenzamide	2.04	2.30	2.85	55	54.5	42
Sulfathiazole	2.66	2.87	3.18	54.6	34	17

* mg/ln t (hours)

skin as well as the temperature of the ointment would have a profound effect on the release rate and thus the efficacy of the drug from topical preparations.

Figures 5-6 show the distribution of the drugs into the agar gel after different times of incubation. In these figures, the concentration of the drug at any distance "d" relative to its initial concentration in the central core with radius "a" is plotted against the relative distances of d/a. The numbers above each curve represent the extent of diffusion of the sulfonamide under investigation (i.e. the value of d/a when C=0); for example, for the 6 hour diffusion curve of sulfacetamide the number is 4.6. The value of "a" in this model is 0.445 cm, so it is expected that, after 6 hours, the concentration of sulfacetamide would be zero at 2.08 cm from the border between the ointment and agar medium. Similarly, the distance for the zero concentration zone for each drug could be estimated after different time intervals. On the other hand, the concentration of the drug at any distance between the border lines and the zero-concentration zone could also be determined from these curves.

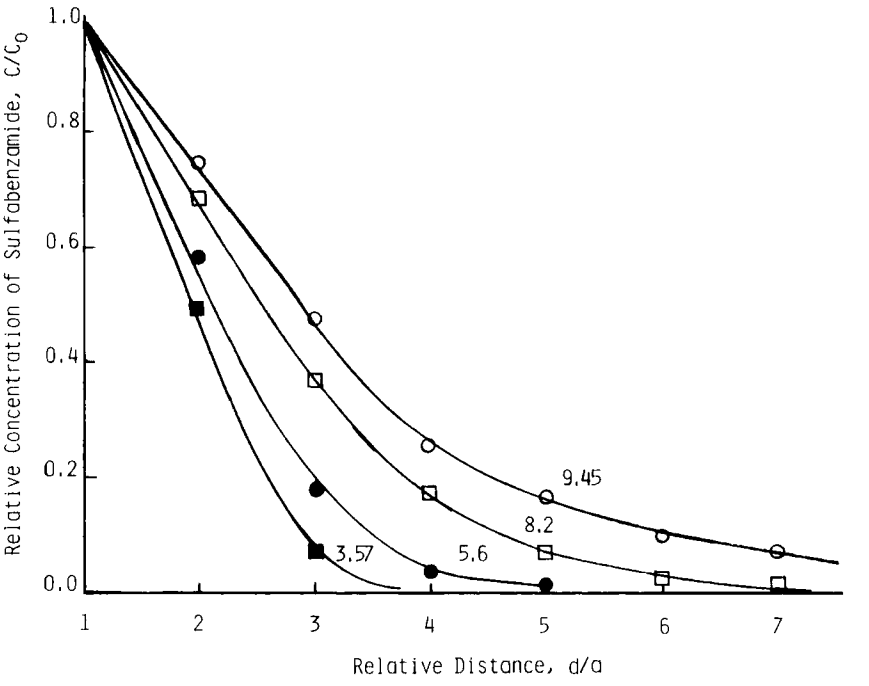

Fig. 5 - Distribution of Sulfabenzamide in agar plate as diffused from PEG Ointment, at 37°C, over different periods of time.
Key: See figure 4.

The diffusion model used in this study postulates that permeation of the sulfonamides in the agar gel occurs in two steps - the first process being a partition at the boundary between the diffusion medium and the ointment, producing freely mobile and diffusible molecules. The second step is a diffusion process in which molecules transport into the medium, by virtue of their random molecular motion, from higher concentration regions to lower concentration regions. Diffusion of the drugs through the agar can also be described in terms of two mechanisms[15]. In the "pore" mechanism, drugs are presumed to permeate the medium by diffusion through micro-channels or pores within the agar gel structure. The rate at which solutes permeate through these chan-

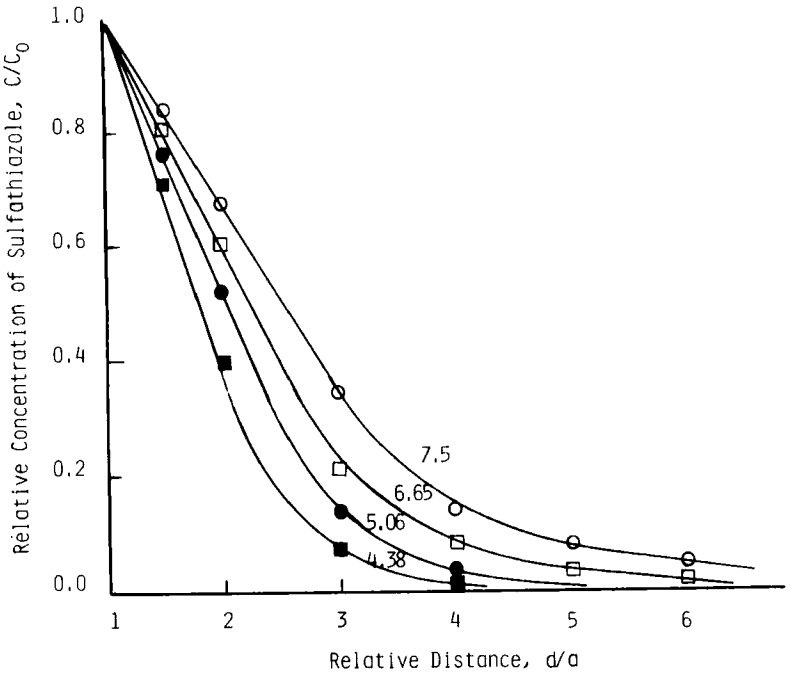

Fig. 6 - Distribution of Sulfathiazole in agar plate as diffused from PEG Ointment, at 37°C, over different periods of time. Key: See figure 4.

nels is controlled largely by the pore size of the gel and the molecular size of the diffusing molecules[16]. The other mechanism is the solution/diffusion or partition process. In this study the three sulfonamides were treated under the same experimental conditions regarding the type of the diffusion medium, time of incubation, and initial drug concentrations and temperatures of the system. Thus, the discrepancies observed in the diffusion coefficient for the three sulfonamides were mostly due to the variation in the molecular size of the drugs as well as the differences in the solubility and partition coefficients of the drugs between the ointment and acceptor phases.

The results obtained in this study showed that a linear correlation existed when the amount of drug released from each ointment base was plotted against the logarithmic time for the specific time periods conducted in this study. The observation of the logarithmic correlation between the amount of drug released and time may be due to the presence of nonlinear diffusional geometry of the system. Nevertheless, the solubility of the drugs in the ointment base and their partition properties into the agar medium played the major roles for the release of the drug from the different bases. At higher temperatures, the release and diffusion of the sulfonamides into the gel were much faster. These results reflect the importance of studying the effect of temperature on the absorption of drugs through the skin. The diffusion model used in this study can be a useful alternative for the test of drug release from different ointment bases. The mathematical analysis and computer simulations of the data will be described in the subsequent paper.

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