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EFFECT OF CERTAIN ADDITIVES ON THE DIFFUSION CHARACTERISTICS OF ASPIRIN, SALICYLAMIDE AND PHENACETIN THROUGH A CELLOPHANE MEMBRANE

II. Effect of aliphatic acids and polyethylene glycol

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ABSTRACT

A study has been carried out showing the effect of succinic, citric and tartaric acids, polyethylene glycols 1500, 2000, 4000 and 6000 on the diffusion rate of aspirin, salicylamide and phenacetin through a standard cellophane membrane. It was found that 2% w/v succinic acid was the most effective concentration of acid that increased the diffusion rate of aspirin. The incorporation of 3% w/v PEG 2000 or 6000 slightly increased aspirin diffusion rate. The effect of the previously mentioned aliphatic acid, urea and PEG 4000 or 6000 in the form of either solid dispersions or physical mixtures with the drug was also studied. It was found that succinic acid in all its tried concentrations increased the diffusion rate of aspirin .

Salicylamide diffusion rate slightly increased in presence of 3% w/v succinic acid, 2 and 3% w/v citric acid and 3% w/v tartaric acid. Salicylamide-succinic acid solid dispersion slightly increased the diffusion rate of the drug while the other tested drug-carrier solid dispersions of physical mixtures retarded the diffusion rate of salicylamide .

3% w/v of each aliphatic acid tested and PEG 6000 increased the diffusion rate of phenacetin. The other tested concentrations of $PEG_{(s)}$ produced insignificant effect on the diffusion rate of the drug. Phenacetin-urea, PEG 4000 or 6000 solid dispersions markedly increased the diffusion rate of phenacetin.

Effect of certain additives on the diffusion characteristics of aspirin, salicylamide and phenacetin through a cellophane membrane: II. Effect of aliphatic acids and polyethylene glycol

INTRODUCTION

Different studies have been carried out showing the effect of certain additives on the diffusion rate of insoluble drugs through membranes.

Barry and Brance[1] studied the permeation of oesterone oestradiol, oestriol and dexamethasone through a cellulose acetate membrane, shah and Nelson[2] recently studied the membrane permeation of a series of alkyl p-aminobenzoate. The use of certain polymeric materials to control the release of certain drugs such as contraceptive steroids[3,4], progestin[5,6] has been adopted. The apparent diffusion coefficient of sodium phenobarbitone was measured for the transport of the drug from the core of micror capsule into the surrounding sink conditions through ethyl cellulose film[7].

Numerous attempts have been made to modify the dissolution characteristics and consequently diffusion of certain drugs, in an attempt to attain more rapid and complete absorption[8] (or diffusion). A unique way of obtaining microcrystalline dispersions of a drug in the gastro-intertinal fluids has been suggested by Sekiguchi and Obi[9,10]. They were the first who proposed the utilization of solid dispersions, using a water soluble carrier as a matrix to increase the dissolution and the subsequent absorption or diffusion of oral poorly soluble drugs. They suggested the formation of an eutectic mixture of the drug with a physically inert easily soluble carrier. Goldberg et al[11]. presented a theoretical arguments which attempted to demonstrate that the results obtained by Sekiguchi and Obi[9,10] were due to the formation of solid solution rather than simple eutectic

mixture. They reported that insoluble drugs dispersed molecularly in the matrix of a soluble inert carrier can increase not only the dissolution rate, but also the solubility of the drug. From the theoretical standpoint, it was reported by Chiou[12] that a poorly soluble or insoluble drug can achieve the fastest rate of dissolution and absorption when dispersed in a glass solution of a water soluble carrier. Upon exposure to aqueous fluids, the active drug will be released in a state of fine particles or single molecules.

In this work the incorporation of certain aliphatic acids and polyethylene glycol with the aqueous solution of the drug has been investigated in order to determine their effect on the diffusion rate of aspirin, salicylamide and phenacetin through a standard cellophane membrane. Also, the effect of certain water soluble carriers either physically incorporated with the drug powder or in the form of their solid dispersions on the permeability characteristics of the drugs molecules through the cellophane membrane has been studied.

EXPERIMENTAL

Materials:

Citric acid[(a)], Succinic acid, tartaric acid[(b)], urea[(c)], polyethylene glycol (PEG) 1500, 2000, 4000 and 6000[(c)] were used.

Solutions:

1,2 and 3% w/v citric acid, tartaric acid and succinic acid solution: 1,2 and 3% w/v of PEG 1500, 2000, 4000 and 6000 solutions were prepared.

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a) Merk Co., L.T.D. Germany b) May & Baker U.K.

c) B.D.H.Poole, U.K.

Procedures :

1- Determination of the In-Vitro Diffusion of Aspirin, Salicylamide and phenacetin through cellophane membrane: as previously described under I.[13]

2- **Preparation of solid dispersions:**

The fusion method was adopted to prepare the solid dispersions of aspirin, salicylamide and phenacetin with each of citric , tartaric and succinic acids, urea , PEG, 4000 and 6000 A physical blend of the drug and each carrier at the eutectic composition was heated in a porcelain dish until the mixture completely melted, and then poured onto a clean cold glass plate. After complete solidification, the plate was placed in vacuum disiccator for 24 hours. The solid masses were pulverized in a mortar and an 80-200-mesh fraction was collected for the diffusion rate study. An accurate weight of the prepared solid dispersions of each drug corresponding to 170 mg of aspirin, salicylamide and to 60 mg of phenacetin was used for each experiment in order to prepare 1 mg/ml solutions of the first two drugs and 0.5 mg/ml of the third drug.

RESULTS AND DISCUSSION

A. Effect of aliphatic acids and Polyethylene glycol:

The data presented in Fig. 1 revealed that all the concentrations of the tested aliphatic acids increased the amount of aspirin diffused. The largest amount of aspirin diffused was observed in presence of 2% w/v succinic acid. From the results illustrated in Fig. 2 it can be concluded that all the investigated concentrations of PEG 1500 and 4000 decreased the amount of aspirin diffused through the cellophane membrane. 3% w/v PEG 2000 or 6000 slightly increased the amount of the drug diffused .

The other tested concentrations of PEG 2000 or 6000 decreased the amount of aspirin diffused.

The effect of citric , tartaric and succinic acid on the amount of salicylamide diffused through the cellophane membrane was presented in Fig. 3. The data revealed that 1% of these acids decreased the amount of salicylamide diffused. The other tested concentrations increased the amount of the medicament diffused. A maximum amount of the drug diffused in presence of 3% w/v succinic acid.

From the data presented in Fig. 4 it can be deduced that all the tested concentration of PEG 1500, 2000,4000 and 6000 not affected the amount of salicylamide diffused. The majority of them showed a slight decrease in the amount of the drug diffused.

In case of phenacetin, the presence of 1% w/v of each acid reduced the amount of the drug diffused. 3% tartaric acid was the most effective one in increasing the amount diffused(the most marked increasing effect was found in presence of 3% w/v tartaric acid followed by 3% w/v succinic acid (Fig. 5).

PEG 1500 and 2000 decreased the amount of drug diffused in all the tested concentrations 1% w/v of either PEG 4000 or 6000 decreased the amount of the drug diffused, while 3% w/v of these PEG increased the amount diffused (Fig. 6).

B- Effect of Solid Dispersion and Physical mixture:

The phase diagrams of each of the three drugs in presence of different water soluble carrier has been constructed. The effect of different water soluble carriers at the eutectic composition on the diffusion rate of aspirin, salicylamide and phenacetin through cellophane membrane was studied and the data presented in Table 1,2 and 3. The diffusion rate of aspirin (Table 1). reduced when it was admixed with tartaric acid,urea,

PEG 4000 and PEG 6000 in a form of either solid dispersion or physical mixture at the eutectic ratio. Citric acid in the solid dispersion form slightly increased the diffusion rate of aspirin. On the other hand, when it was physically mixed with aspirin the diffusion rate of the drug decreased. succinic acid is the only carrier that enhanced the diffusion rate of aspirin when it was admixed in a fused or physical mixture.

Table 2 shows that, the presence of either citric acid or succinic acid in a fused mixture with the drug increased the diffusion rate of slaicylamide through the cellophane membrane . On the other hand, when these two water soluble carriers were physically mixed with slaicylamide, they reduced the amount of the drug diffused. The presence of the other water soluble carriers decreased the diffusion rate of salicylamide as compared with the control.

In case of phenacetin, the diffusion rates of phenacetin solid dispersion and physical mixture at the eutectic composition for each carrier, is presented in Table 3. The data obtained revealed that, all the tested acids when they were separately incorporated with phenacetin in the form of either fused or physical mixtures, decreased the diffusion rate of the drug. While the presence of urea, PEG 4000 or 6000 in fused mixtures with the drug increased the diffusion rate of the drug. When these carriers were physically admixed with the drug its diffusion rate correspondingly decreased .

In conclusion, succinic acid in all tested concentrations increased the diffusion rate of aspirin when it was either fused or physically mixed with the drug, followed by tartaric acid. 2% w/v of these acids produced the highest diffusion rate PEG generally retarded the diffusion rate of the drug except

3% w/v PEG 2000 or 6000 slightly increased the diffusion rate.

In case of salicylamide, a slight increase in its diffusion rate in presence of 3% w/v succinic acid, 2 and 3% w/v citric acid and 3% w/v tartaric acid.

Salicylamide-succinic acid solid dispersion slightly increased the diffusion rate of the drug as compared with the other tested carriers when they blended with salicylamide in the form of either fused or physical mixture.

The incorporation of 3% w/v of each aliphatic acid tested and PEG 6000 increased the diffusion tate of phenacetin. While the other tested concentrations and other $PEG_{(s)}$ produced insignificant effect on the diffusion rate of the drug. Urea , PEG 4000 or PEG 6000 markedly increased in the diffusion rate of phenacetin when they were present in the form of solid dispersion with the drug. This finding could be explained, based on the theoretical consideration of molecular size difference between the polymers and the drug.[14,15]. This molecular size difference forms an essential criterion for the formation of an essentail solid solution. Accordingly the use of high molecular weight PEG was more favourable than low molecular weight PEG in enhancing the diffusion rate of the dispersed drug, i.e. the greater the difference between the molecular weight of the polymer and that of the dispersed drug, the more pronounced will be the enhancement in the dissolution and hence the diffusion rate of the drug.

Moreover the supercooling and viscous effect of the drug PEG melt forms an essential determining factor that influences the reduction in particle size[16]. This could be explained by the fact that during solidification of the system crystallization of

the dispersed drug will be retarded due to the slow migration and the difficulty of nucleation of the drug in the viscous medium[17,18]. Accordingly, the drug will not nucleate and micro-crystals form with the corresponding reduction in the particle size of the dispersed drug, and the subsequent enhancement in its dissolution and diffusion rates.

The corresponding physical mixtures of $PEG_{(s)}$ with the drug and the drug-aliphatic acids either physical mixture or solid dispersions decreased the diffusion rate of the drugs as compared with that of the control.

Table 1: Diffusion rate of aspirin solid dispersions and physical mixtures (at the Eutectic composition) through a cellophane membrane, at 37°C.

Time (minutes)	Amount of Aspirin Diffused (mcg/ml) in Presence of the following Carriers												Control
	Citric acid		Tartaric acid		Succinic acid		Urea		PEG 4000		PEG 6000		
	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	
10	23	15	12	18	15	15	11	12	11	11	9	10	23.39
20	29	26	23	28	41	37	26	27	21	21	23	25	29.03
30	41	41	35	42	50	47	37	39	36	34	34	36	38.71
40	51	51	46	51	62	55	50	53	48	45	50	52	50.00
50	64	63	59	66	80	62	62	61	56	59	63	54	63.71
60	79	73	70	74	94	71	75	73	70	69	73	67	79.03

Table 2: Diffusion rate of salicylamide solid dispersions and physical mixtures (at the eutectic composition) through a cellophane membrane at 37°C.

Time (minutes)	*Amount of salicylamide diffused (mcg/ml) in Presence of the following carriers:*												*Control*
	Citric acid		*Tartaric acid*		*Succinic acid*		*Urea*		*PEG 4000*		*PEG 6000*		
	S.D.	*P.M.*	*S.D.*	*P.M.*	*S.D.*	*P.M.*	*S.D.*	*P.M.*	*S.D.*	*P.M.*	**S.D.**	**P.M.**	
10	17.43	9.17	9.17	7.34	14.68	10.09	8.25	12.84	15.60	5.50	8.26	6.42	17.49
20	25.09	20.18	23.85	17.43	28.81	21.10	18.35	22.02	22.94	14.68	12.84	20.18	21.66
30	29.36	29.36	31.19	25.69	44.04	29.36	27.52	24.77	31.19	17.43	23.85	24.77	35.00
40	39.45	37.61	37.61	39.45	56.88	38.53	39.45	31.19	33.03	29.36	34.86	34.36	39.16
50	48.62	46.79	47.41	45.87	68.81	53.21	46.79	44.03	43.12	34.86	44.03	50.46	48.33
60	59.63	54.13	57.80	52.29	81.65	66.05	56.88	55.04	50.46	46.89	76.79	54.13	56.66

Table 3: Diffusion rate of phenacetin solid dispersion and physical mixtures (at the eutectic composition) through a cellophane membrane at 37°C.

Time (minutes)	Amount of Phenacetin Diffused (mcg/ml) in Presence of the following Carriers												Control
	Citric acid		Tartaric acid		Succinic acid		Urea		PEG 4000		PEG 6000		
	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	S.D.	P.M.	
10	5.32	3.19	-	6.38	- -	- -	10.64	8.51	10.11	8.51	11.17	7.98	13.97
20	7.10	6.38	3.19	8.51	9.57	5.32	20.10	13.30	17.55	11.70	23,12	11.70	16.91
30	8.51	11.70	7.45	13.83	17.02	13.83	29.25	19.25	30.85	17.20	31.91	17.55	21.32
40	12.77	19.14	12.77	20.21	23.40	20.21	35.10	23.94	37.23	22.87	38.30	24.47	24.36
50	18.08	26.60	15.95	22.34	26.59	26.60	39.36	30.85	45.74	32.45	43.08	31.91	27.20
60	24.47	29.79	22.34	27.66	36.17	37.23	43.08	35.64	53.81	38.30	47.87	37.50	30.88

S.D. : Solid dispersion

P.M. : Physical mixture.

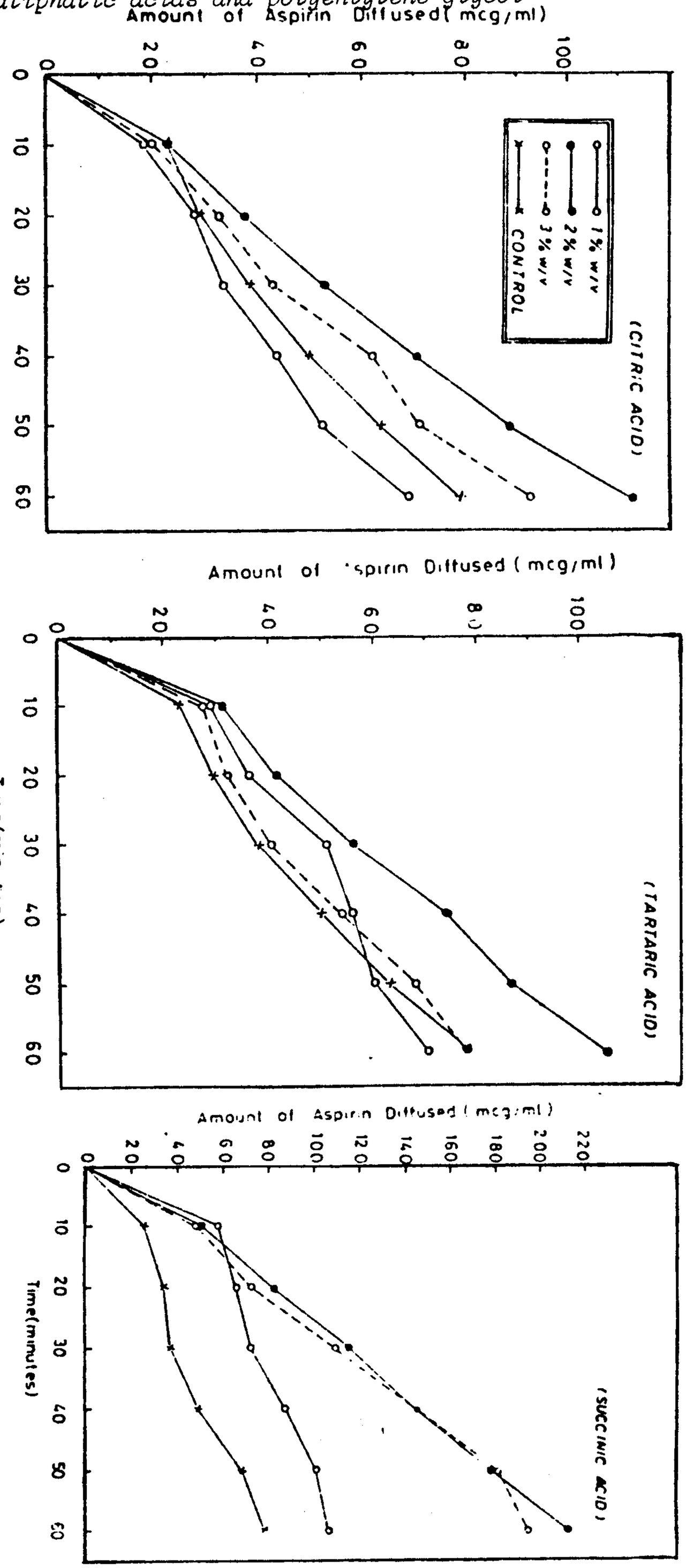
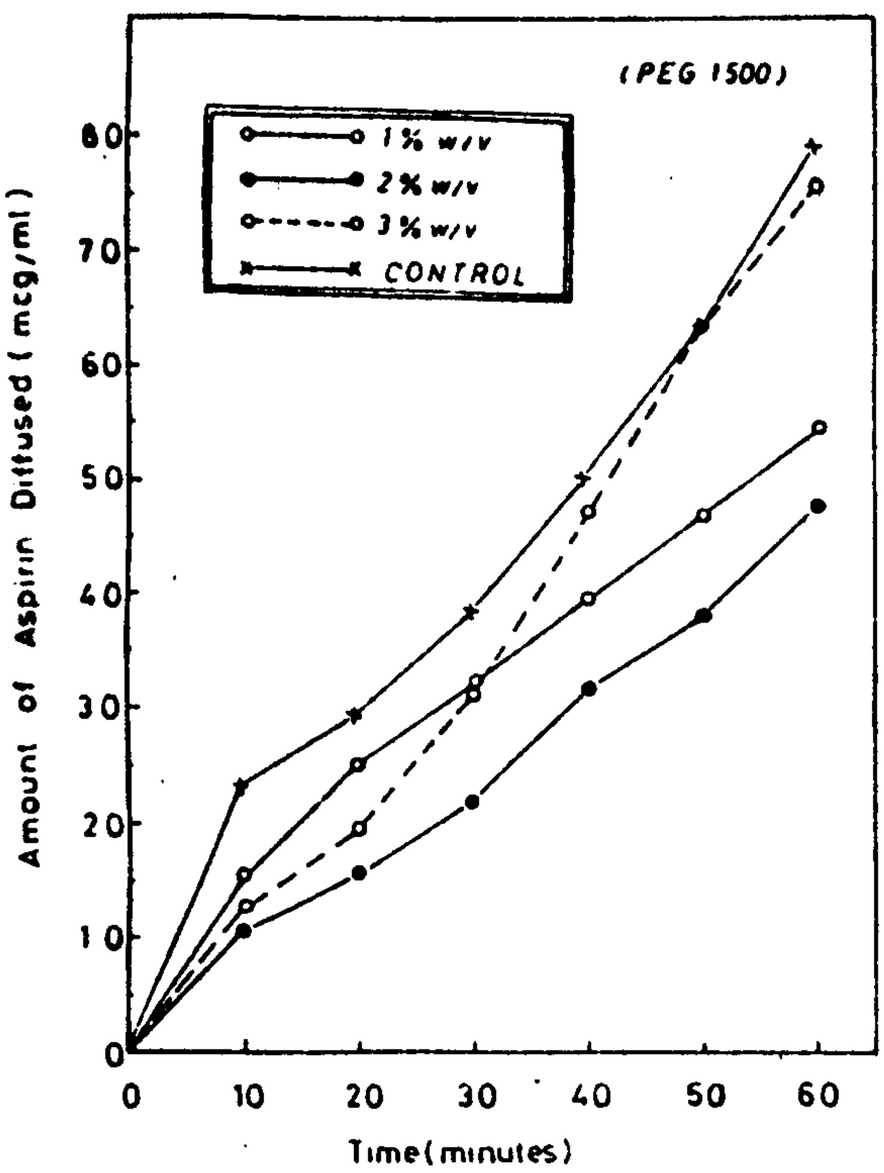
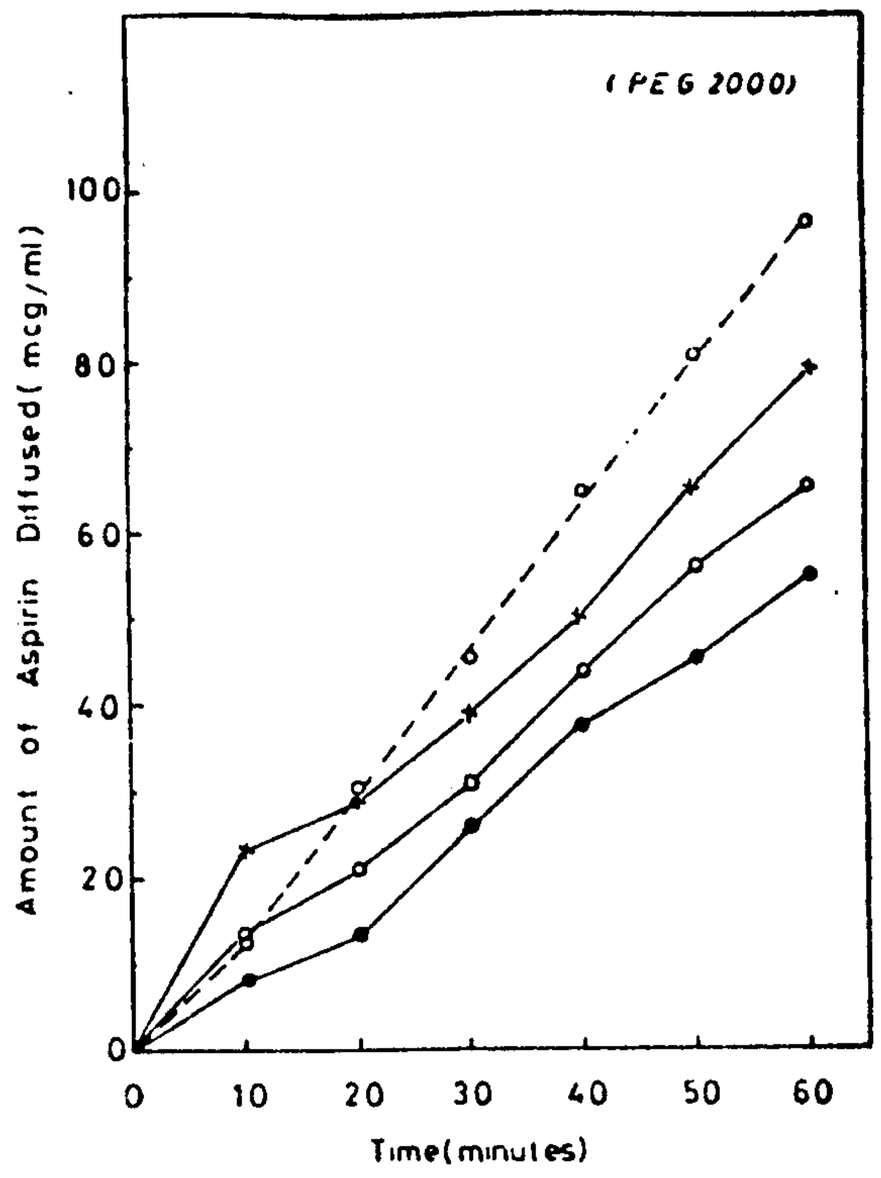
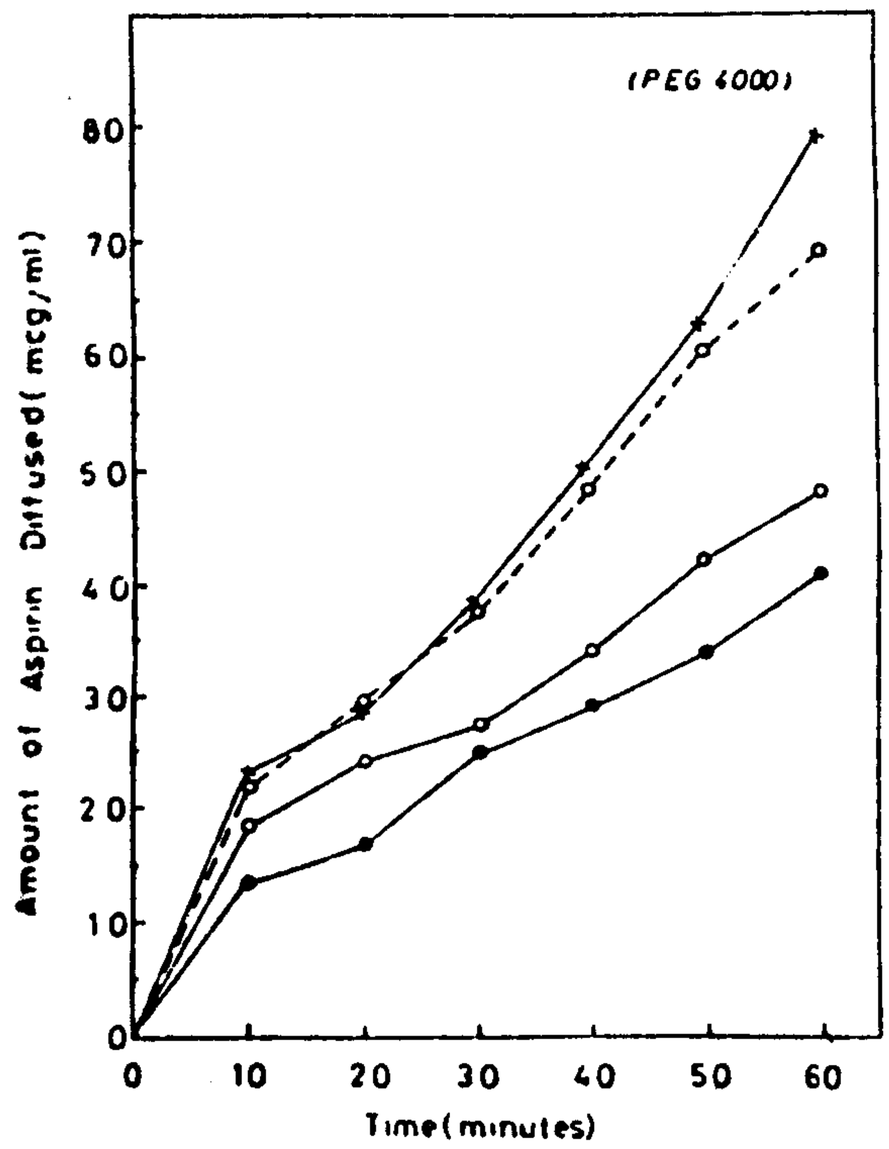


Fig 1: Effect of different concentrations of certain aliphatic acids on the diffusion rate of aspirin through cellophane membrane at 37°







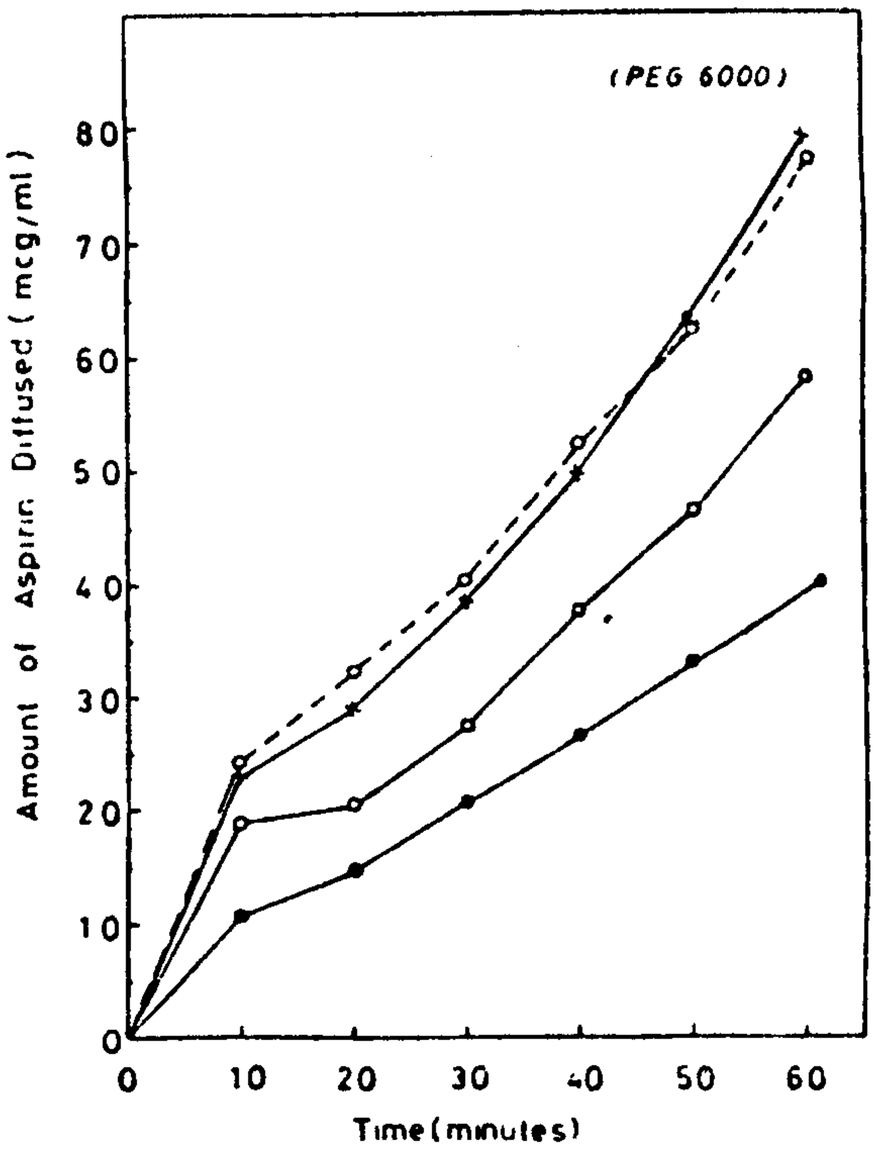


Fig 2: Effect of different concentrations of PEG on the diffusion rate of aspirin through cellophane membrane at 37°

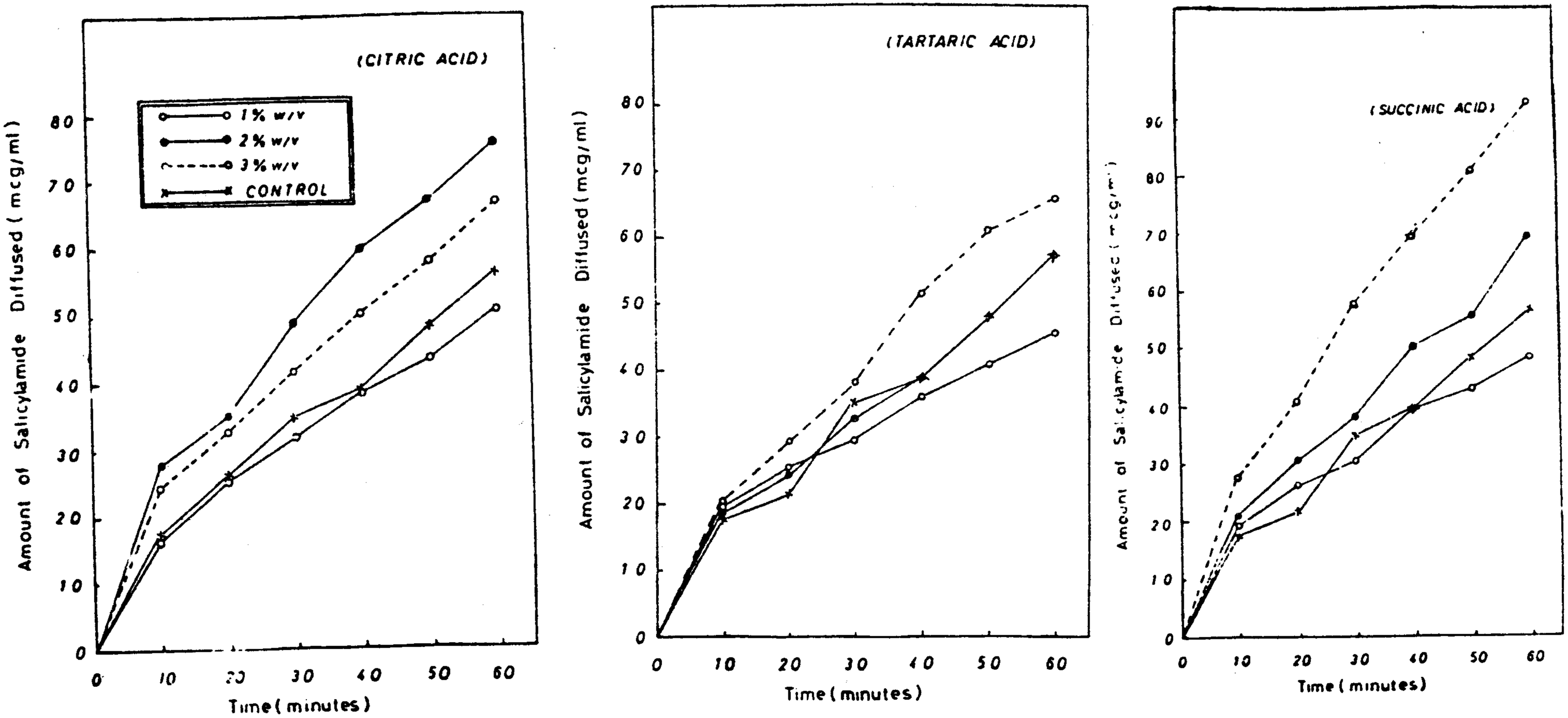


Fig. 3: Effect of different concentrations of certain aliphatic acids on the diffusion rate of salicylamide through cellophane membrane at 37°

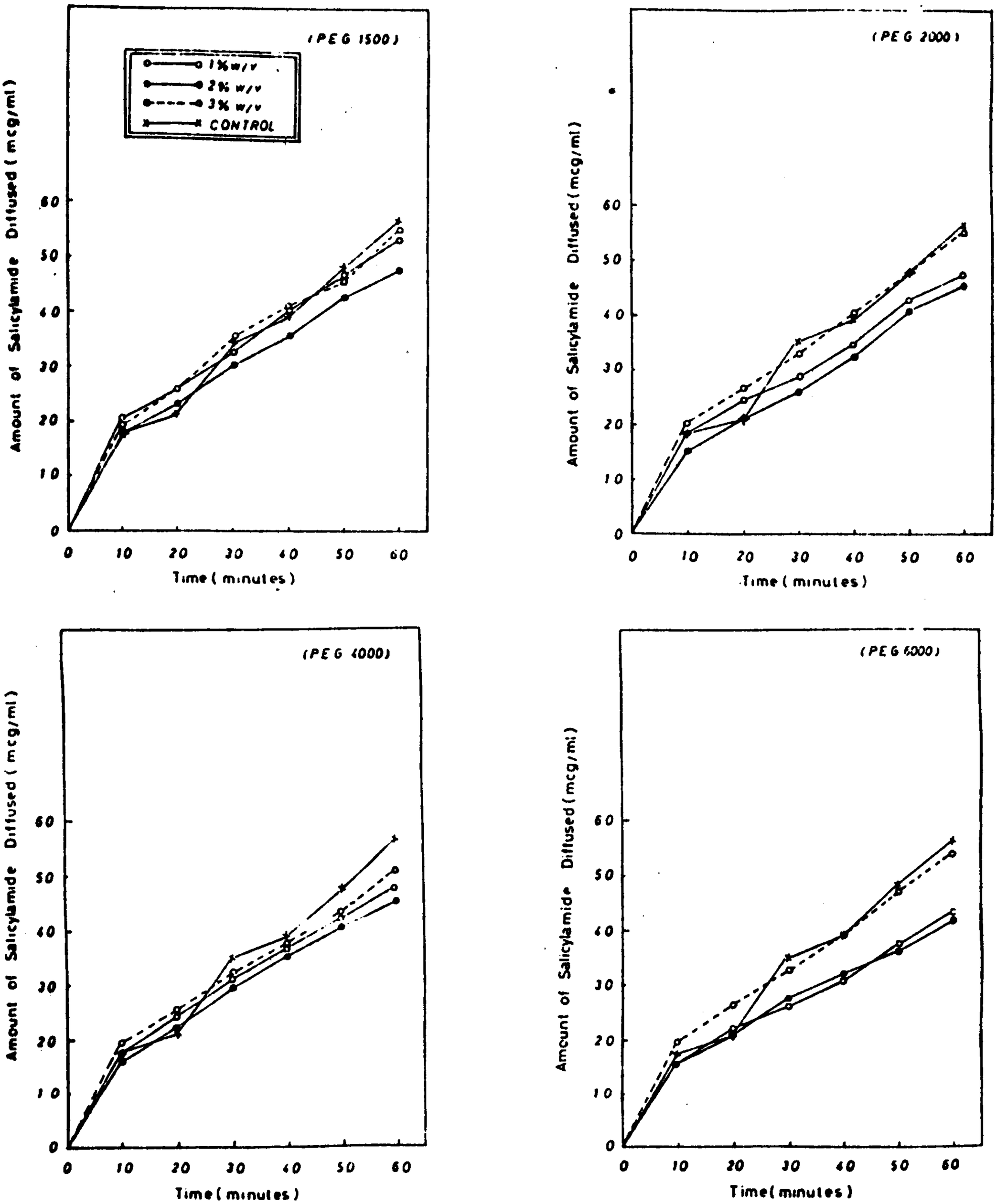


Fig. 4: Effect of different concentrations of PEG on the diffusion rate of salicylamide through cellophane membrane at 37°

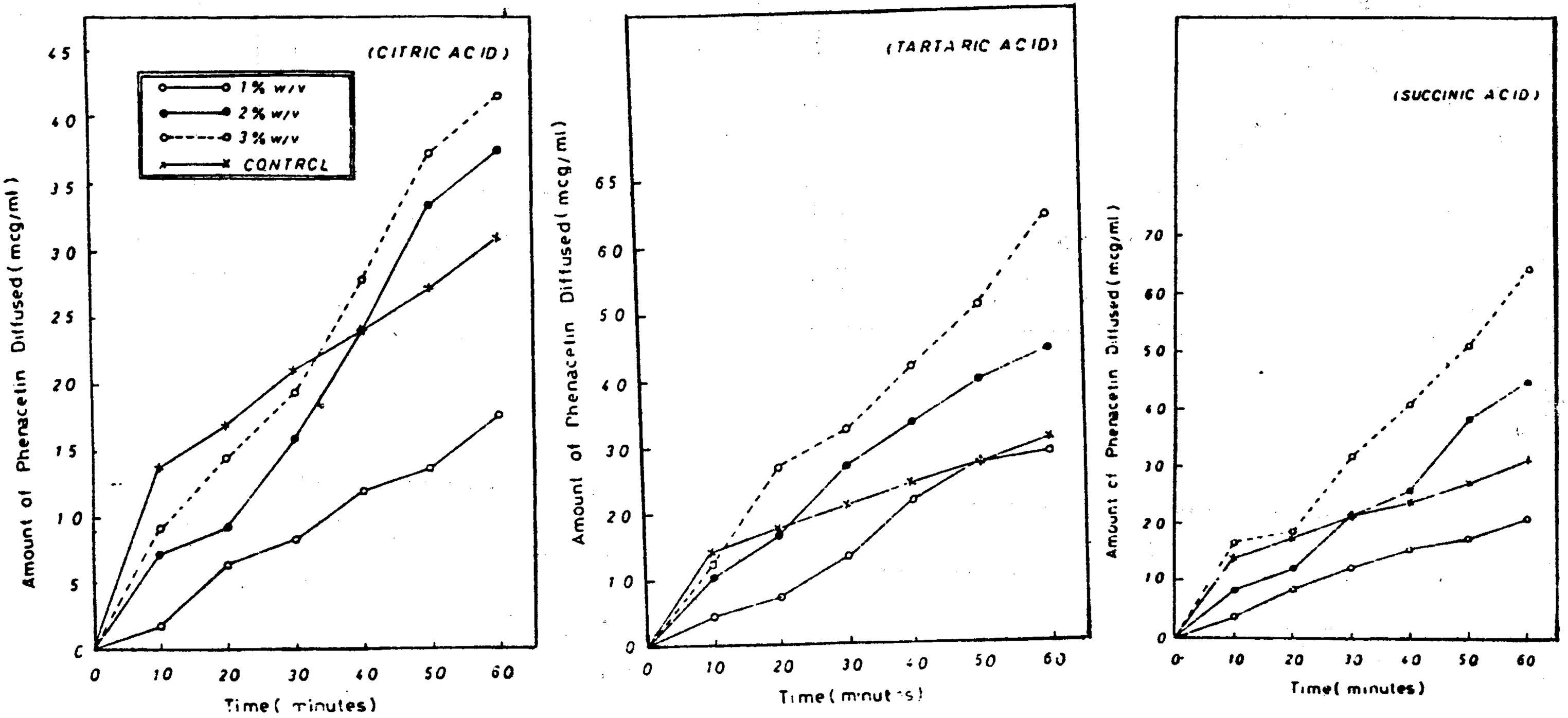


Fig. 5: Effect of different conenctrations of certain aliphatic acids on the diffusion rate of phenacetin through cellophane membrane at 37°

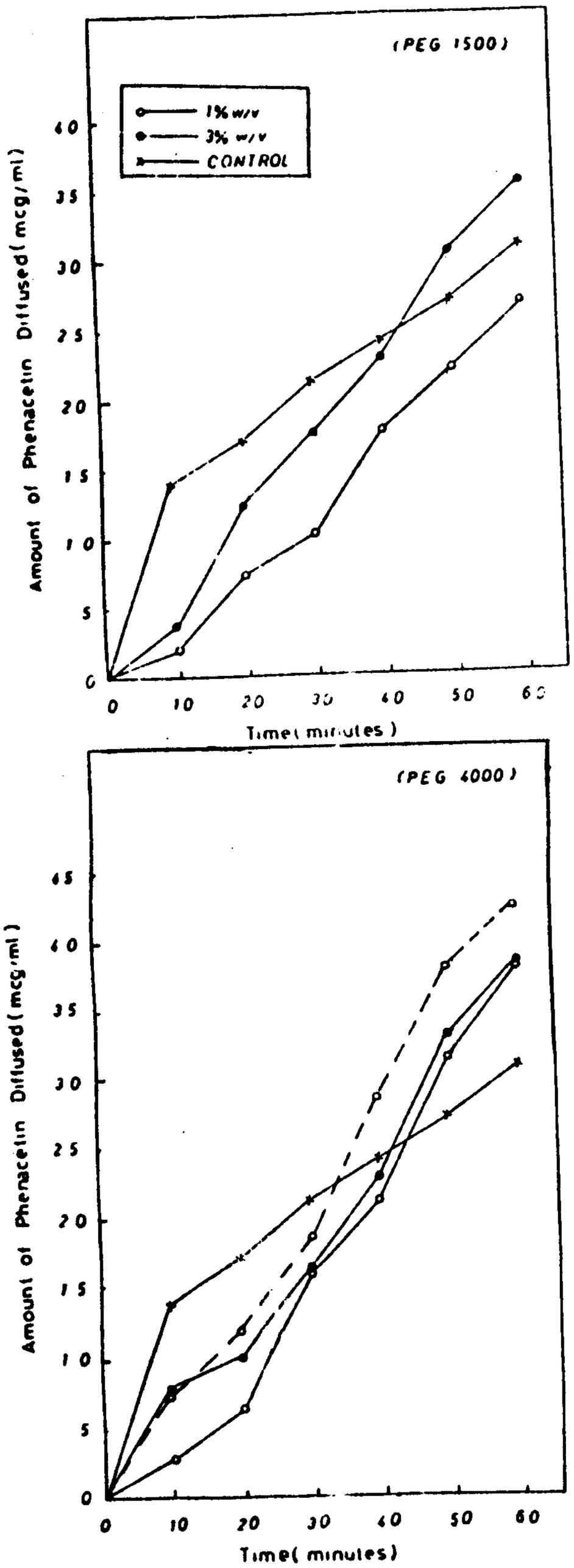


Fig. 6: Effect of different concentrations of PEG on the diffusion rate on phenacetin through cellophane membrane at 37°

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تأثير بعض الأضافات على خواص أنتشار الأسبرين ، السالسبلاميد وكذلك الفيناسيثين من خلال غشاء السيلوفان تأثير الأحماض الأليفانيه والجليكولات عديدة الأثيلين

حمدى عبدالستار الصردى ـ فوزيه سيد حبيب ـ سيد اسماعيل محمد

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تمفىهذا البحث دراسة تأثير بعض الأضافات الصيدليه على معدل انتشار الأسبرين ، السالسبلاميد وكذلك الفيناسيثين من خلال غشاء السيلوفان ٠

واتضح من الدراسه أن معدل انتشار الأسبرين والسالسبلاميد من خلال الغشاء السيلوفانى يزدادان زياده ملحوظه فى حالة تواجد حمض السكسنيك ٠

أما الفيناسيثين فقد زاد معدل انتشاره فى وجود حمض الطرطريك وباستخدام محاليل محضره من مشتقات صلبه لكل من الأسبرين والسالسيلاميد فى حمض السكسينيك لوحظ أن معدل انتشار هذين العقارين قد زاد زياده ملحوظه من خلال الغشاء السلوفانى ٠ أما فى حالة الفيناسيثين فقد لوحظ أن أعلى معدل انتشار له قد حدث باستخدام تحاليل للعقار محضره من مشتقاته الصلبه فى جليكولات عديد الأثيلين ٤٠٠٠ ، ٦٠٠٠ وكذلك مع البولينا ٠

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