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INTERACTIONS OF RIBOFLAVINE WITH CERTAIN ANALGESICS

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ABSTRACT

The interaction of riboflavine with certain analgesics viz, paracetamol, phenazone, aspirin and acetanilide was investigated. The solubility of riboflavine was increased linearly with increasing the concentration of both paracetamol and phenazone. Aspirin and acetanilide however showed no effect on the solubility of riboflavine. The apparent partition coefficient of riboflavine between chloroform and water was decreased to variable extents in the presence of different molar ratios of riboflavine and each of the tested analgesics. The diffusion rate of riboflavine through cellophane membrane was enhanced in presence of paracetamol followed in decreasing order by aspirin and phenazone. However, acetanilide, showed no increasing effect on the diffusion rate of riboflavine. The presence of these analgesics showed marked changes in the UV and IR absorption spectra of riboflavine. The Job's method of continuous variation was adopted to investigate these interactions and complexes of 1: 1 molar ratio were revealed between riboflavine and each of paracetamol, aspirin and phenazone. It could be concluded that complexation between riboflavine (a very slightly soluble drug in water) and the commonly used analgesics viz., paracetamol, aspirin and phenazone led to changes in the solubility, partition and diffusion rate of the vitamin which in turn could affect its absorption and availability.

INTRODUCTION

It is deduced that the interaction of one drug with another drug, can result in the formation of complexes having physicochemical properties appreciably different from those of the drug itself. Among the properties of interest, is the effect on the solubility in appropriate aqueous systems, partition coefficient,

relative rates of diffusion of the free and complexed drug across biologic membranes and spectral behaviour of the drug.

Analgesics and anti-inflammatory drugs are therapeutic class of drugs which have great potential for drug or excipient interactions[1-6]. Since they may be purchased over-the-counter they are widely used by the public and may be taken concurrently with many drugs. It has been found that there is a change in partitioning characteristics of propanolol and oxprenolol in presence of a range of nine anti-inflammatory drugs[2]. On the other hand, the presence of caffeine with salicylates, except sodium gentisate, decreases their rate of transport[3]. Chiba et al,[5], showed that the persistence of sulfamethizole in plasma was prolonged by coadministration of three non-steroidal anti-inflammatory drugs; alclofenac, diclofenac and tiaprofenic acid. The prolonged action has been attributed to the competitive interactions between sulfamethizole and these drugs at renal secretory level[5]. Paracetamol was reported to form 1 : 1 complex with antipyrine which is shown to be stabilized through hydrogen bonding[7].

Ribolfavine is a component of the flavoprotein enzymes which form part of an enzyme system for the transference of hydrogen[8]. The flavoproteins are necessary for the oxidation of carbohydrates, amino-acids aldehydes and other products of metabolism. Before it can be utilized, riboflavine must be phosphorylated, the process occuring in the intestinal wall, liver and red blood-cells[8].

It has been reported that salicylates, cause the breakdown of some high-energy intermediate involved in the phosphorylation process of ribobflavine. Byung et al[1], examined the molecular interaction between salicylates and riboflavine in non aqueous solvents. They found that salicylates produce marked changes in the absorption spectra of riboflavine. These spectral changes were attributed to the formation of the hydrogen-bonded dimer. It appeared that strongest complex has formed with salicylic acid, a weaker one with aspirin and even weaker onewith salicylamide[1].

Interactions of Riboflavine with Certain Analgesics

The aim of this study is to examine the molecular interaction between riboflavine and certain household analgesics viz., paracetamol, aspirin, acetanilide and phenazone. Riboflavine is chosen because, first; it is absorbed from the gastro-intestinal tract by specialized transport system[9]. Second; it is considered a low dose drug and alteration of its physicochemical properties can produce significant changes in the rate and extent of riboflavine absorption from GI tract. Third, it is a component of flavoprotein enzymes, thus, it is present naturally in the body and any alteration in its physicochemical properties may impair the physiologic activities of these enzyme systems.

EXPERIMENTAL

Materials :

Riboflavine	(Nile Co. ; Cairo, Egypt).
Paracetamol	(E.Merck Darmstadt, W-Germany),
Phenazone	(AL-Gamhoria Egypt),
Aspirin,Acetanilide,Sodium Hydroxide,	
Chloroform	(El-Nasr Pharma. Co., Egypt),
Potassium dihydrogen phosphate	(May & Baker LTD, England).

All the chemicals were of pharmaceutical grade and were used without further purification.

Apparatus :

- Thermostatically controlled shaker
  (Unitronic 320 OR (Selecta).
- Self-recording spectrophotometer (UV)
  (Pye-Unicum, SP-1750, England).
- Unicam SP 1025 Infrared Spectrophotometer, England).
- Spectrophotometer (UV-150-02 Shimadzu, Japan).
- PH-Meter titrimeter (U9N Tacussel Electronique, Solea).

Methods :

Solubility Studies :

The solubility of riboflavine alone and in the presence of different concentration of the examined analgesics was determined using thermostatically controlled shaker. Excess of riboflavine was equilibrated 2 hr. at 37°C with 20 ml of different concentrations of analgesic solutions in 50-ml conical flasks. Samples were withdrawn by pippet fitted with filter and their riboflavine content was determined spectrophotometrically at 446 nm. It was found that the presence of analgesics, under investigation, did not interfere with riboflavine determination at this wavelength.

Equilibrium Partition Studies :

Solutions of analgesic drugs and riboflavine were prepared in phosphate buffer pH 7.4. In a 50-ml glass stoppered conical flask was placed 5 ml solution of riboflavine in phosphate buffer plus 5 ml either of; phosphate buffer or of the analgesic solution in phosphate buffer, and 10 ml chloroform. Chloroform and buffer solution were presaturated with each other. Concentrations were calculated so that ratios of riboflavine and the analgesic drugs were adjusted to be 1 : 1, 1 : 2 and 2 : 1. The flasks were equilibrated at 37°C in thermostatically controlled shaker. The agitation rate was 70 r.p.m. for 24 hr. The chloroform layer was removed by aspiration and aliquots of the aqueous phase were submitted to spectrophotometric determination of riboflavine at 446 nm. light must be avoided in all determinations. Each experiment was performed in triplicate, and the concentration of drug in the organic phase was deduced by subtraction and the apparent partition coefficients [K O/W (app.)] was calculated.

Diffusion Studies :

An equilibrium dialysis cell composed of two conical shaped compartments (each 200 ml capacity) and connected together at a 1 cm distance from the bottom was utilized. In the junction between the two compartments (a circle with 2.6 cm diameter) a standard cellophane membrane was fastened and tested carefully for leaks. In one of the compartments (receiving), 150 ml phosphate buffer was placed and in the other compartment (source), either 150 ml riboflavine

solution in phosphate buffer or mixture of riboflavine-analgesic solutions of different molar ratios (1 : 1, 1 : 2, and 2 : 1). The sampling holes in the top of the cells were closed, and the diffusion cells were agitated at a rate of 50 r.p.m. in a thermostatically controlled water bath at 37°C. At time intervals, samples of 5 ml each were withdrawn from the receiving compartments. Samples were compensated by the same quantity of phosphate buffer each time, and samples were subjected to spectrophotometric determination of riboflavine at 446 nm.

Job's Method of Continuous Variation :[10]

From two equimolar aqueous solutions of riboflavine and each analgesic, the following series of dilutions were prepared :

1- Mixtures of riboflavine and the analgesic of different molar ratios, but of the same final molar concentration.
2- Solutions of riboflavine corresponding to those in step (1), but without the addition of the analgesic solution and completed to the final volume with water.
3- Solutions of the analgesic corresponding to those in step (1), but without the addition of riboflavine solution and completed to the same final volume with water.

The observed spectrophotometric absorbance values, obtained at various mole fractions in Step (1) were subtracted from the corresponding values that obtained from summation of the absorbance values obtained in Step (2). This difference was then plotted against mole fraction.

Differential Ultraviolet Spectrophotometric Studies :

Differential ultraviolet absorption sepctra of riboflavine in presence of analgesic was made as follows : Solution containing 10 ug/ml riboflavine in water and in different concentrations of the investigated analgesics were measured against blank solutions containing the same concentration of the respective analgesic.

Infrared Studies :

Potassium bromide discs were prepared for riboflavine, the investigated analgesic and their (1:2) physical mixtures.

RESULTS AND DISCUSSION

1- Solubility Studies :

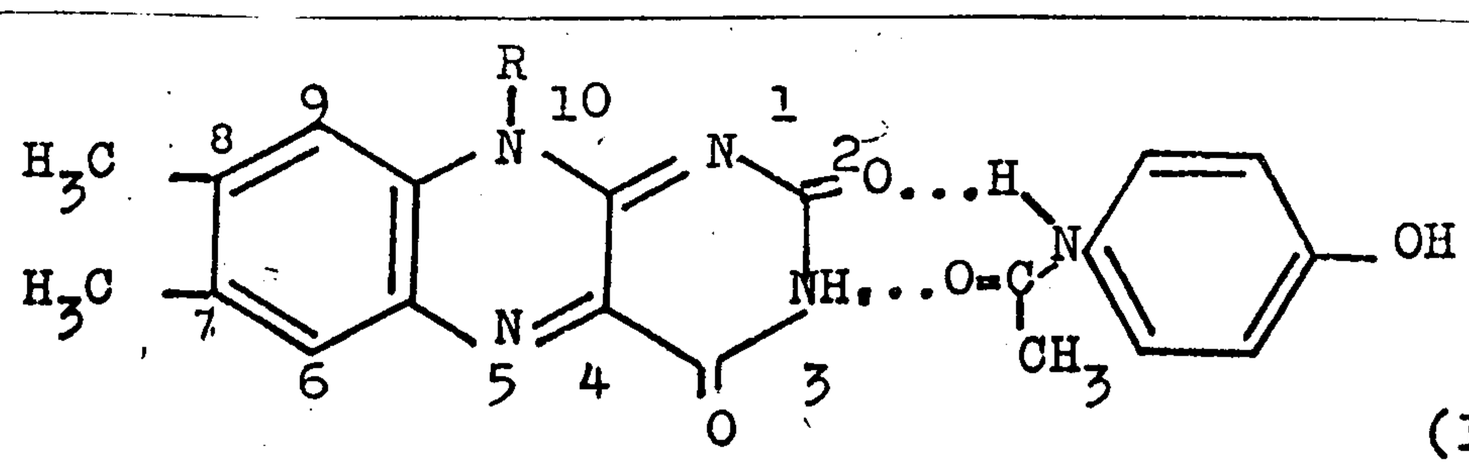
The effect of paracetamol, aspirin, acetanilide and phenazone on the water solubility of riboflavine was studied. It was observed that paracetamol and phenazone enhanced the solubility of riboflavine while acetanilide and aspirin showed negative effect at the concentration range studied. These concentrations were low because of their limited solubility. The graphical representation of riboflavine dissolved as a function of the analgesic concentration was illustrated in Figure 1. A linear relationship existed between the solubility of riboflavine and the analgesic concentration. Table 1 showed the solubilizing power of paracetamol and phenazone calculated as mole riboflavine solubilized per one mole of analgesic. It was obvious from this table that the solubilizing power of paracetamol is higher than that of phenazone. The solubility enhancement effect of phenazone and paracetamol towards riboflavine was found to be pH independent at pH range 3-7. The range between which lies the pH's of the analgesic solutions.

2- Partition Studies :

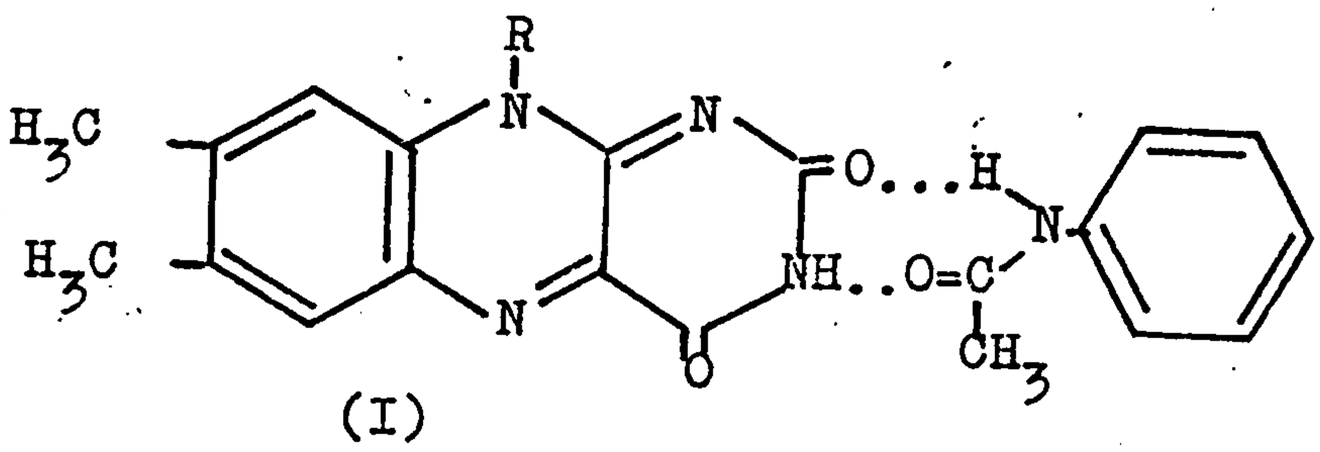
The values of the apparent partition coefficient [K O/W(app.)] of riboflavine between chloroform and phosphate buffer pH 7.4, were listed in table 2. The apparent partition coefficient of riboflavine was found to decrease in the presence of the tested analgesics. The following was the decreasing rank order correlation; paracetamol> aspirin > phenazone > acetanilide, at all tested molar ratios.

The ability of analgesic to decrease the K O/W (app.) of riboflavine is presumably a function of the chemical nature of the particular analgesic. The decreasing effect on K O/W (app.)by paracetamol (II) compared to acetanilide (III) which exhibited the least decreasing effect may be explained on comparing the chemical structure of both. The phenolic-OH group in paracetamol molecule is responsible for increasing the hydrophilicity of the molecule and hence

forming a more water soluble ion-pair between riboflavine (I) and paracetamol (II), the ion pair association may be represented as follows :



(II)



(I) (III)

The reduction in K O/W (app.) was concentration dependent. This dependency may lead to the conclusion that there was a sort of interaction between riboflavine and analgesics under investigation. The possible interaction was hydrogen bond formation as previously reported[1].

Permeation Rate Studies:

The diffusion of riboflavine across cellophane membrane from one compartment (the source compartment) to another (the receiving compartment) in absence and presence of the studied analgesics at different riboflavine : analgesic molar ratios was illustrated in figure 2 (A,B,C and D). It was obvious that the presence of paracetamol and aspirin increased the diffusion rate of riboflavine at molar ratios of 1 : 1 and 1 : 2 but at a molar ratio of 2 : 1 an

initial increase was observed followed by a decline after about 6 hrs. Phenazone showed the same effect but to a lesser extent. On the other hand, presence of acetanilide decreased the diffusion rate of the vitamin at 1 : 1 and 2 : 1 molar ratios but at 1 : 2 molar ratio the effect was not pronounced.

The effect of the investigated analgesics on the values of the permeability coefficient "P" of riboflavine was listed in table 3. This term was calculated from the following equation which was derived from the first law of Fick[10].

$$\text{Log } C_d = \text{Log } C_d(O) - \frac{PSt}{2.303\ V_d}$$

Where :

C_d = Concentration in source phase.
S = Surface area.
V_d = Source phase volume.
t = Time.
$C_d(O)$ = Initial concentration in the soure phase.

Plotting log C_d versus t resulted in a linear relationship with correlation coefficients listed in table 3. The value of the permeability coefficient "P" was calculated from the slope of the line. It is obvious from the table that "P" of riboflavine increased in the presence of paracetamol and aspirin at 1:2 and 1:1 riboflavine analgesic molar ratios. However, the presence of phenazone at those molar ratios and acetanilide at 1:2 molar ratio, statistically had no significant effect on "P" of riboflavine with 99% certainty.

The value of "P" of riboflavine was decreased in presence of all tested analgesic at 2:1 molar ratio. It can be concluded from the above discussion that analgesics that increase "P" value of riboflavine cause much decrease in K O/W (app.) of the vitamin at 1:1 and 1:2 molar ratios (compare table 2 and 3).

Interactions of Riboflavine with Certain Analgesics

Differential UV Spectrophotometric Studies:

The differential ultraviolet absorption spectra of aqueous riboflavine solutions at various analgesic concentrations were constructed (Fig. 3-6). It is clearly obvious that the absorption band at 220 nm in the spectrum of riboflavine completely vanished in presence of all tested analgesics. Moreover the wavelength of maximum absorption of ribolavine at 262 nm was shifted to longer wavelength (bathochromic shift). There was hypochromic effect in the spectrum of riboflavine at this wavelength in the presence of phenazone, paracetamol and acetanilide (Fig.3-5). It is worthy to note that on increasing the concentration of these analgesics both the bathochromic shift and the hypochoromic effect were increased. An isosbestic point apeared in the spectrum of riboflavine at 288 nm in the presence of paracetamol. On the other hand, there was hypsochromic shift in the absorption of riboflavine at 262 nm in presence of aspirin (Fig. 6). The hypsochromic shift was increased as the concentration of aspirin was increased from 0.002 to 0.006 M. Moreover, a new absorption band appeared at 286 nm in the spectrum of riboflavine in the presence of 0.004M aspirin. The absorption band of riboflavine at 262 nm disappeared completely in presence of 0.006 M aspirin.

The two absorption bands in the riboflavine spectrum at 220 and 262 are in the range of B-bands (benzenoid bands) which characterize the spectra of heteroatomic molecules[11]. It was reported that benzene shows a broad multiple peaks or fine structure in the near UV region between 230-270 nm[11], the fine structure arises from vibrational sublevels accompanying the electronic transitions. When $n \rightarrow \pi^*$ is shifted to longer wavelength, the characteristic fine structure of the B-bands may be absent in the spectra of substituted aromatics and is often destroyed by the use of polar solvents[11], that means when hydrogen bonds formed. The $n \rightarrow \pi^*$ arises in presence of chromophoric groups such as carbonyl groups, as in the case of

riboflavine. The charge density of C-2 carbonyl oxygen atom in the isoalloxazine ring in riboflavine is greater than that of the C-4 carbonyl oxygen atom, the N-3 proton is extremely labile and a good electron acceptor, since the charge density of N-3 nitrogen atom is higher than any of the other heteroatoms. Thus, the most probable hydrogen-bonded dimer is through the N-3 proton and C-2 carbonyl oxygen of the isoalloxazine ring[1].

The data also revealed that there was no change in the absorption maxima of riboflavine at 370 and 446, in presence of all analgesics. The transition in riboflavine occured at 446 nm due to-N=N- conjugation with the other two aromatic rings, and the π orbitals extended over the whole molecule and the levels were brought closer together[12]. This transition is not altered in presence of the tested analgesics.

From the above discussion it was concluded that there may be a sort of molecular interaction between ribofalvine and the investigated analgesics. These interactions affect the electronic state of riboflavine molecules via hydrogen bond formation.

The difference between the measured absorbance values at 266nm of riboflavine and the analgesic solution and those expected if no complexation takes place, as a function of mole fraction is graphically illustrated in figure 7. It could be concluded from the figure that riboflavine formed 1:1 complexes with each of paracetamol, phenazone and aspirin. Acetanilide showed no absorbance differences at all molar ratios tested,thus complexation between the vitamin and acetanilide did not take place.

IR Spectral Studies:

Discussion will focus on the regions from 3500-3000 cm^{-1} (N-H stretching bands) and from 1800-1640 (C=O stretching bands)[11].

Interactions of Riboflavine with Certain Analgesics

In Figure 8 the N-H absorption bands of the physical mixture of riboflavine and each of the tested analgesics differed from riboflavine alone. In this region riboflavine showed three absorption bands at 3230,3350 and 3500 cm^{-1}. The absorption band at 3500 cm^{-1} disappeared when the vitamin was mixed with paracetamol, phenazone and acetanilide. While the absorption band at 3230 cm^{-1} became broad with paracetamol (may be due to the coupling with the absorption band of paracetamol) and disappeared with phenazone, acetanilide and aspirin. On the other hand, the absorption band at 3350 cm^{-1} is still present on mixing with all analgesics.

In the carbonyl stretching absorption area (Figs. 9-12), the IR spectrum of riboflavine showed two absorption bands; 1640, and 1725 cm^{-1}. These absorption bands are shifted to 1650 and 1730 cm^{-1} and are much reduced in intensity on mixing with aspirin (Fig. 9). Moreover, aspirin spectrum has undergone changes on mixing with riboflavine; the absorption band at 1770 cm^{-1} in aspirin spectrum shifted to 1755 cm^{-1} with marked reduction in intensity. On mixing with phenazone (Fig. 12) the absorption band of riboflavine that appeared at 1725 cm^{-1} was shifted to 1730 cm^{-1} became sharper, and that at 1640 cm^{-1} shifted to 1655 cm^{-1} (this may be due to coupling with analgesic band). No change can be detected in carbonyl stretching zone of riboflavine spectrum in the presence of acetanilide and paracetamol (Figs. 10,11).

The changes observed in the spectrum of the mixture of the vitamin and each of the tested analgesics, indicated a change of the electronic environment of the N-H and/or C=0 group of riboflavine due to its molecular interaction with the tested analgesics. The most accepted mechanism, as discussed before, is hydrogen bond formations.

Table 1: The Solubilizing Power of Paracetamol and Phenazone Towards Riboflavine at 37°C.

Analgesic Conc./M.	Mole riboflavine solubilized per mole analgesic	
	Paracetamol x 10^3	Phenazone x 10^5
0.015	3.7	-
0.04	2.1	-
0.06	2.4	-
0.08	2.2	-
0.10	2.1	-
0.20	-	0.0
0.6	-	6.1
0.8	-	14.6
1.0	-	12.5
2.0	-	10.2
3.0	-	9.5
4.0	-	10.5
5.0	-	9.8

Interactions of Riboflavine With Certain Analgesics.

Table 2: Effect of the Analgesics on Partition Coefficient of Riboflavine

Analgesic	Ratio added (Riboflavine:Analgesic)								
	2:1			1:1			1:2		
	K O/W	SD	Var.	K O/W	SD	var.	K O/W	SD	Var.
Paracetamol	0.1165	0.0023	3.6×10^{-6}	0.0673	0.0080	4.4×10^{-5}	0.0440	0.0015	1.6×10^{-6}
Phenazone	0.3582	0.0081	4.4×10^{-5}	0.2873	0.0075	3.8×10^{-5}	0.2237	0.0051	1.8×10^{-5}
Aspirin	0.2190	0.0056	1.6×10^{-5}	0.1480	0.0017	2.0×10^{-6}	0.0670	0.0072	3.5×10^{-5}
Acetanilide	0.4600	0.0023	3.6×10^{-6}	0.3700	0.0021	2.9×10^{-6}	0.2813	0.0074	3.6×10^{-5}

K O/W of riboflavine = 0.5102

Table 3: Effect of the Analgesics on the Permeability Coefficient(P) of Riboflavine

Analgesics	Molar ratio(riboflavine: analgesics)					
	1:1	r	1:2	r	2:1	r
Paracetamol	0.5952	0.99297	0.4721	0.98561	0.2263	0.97533
Phenazone	0.3372	0.99516	0.3442	0.99749	0.2360	0.96898
Aspirin	0.4362	0.99257	0.4498	0.99647	0.2574	0.99873
Acetanilide	0.1624	0.98024	0.3513	0.99478	0.2010	0.99849

"P" for riboflavine = 0.3819 r=0.9864 r= correlation coefficient.

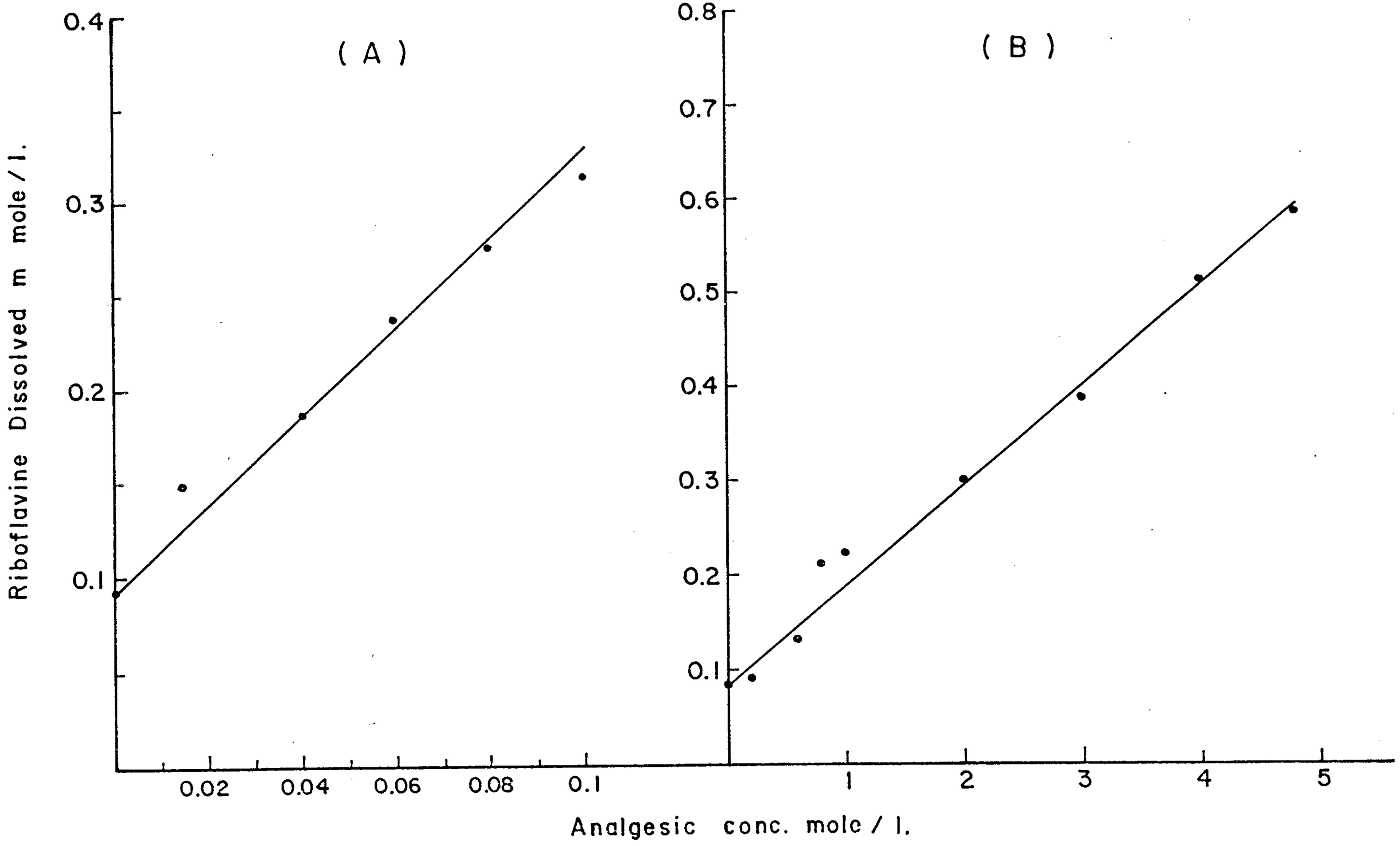


Fig.(1): Effect of paracetamol (A) and phenazone (B) on the water solubility of riboflavine.

Interactions of Riboflavine With Certain Analgesics.

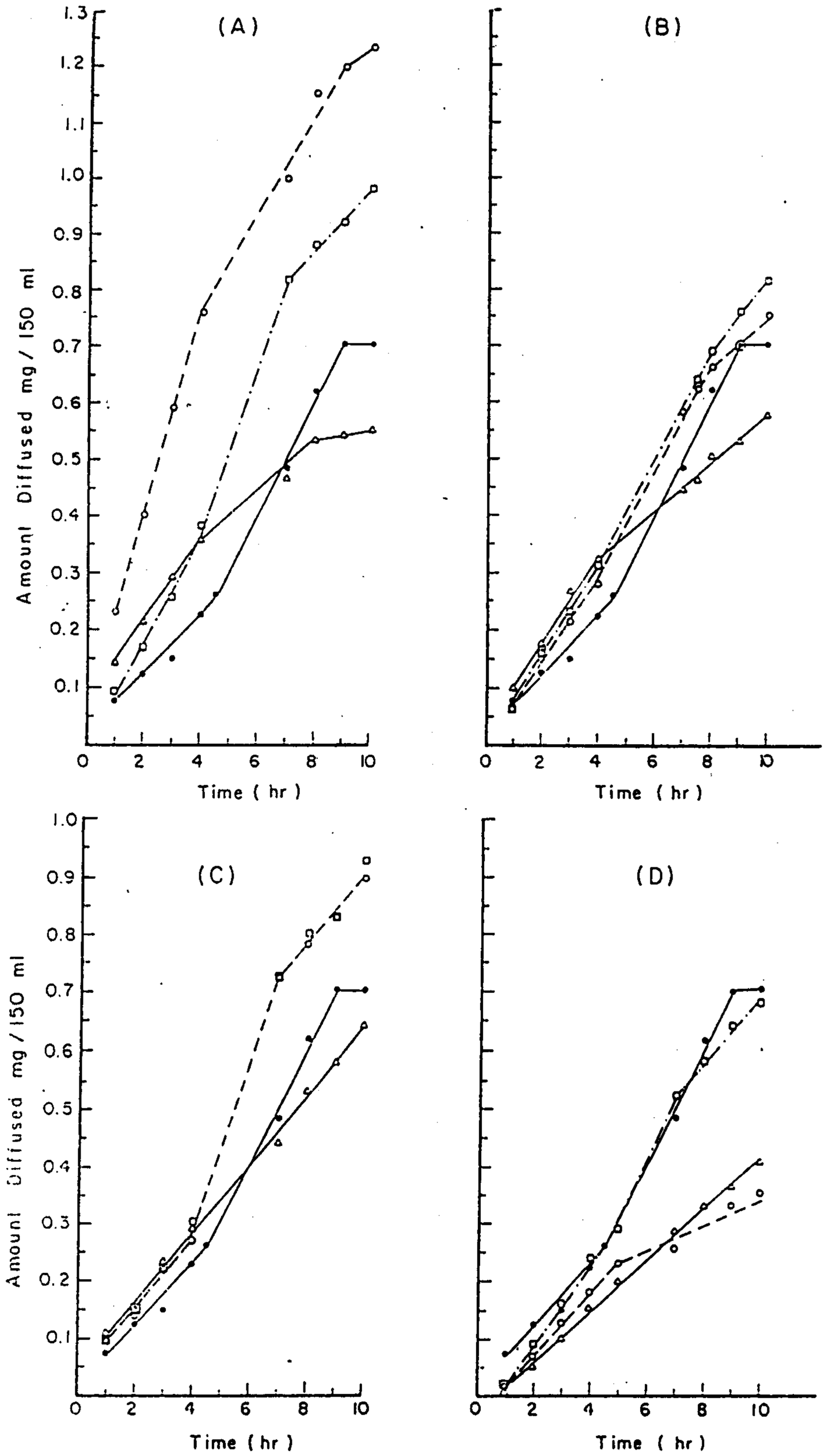


Fig.(2): The diffusion rate of riboflavine in presence of, (A) paracetamol, (B) phenazone, (C) aspirin and (D) acetanilide (●) riboflavine alone (○) riboflavine in presence of analgesic 1:1 ratio (□) 1:2 ratio and (△) 2:1 ratio

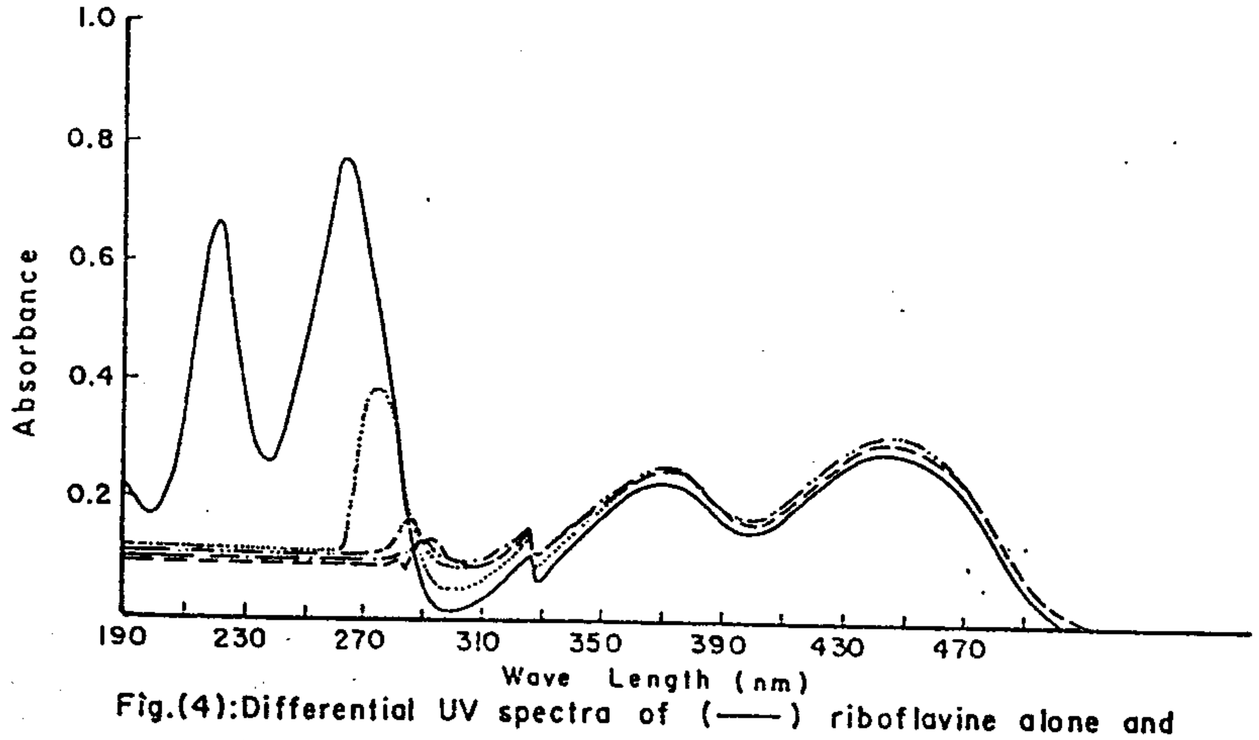


Fig.(4):Differential UV spectra of (——) riboflavine alone and in presence of different molar concentration of paracetamol (·····) 0.001 M, (–·–) 0.002 M, (–·–) 0.004 M, (–––) 0.006 M.

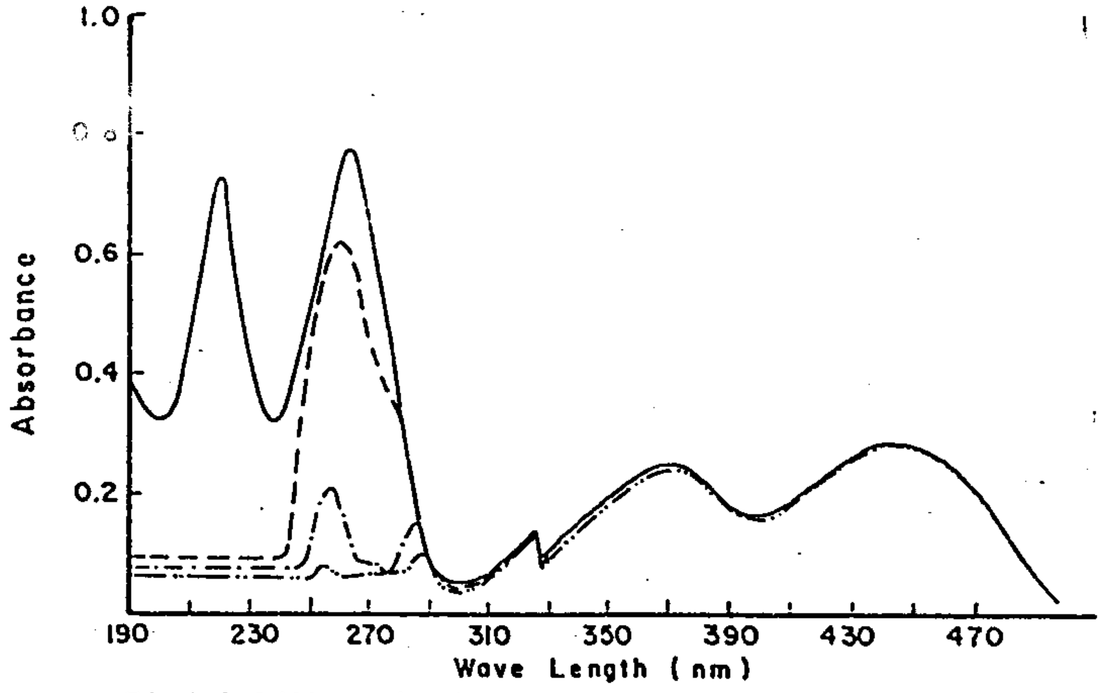


Fig.(6):Differential UV spectra of (——) riboflavine alone and in presence of different molar concentration of aspirin (– – –) 0.002 M, (–·–) 0.004 M (–··–) 0.006 M.

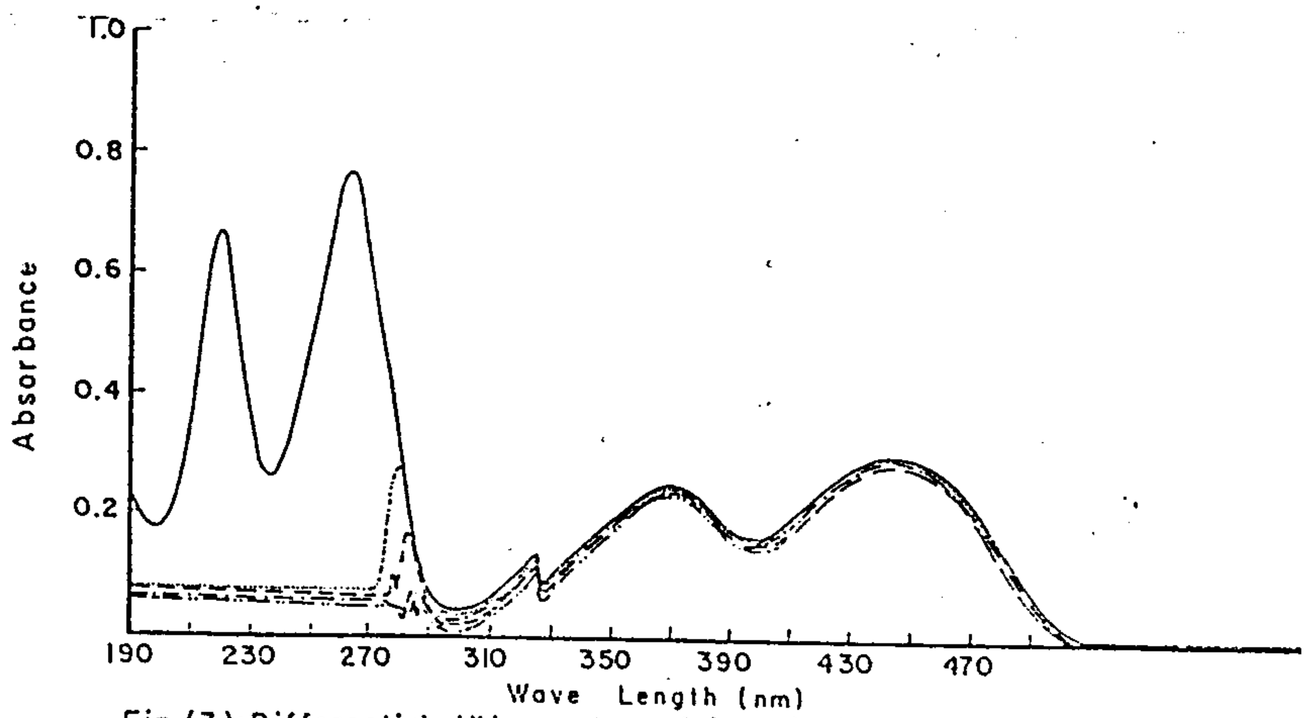


Fig.(3):Differential UV spectra of (——) riboflavine alone and in presence of different molar concentration of phenazone. (·····) 0.001 M, (– –) 0.002 M, (–·–) 0.004 M, (–··–) 0.006 M.

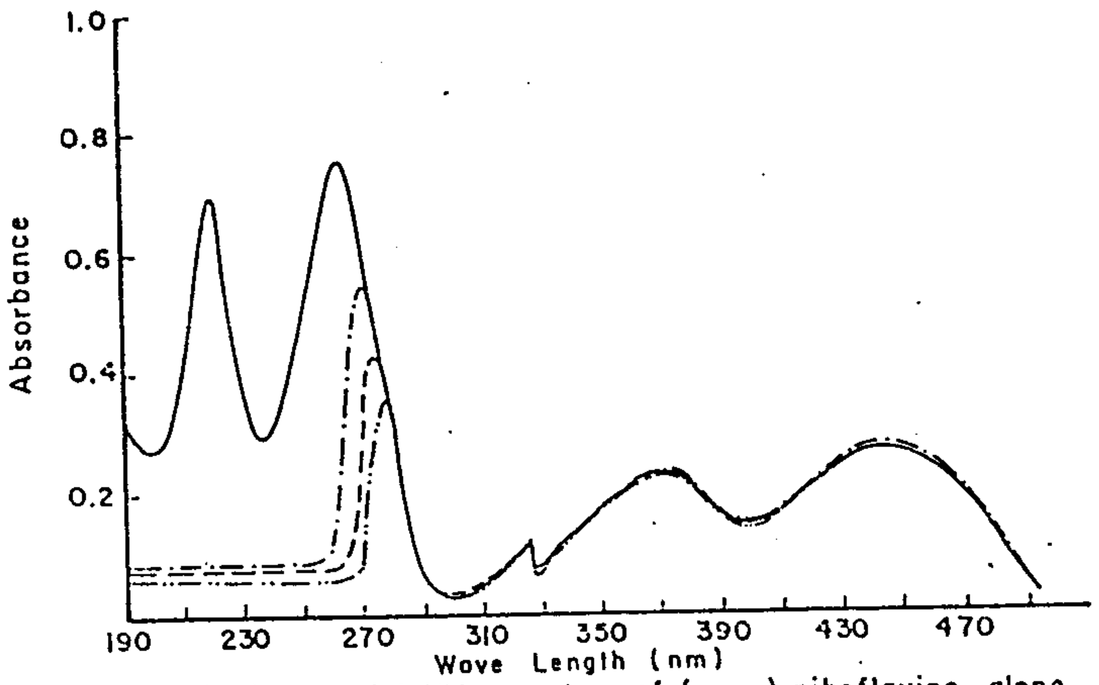


Fig.(5):Differential UV spectra of (——) riboflavine alone and in presence of different molar concentration of acetanilide (–·–) 0.002 M, (– – –) 0.004 M, (–··–) 0.006 M.

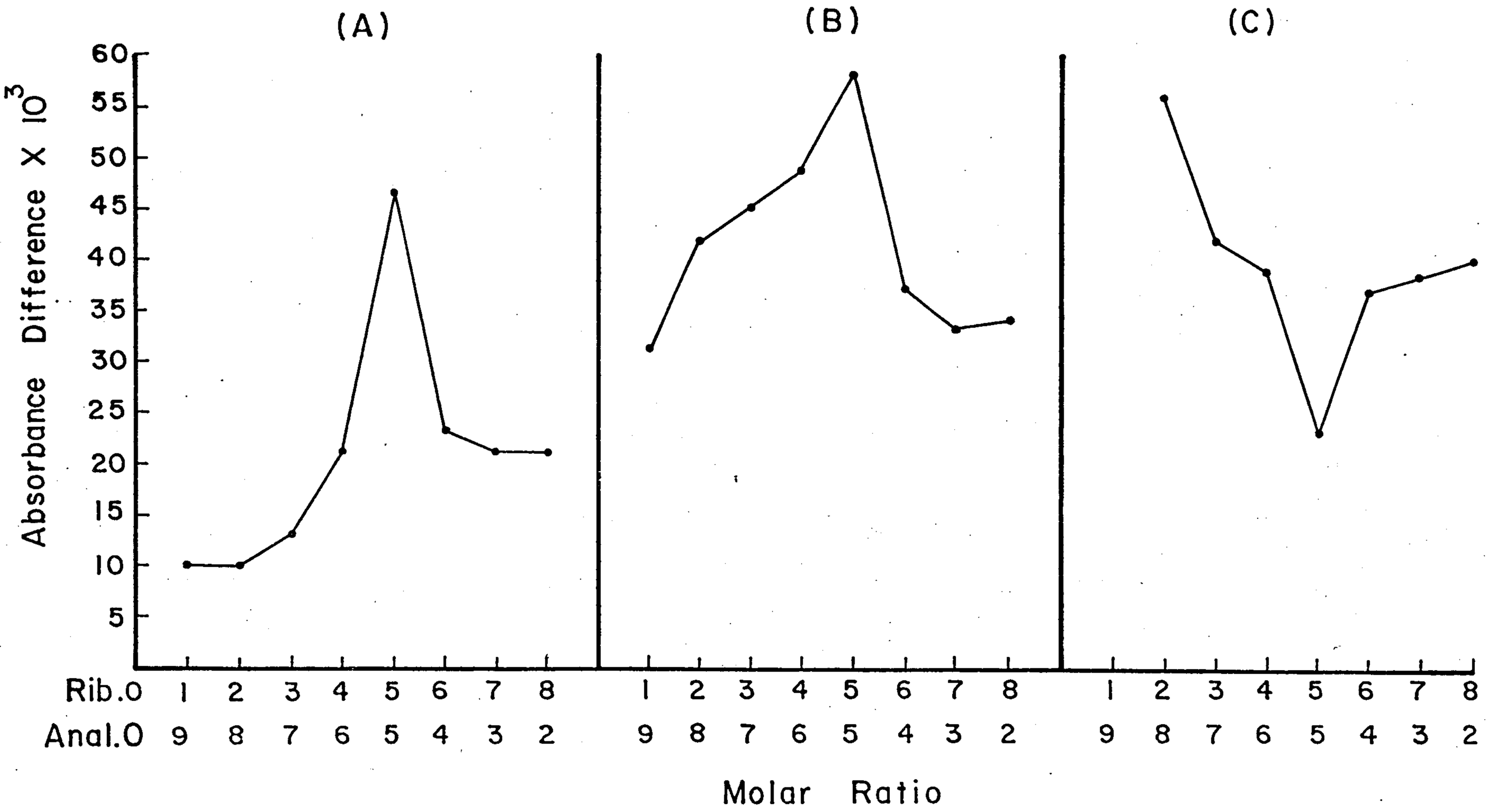


Fig.(7): Absorbance difference as function of molar ratio of riboflavine – analgesics solution in water at 25 C°.
(A) Paracetamol (B) Phenazone (C) Aspirin

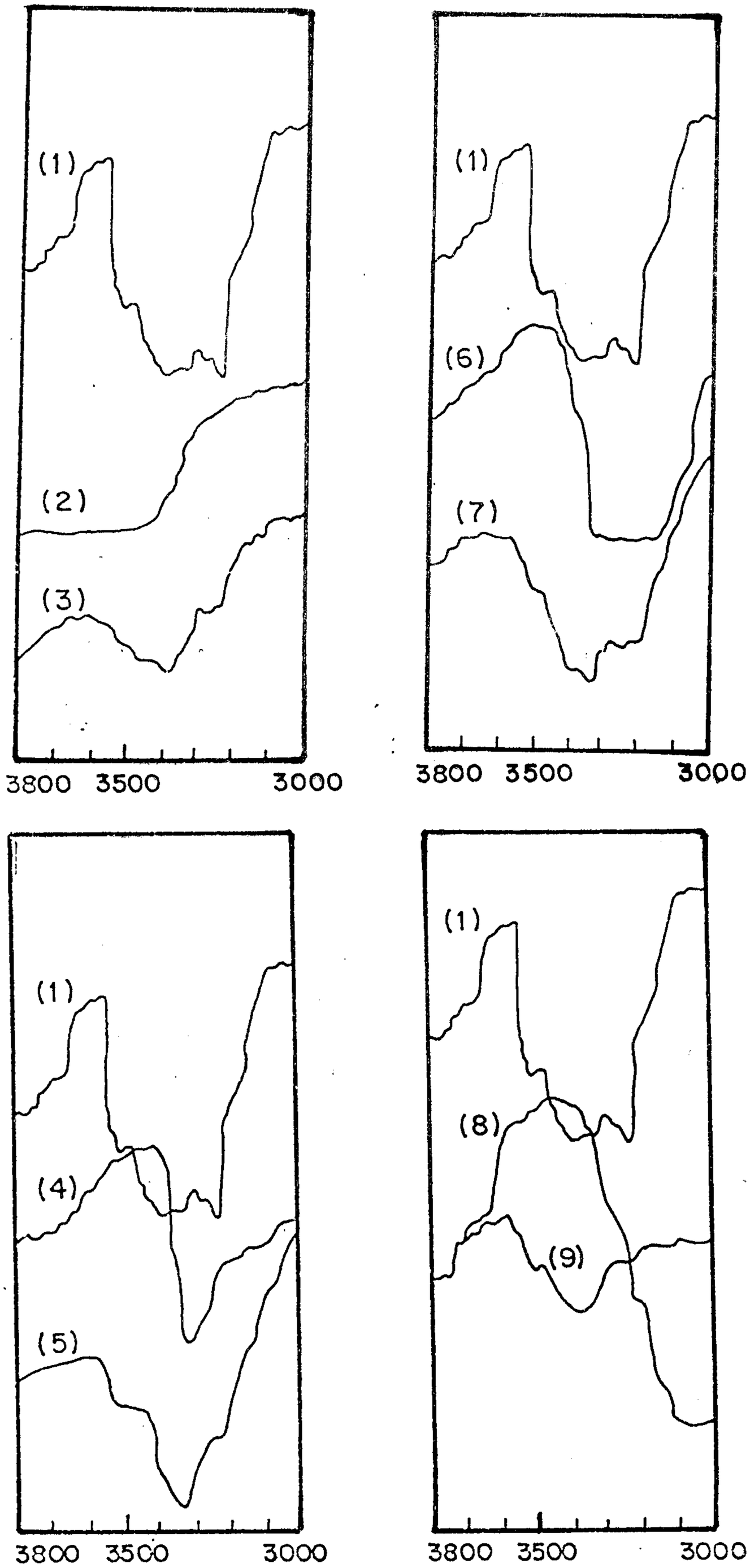


Fig.(8): IR spectra of ; (1) riboflavine, (2) phenazone, (4) acetanilide, (6) paracetamol (8) aspirin and (3), (5), (7), (9) riboflavine_analgesic mixture respectively .

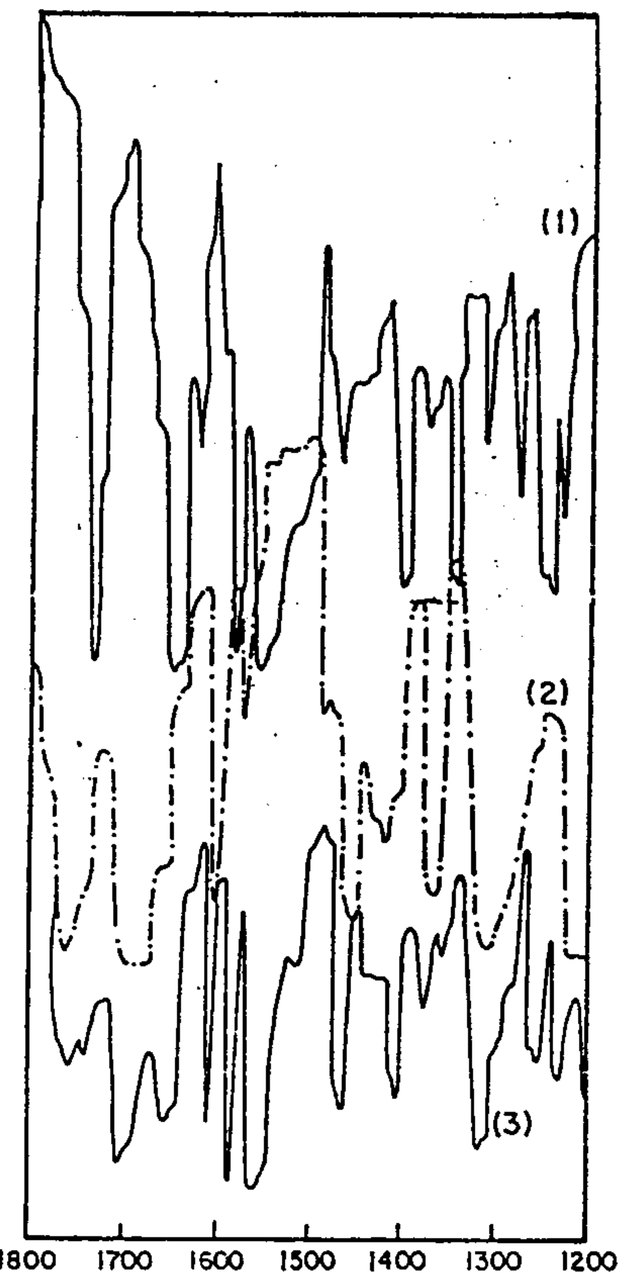


Fig.(9): IR spectra of ; (1) riboflavine (2) aspirin and (3) their physical mixture.

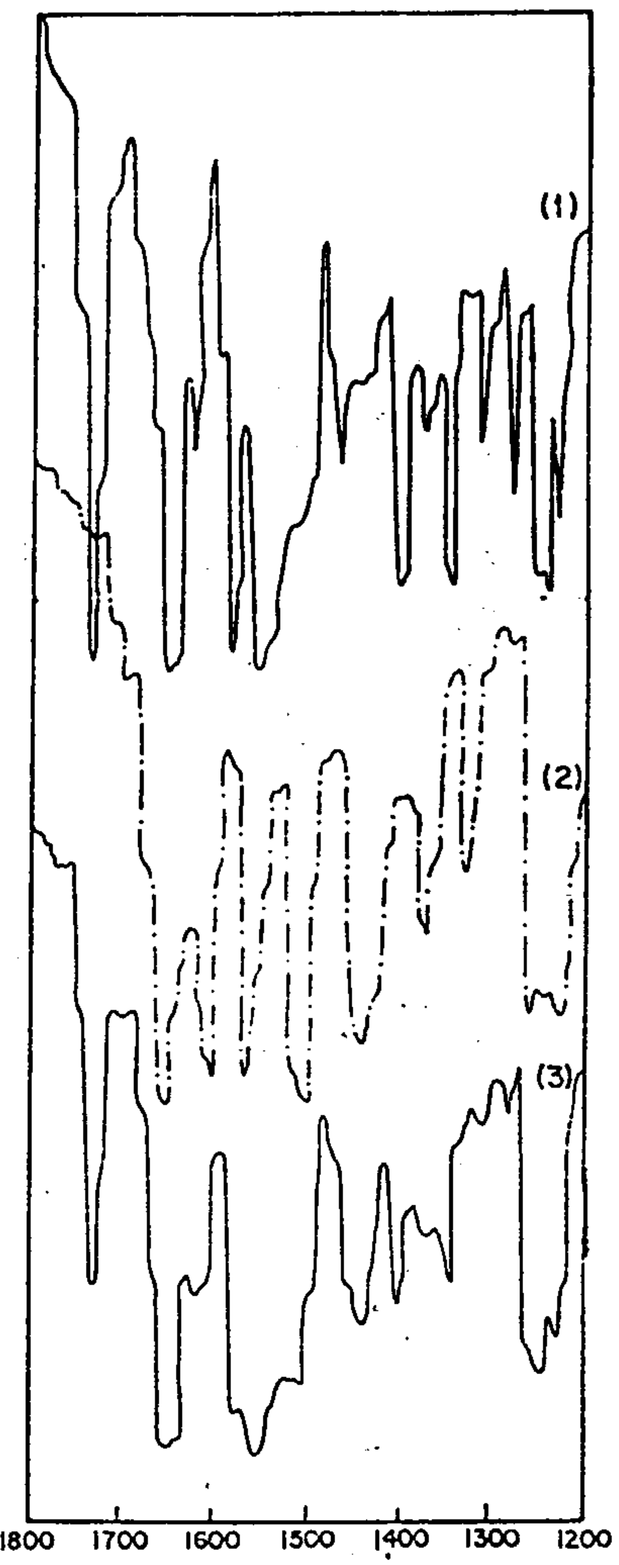


Fig.(10):IR spectra of ; (1) riboflavine ,(2) paracetamol and (3) their physical mixture.

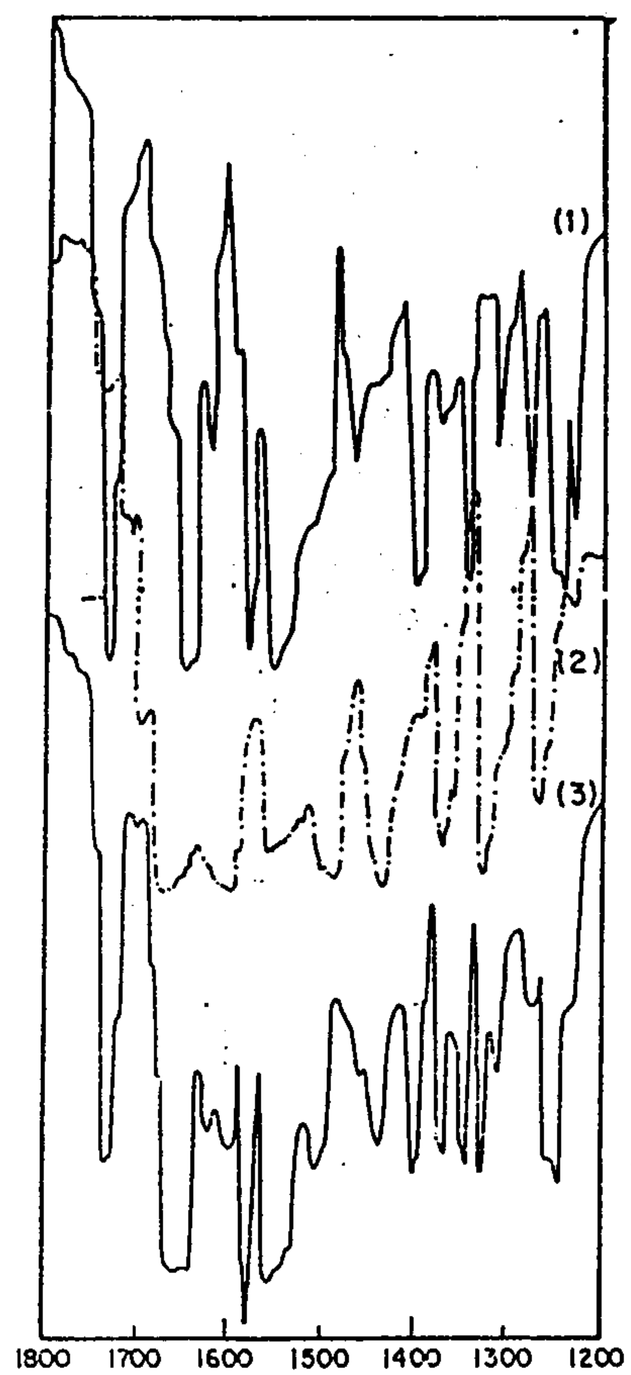


Fig.(11): IR spectra of ; (1) riboflavine (2) acetanilide and (3) their physical mixture.

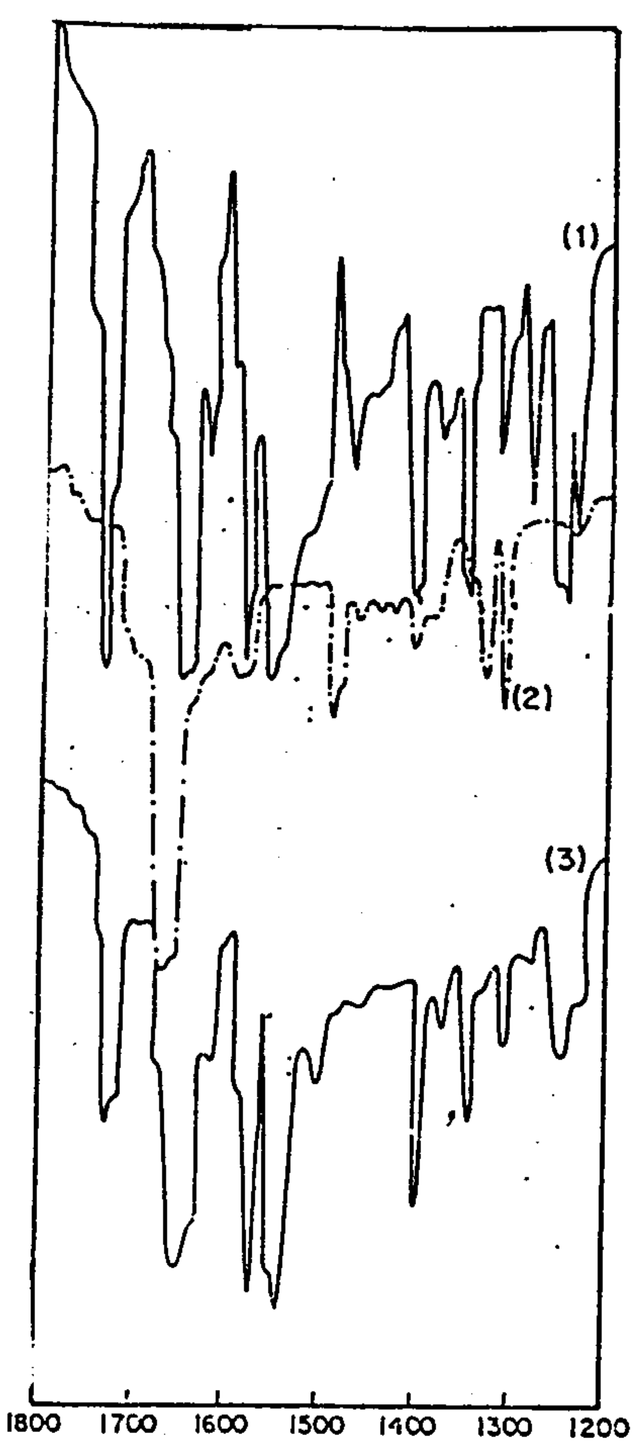


Fig.(12):IR spectra of ; (1) riboflavine (2) phenazone (3) their physical mixture .

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دراسة التفاعلات بين الريبوفلافين وبعض المسكنات

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فى هذا البحث قد تمت دراسة التفاعل بين الريبوفلافين وبعض المسكنات مـــن بينها الباراسيتامول والفينازون والاسبرين والاسيتانيلايد • وقد وجد من هـــذه الدراسة أن ذوبان الريبوفلافين يزداد زيادة خطية بزيادة تركيز كل من الباراسيتامول والفينازون • وكان للباراسيتامول تأثير أكثر من الفينازون • ولم يكن أى تأثيـــر للاسبرين والاسيتانيليد ، بالتركيزات المستعمله ،على ذوبان الريبوفلافين • وقد لوحظ أيضا من الدراسة أن معامل التجزئة الظاهرى للريبوفلافين بين الكلوروفورموالماء يقـــل بمعدلات مختلفة فى وجود نسب جزيئية مختلفة من الريبوفلافين وكل من المسكنـــات المختبرة • وقد كان للباراسيتامول تأثير ملحوظ فى تقليل معامل التجزئة الظاهـــرى للريبوفلافين يتبعه فى الترتيب الاسبرينوالفينازون والاسيتانيلايد هذا فى وجود أى من النسب المستعملة •

وقد تأثرت درجة نفاذية الريبوفلافين خلال غشاء السيلوفان الى حدود متفاوته فى وجود ثلاثة من هذة المسكنات وعامة فقد زادت درجة نفاذية الريبوفلافين فى وجود الباراسيتامول وبعده فى الترتيب الاسبرين ويليه الفينازون • ولم يساعد الاسيتانيلايد على زيادة نفاذية الفيتامين خلال الغشاء السيلوفانى • ويشير هذا التغيير فى الخواص الفيزيوكيميائية للفيتامين أن هناك تفاعلات بين هذا الفيتامين والمسكنات أحدثـــت تغيرات ملحوظه فى درجة امتصاص الفيتامين للاشعة الفوق بنفسجية والاشعة تحت الحمراء وقد استخدمت طريقة " جوب " للتغيرات المستمرة للاستدلال على هذة التفاعلات ووجـــد أن الريبوفلافين يدخل فى التفاعل مع كل من الباراسيتامول والاسبرين والفينازون بنسبة جزيئية واحـــدة (١ : ١) •

ويستنتج من هذا أن هناك نوع من المتراكبات بين الريبوفلافين (عقار قليـــل الذوبان جدا فى الماء) وبعض المسكنات شائعة الاستعمال مثل الباراسيتامولو الاسبرين والفينازون مما يؤدى الى تغيرات فى الذوبان والمعامل التجزيئى وسرعة النـــفاذ للفيتامين الذى بدوره سوف يؤثر على امتصاصه وتمثيله فى جسم الانسان •

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