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# STUDIES I ON THE SOLUBILITY OF RIFAMPICIN
## I. Effect of Co-Solvents and Nonionic Surfactants on the Solubility of Rifampicin

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*The effect of a number of water-miscible co-solvents namely; glycerin, glycerin formal, propylene glycol, polyethylene glycol; 200, 300, and 400 polypropylene 420, dimethylformamide and dimethyl sulfoxid in various concentrations up to 50% with water, as well a number of nonionic surfactants namely; tween 20, tween 40, tween 60 and tween 80 in various concentrations up to 10% in water, on the equilibrium solubility of rifampicin was evaluated. It was found that the solbility of rifampicin is promoted to a marked extent in presence of the co-solvents and the nonionic surfactants. However, the extent of the solubility-promoting effect was dependent on the type and concentration of the co-solvent and the surfactant used. Presence of 50% co-solvents with water increased the solubility of rifampicin to 1.15, 1.2, 1.5, 6,9, 14, 14.6, 60 and 121.3 times its original water-solubility in cases of; propylene glycol, glycerin-formal,glycerin, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, dimethyl sulfoxide, polypropylene glycol 420 and dimethylformamide respectively. A 10% surfactant concentration in water, increased the solubility of rifampicin to 9.6, 8.52, 7.74 and 7.35 times its original water solubility in cases of tween 20, tween 40, tween 80 and tween 60 respectively.*

Formulation of drugs in equeous solutions is essentially important when uniformity of dosage, rapid and constant absorption should be insured. However, the limited solubility of certain drugs in water makes this requirement not easily accessible.

The solubility of such drugs could be made adequate for aqueous solution formulations through a number of approaches viz; formulating at appropriate pH employing suitable buffers, incorporating water miscible non

aqueous solvents, solubilization by means of surfactants, complexation with macromolecules and introduction of specific additives in system[1,2].

The antibiotic drug, rifampicin is reported to have a slight water-solubility [3,4] which is inadequate for formulating it in aqueous solution for therapeutic use. So, an investigation is enitiated to augment its aqueous solubility through various approaches. In the presented work, the effect of a number of water miscible non aqueous solvents namely; glycerin, glycerin formal, 1,2 propylens glycol, polyethylene glycols; 200, 300 and 400, polypropylene glycol 420, dimethylformamide and dimethyl sulfoxide in cocentrations up to 50% with water on the equilibrium solubility of rifampicin is evaluated. In addition, the solubilizing effect of a number of nonionic surfactants of the tween groups namely; tween 20, tween 40, tween 60, and tween 80 is also evaluated.

## EXPERIMENTAL

### Materials

Pharmaceutical or pure grade of rifampicin, glycerin, glycerin formal, 1,2 propylene glycol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, polypropylene glycol 420, dimethyl sulfoxide and dimethylformamide.

### Equipment:

Rotating bottle dissolution apparatus with constant temperature water bath (± 0.1).

Spectrophotometer (*Spektromom 204*).

### Solubility measurement:

Excess amounts of the medicament were placed in a series of glass stoppered tubes (50 ml capacity). Five ml. of the liquid to be tested was added to each tube. The tubes were tightly closed and then rotated at 45 r.p.m. in a constant temperature water bath at 20°C. After equilibrium was attained (90 minutes) the contents of the tubes were filtered rapidly and the extent of rifampicin dissolved was determined in an aliquot of the filtrate using direct spectrophotometry at 485 nm after appropriate dilution with methanol, comparing its absorbance to that of a freshly prepared standard methanolic solution.

## RESULTS AND DISCUSSION

Fig. 1 depicts the effect of incorporating the lower hydroxy co-solvents; glycerin, glycerin formal and 1,2 propylene glycol with water on the equilibrium solubility of rifampicin. It is obvious from this figure that these co-solvents produce a significant increase in the solubility of rifampicin. However, this effect was dependent on the type of the co-solvent and proportional to its concentration in the system. Fifty per cent(w/v)concentration of co-solvent in the system resulted in incresed solubility of rifampicin to 1.5, 1.27 and 1.15 times its original solubility inwater in cases of glycerin, glycerin formal and 1,2 propylene glycol respectively. The difference in solubility increasing capacity of these co-solvents towards rifampicin could be correlated to the difference in chemical structure of the co-solvents specially the number of hydroxyl groups per molecule.

In figure 2, the effect of polymeric glycols as co-solvents on the equilibrium solbility of rifampicin is illustrated. It is evident from this figure that incorporation of these cosolvents with water markedly augments the solubility of rifampicin. However, the extent of such effect is dependent on both the type and the concentration of the polymeric glycol in the system. polypropylene glycol 420 showed the highest solubilizing effect compared to the polyethylene glycols tested. Comparing the three polyethylene glycols evaluated, it could be observed that rifampicin solubility augmenting capacity of these co-solvents increases as the mumber of the monomer unit and hence the molecular weight of the molecule increases. Thus the solubilizing effect of polyethylene glycol 400 > polyethylene glycol 300 > polyethylene glycol 200. Fifty per cent(w/v)concentration of the co-solvent in the system resulted in increased solubility of rifampicin to 6, 9, 14, and 60 folds its original solubility in water, in cases of polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and polypropylene glycol 420 respectively.

Figure 3 illustrates the solubility of rifampicin in blends of water and various concentrations of dimethylformamide and dimethyl sulfoxide. It is apparent from this figure that rifampicin solubility is augmented in blends of both co-solvents with water compared to its original solubility in water. This effect is increased as the percentage of co-solvent in the blend increased. The solubility augmenting capacity of dimethylformamide is much greater than that of dimethyl sulfoxide. Fifty per cent concentration of co-solvent in the blend resulted in increased solubility to 14.4 and 121.23 times its original water-solubility in cases of dimethyl sulfoxide and dimethylformamide respectively.

The effect of incorporating non-ionic surfactants of the polyoxyethylene sorbitan ester (tween) types with water on the apparent equilibrium solubility of rifampicin is illustrated in figure 4. It is quite evident from this figure that presence of either of the tested surfacrants in water results in increased solubility of rifampicin. However, the extent of this solubilizing effect is dependent on the specific type of the tween surfactant used and directly proportional to its concentration in the system. The rank order of the solubilizing power of the tested surfactants is, tween 20, tween 40, tween 80 and finally tween 60. Ten per cent surfactant concentration in water resulted in increased rifampicin solubility to 9.6, 8.52, 7.74, 7.35 times its original water-solubility in cases of tween 20, tween 40, tween 80 and tween 60 respectively. As the concentrations of the surfactant used were above their critical micelle concentrations their solubilising effect could be attributed to the micellar solubilization which is increased directly as the number of the micelles increased by increasing the concentration of the surfactants (5). The observed difference between the solubilizing capacity of the tested surfactants could be attributed to the difference in the mean number of ethylene oxide units per monomer among these surfactants (6). The high the mean number of ethylene oxide units per monomer, the greater the solubilizing capacity of the surfactant towards rifampicin.

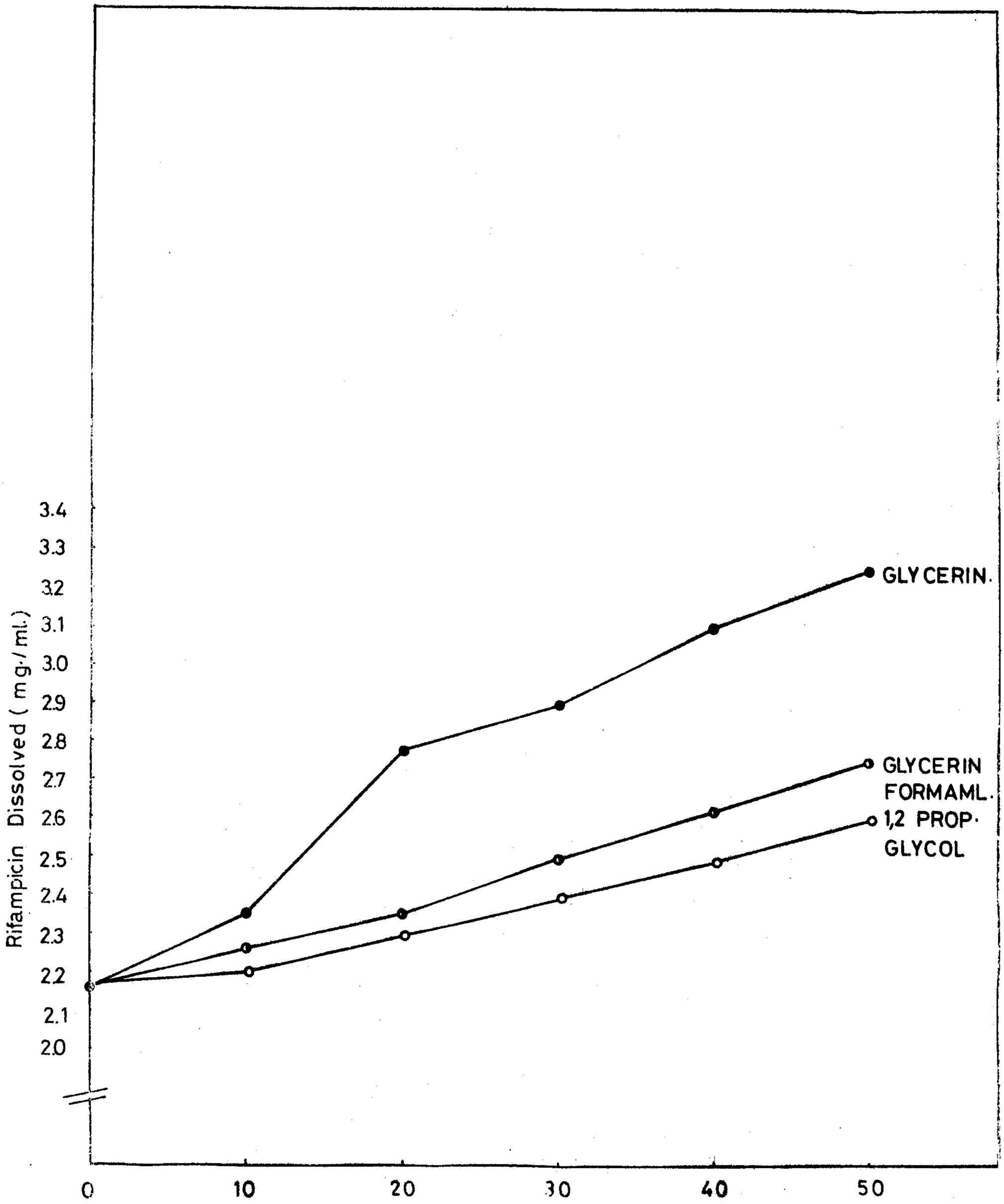



Fig: 1 Effect of Glycerin, Glycerin Formal, and 1,2 Propylene Glycol on the Solubility of Rifampicin

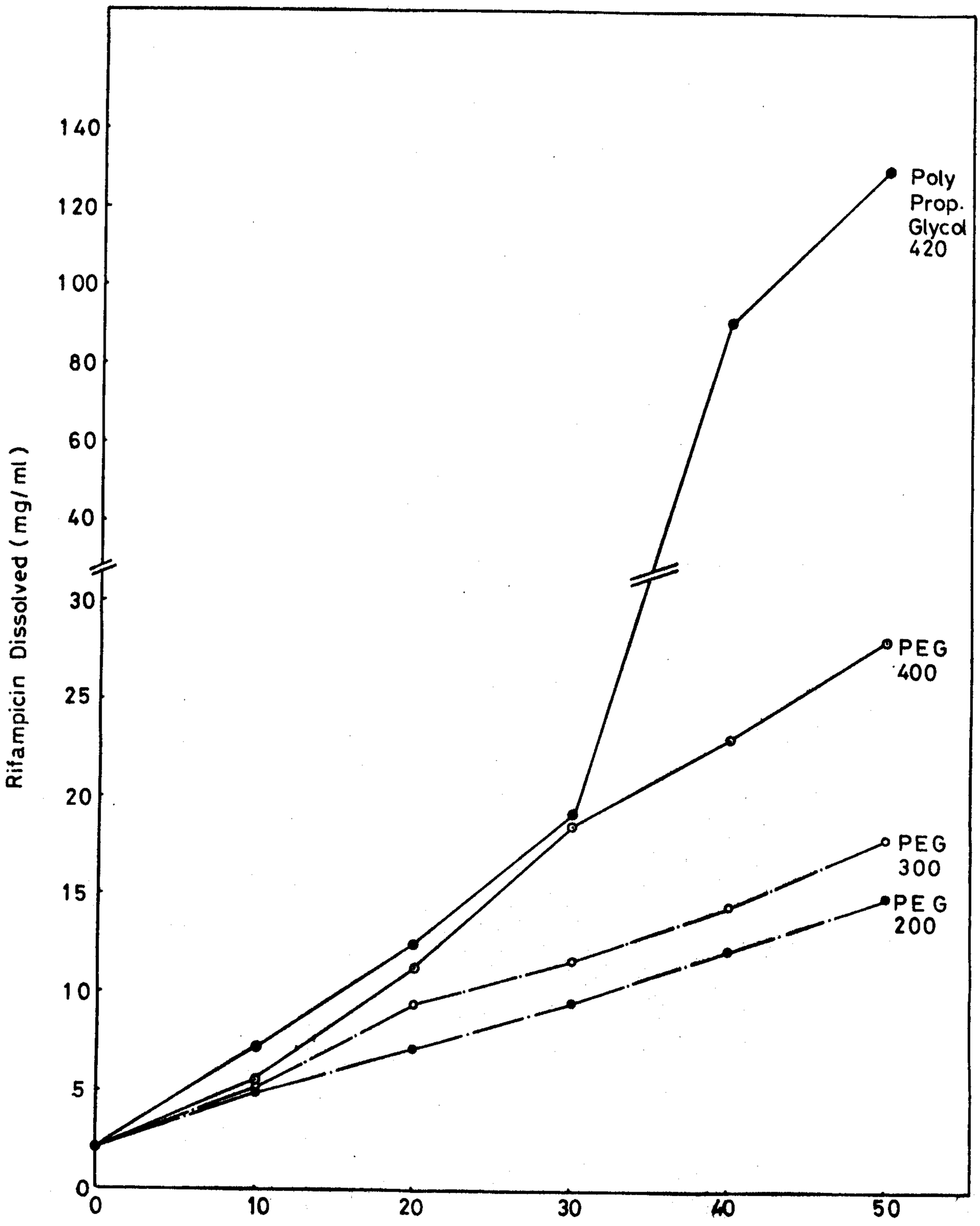
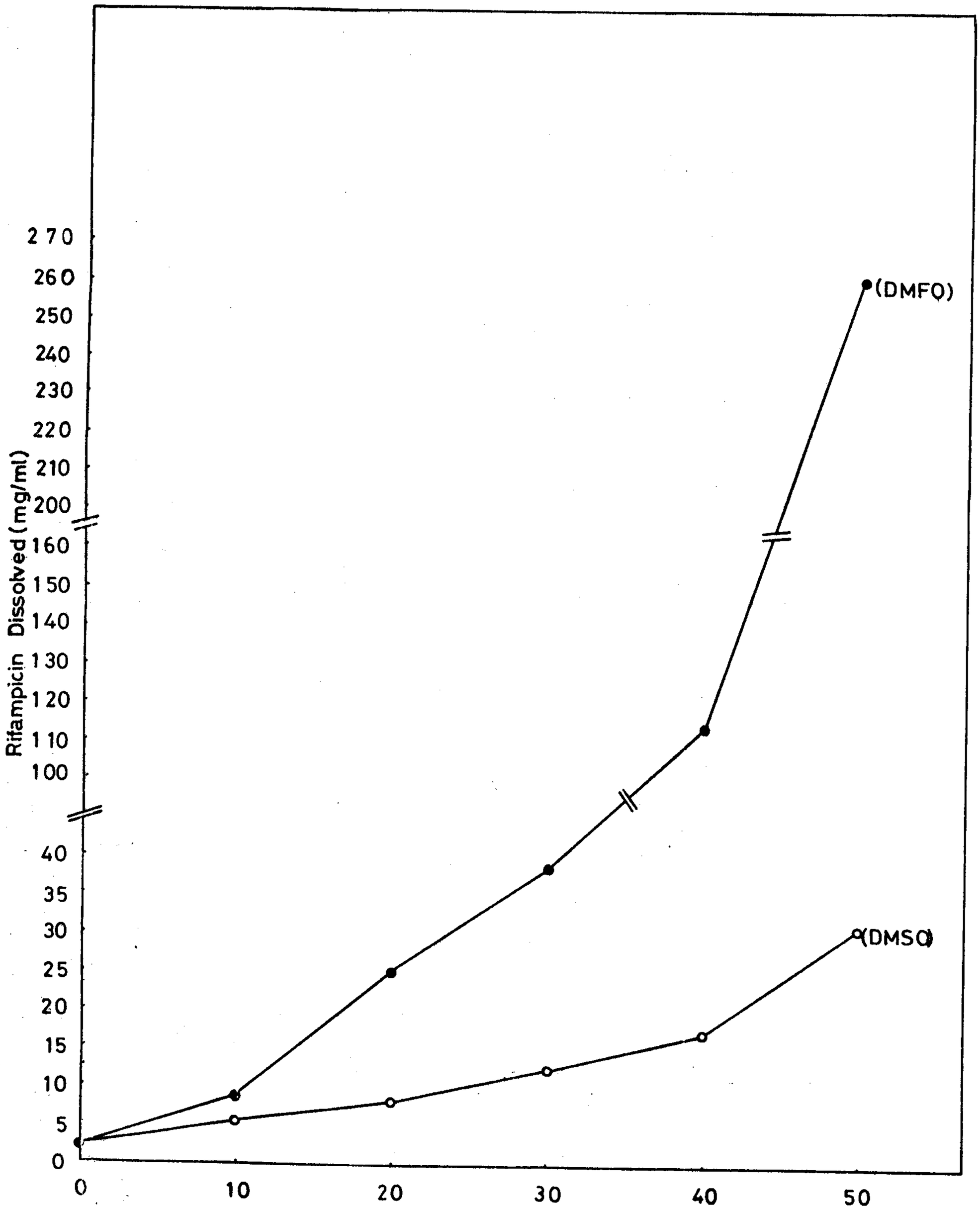



Fig: 2 **Effect of Polymeric Glycols on the Solubility of Rifampicin in Water at 20°**




Fig; 3, Effect of Dimethylformamide and Dimethylsulfoxide on the Solubility of Rifampicin in wate at 30°

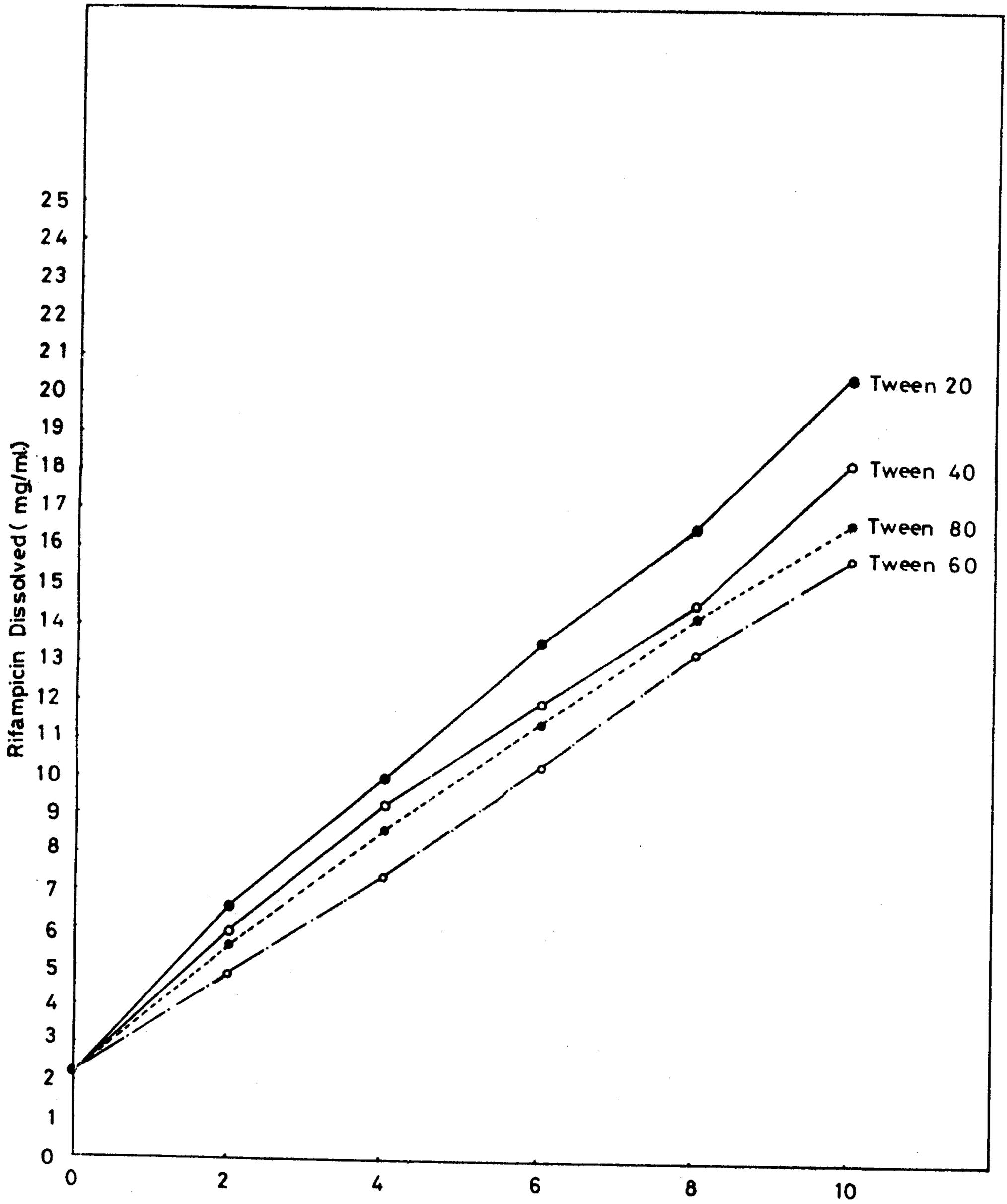



Fig. 4 : Effect of tween Surfactants on the Solubility of of Rifampicin in Water at 20°

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(6) *Ibid P. 149.*

# دراسات على ذوبـــان الريفاميســـــــــن

## ١ــ تاثير المذيبات المعاونة والمواد ذات النشاط السطحى للايونية

السيد على ابراهيم ــ على طوقاسم ــ اسماعيل عطيـه ــ سيد اسماعيل محمـد
قسم الصيدلانيات ــ كلية الصيـــــــــــدلة ــ جامعة اسيوط

تـم تقييم تاثير عـدد من المذيبات المعاونة الممتزجـة مع الماء وهى الجلسرين والجلسرين فورمـال وجليكول البروبابلين وجليكول متعـدد الاثيلين ٢٠٠ ، ٣٠٠ ، ٤٠٠ وجليكول متعـدد البروبابلين ٤٢٠ وثنائى ميثيـل الفرماميـد وثنائى ميثيل السلوكسيد فى تركيزات مختلفة حـتى ٥٠٪ مع الماء وكذلك تاثير عـدد من ذوات النشاط الســـــطحى للايونية مثـل تهين ٢٠ ، تهين ٤٠ ، تهين ٦٠ ، تهين ٨٠ بتركيزات مختلفة حتـــى ١٠٪ فى المـــاء على الذوبـــان التوازنـى للريفاميسيـن .

وقد وجد ان ذوبان الريفاميسين يزداد الى حد ملحوظ فى وجود المذيبات المعاونـــة وذوات النشاط السطحى للايونيـة ولكن كان التاثير المنمى للذوبان يعتمد على نـــــوع وتركيز المذيب المعاون او ذى النشاط الشطحى المستعملـــه وقد نتج عن وجود تركيزه ٥٠٪ من المذيبات المعاونة زيادة فى ذوبان الاساس فى الماء قدره ١٫١٥ ، ١٫٢٠ ، ١٫٣٠ ، ١٫٩٦ ، ١٤٫٤٠٦ ، ٦٠٫٤ ، ١٢١ فى حالة استخدام جليكول البروبابلين ، جلسرين جلسريـــن فورمال ، جليكول متعدد ميثيل الاثيلين ٢٠٠ ، جليكول متعدد الاثيلين ٣٠٠ ، وجليكـول متعدد الاثيلين ٤٠٠ ، ثنائى ميثيل السلفوكسيد جليكول متعدد البروبابلين ٤٢٠ ، ثنائى ميثيل الفورماميد على التوالى .

وقد نتج عن وجود ١٠٪ من ذوات النشاط السطحى للايونية ازدياد فى ذوبان الريفاميسين الى ٦٫٩ ، ٨٫٢ ، ٧٫٧٤ ، ٧٫٣٥ قدرا من ذوبان الاساس فى الماء فى حالة استعمـــال تهين ٢٠ ، تهين ٨٠ ، تهين ٦٠ على التوالى .