

## DISSOLUTION ENHANCEMENT OF THIACETAZONE I: VIA SURFACE HYDROPHILIZATION

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### ABSTRACT

Hydrophilized systems of thiacetazone with different hydrophilic carriers viz., surfactants, polymers, sugar alcohols and isoniazid were prepared. The tested drug was intimately wetted with small volume of alcoholic carrier solution, and left aside to dry at room temperature. The wettability and dissolution rate tests of the hydrophilized systems and their corresponding physical mixtures were performed. Also, the effect of the tested carriers on the aqueous solubility of thiacetazone was investigated. The USPXX dissolution test, exhibited a pronounced increase in dissolution of thiacetazone from its hydrophilized systems as compared to that of their physical mixtures and pure drug. Generally, a direct correlation was found between the wettability and dissolution rates. Hydrophilized systems with surfactants gave the highest dissolution and good wettability next to isoniazid. Surfactants then followed in order by sugar alcohols and then by polymers. The effect of surfactants is directly proportional to the concentration. After 10 minutes the relative dissolution rate was 14.34, 13.86 or 14.43 for 5% w/w Tween 40, 60 or Myrj 53 respectively. However, with the other carriers higher concentrations led to reduction in the dissolution enhancing effect. The results denote the potential use of this technique to enhance thiacetazone dissolution.

### INTRODUCTION

Thiacetazone, is considered one of the secondary antituberculous agents but still used successfully in schedules for primary treatment<sup>1</sup>. Although, thiacetazone showed a high

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antituberculous activity it exhibited also some toxicity especially in high dosage<sup>1</sup>. A combination of thiacetazone with isoniazid was shown to be an effective and cheap combination with no toxicity in the moderate dose for the treatment of tuberculosis<sup>2</sup>.

Thiacetazone, is practically insoluble in aqueous solutions, in addition, its therapeutic dose is fairly large (150 mg daily). Thus, dissolution could be rate limiting process in the gastrointestinal absorption from solid dosage forms<sup>1</sup>. Diverse techniques have been made to modify the dissolution characteristics of hydrophobic drugs to attain more rapid and complete absorption<sup>2-12</sup>. Since, thiacetazone has limited solubility in organic solvents, as well as it decomposes on melting<sup>1</sup>, the crystallization technique<sup>3</sup> or solid dispersion formation with hydrophilic carriers (through fusion and co-precipitation) can not be adopted to enhance the drug dissolution<sup>4-9</sup>.

Adsorption phenomena may be used for the enhancement of the dissolution of hydrophobic drugs<sup>10,11</sup>, by the use of adsorbent suspended in the dissolution medium<sup>10</sup>, or the drug may be precipitated on the surface of an adsorbent<sup>11</sup>.

On the other hand, hydrophilic materials or surface active agents may be adsorbed on the surface of the drug particles to increase its wettability and hence to increase its dissolution rate. In this respect, de Jong<sup>12</sup> have described the surface hydrophilization technique. The mechanism of this technique has been fully discussed later on by Lerk *et al.*<sup>13</sup>, for increasing the release rate of the hydrophobic hexobarbitone from hard capsules. It involves the conversion of hydrophobic surface of the drug to hydrophilic one by the intensive mixing with small amount of a film forming polymer solution (hydroxyethylcellulose).

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The method appears similar to a conventional granulation technique and simply relies on improving the wettability and dissolution of hydrophobic drugs. Felt et al.<sup>14</sup> found that the rate and extent of bioavailability of griseofulvin hydrophilized with 10% ethanolic solution of hydroxypropylcellulose were increased significantly when compared with non treated powder. Moreover, Finholt<sup>15</sup> reported that the dissolution of phenacetin can be improved by granulating phenacetin powder with hydrophilic binder (gelatin). The use of surfactants to increase the dissolution of insoluble drug through this technique was first described by Chiou et al.<sup>3</sup> The drug was dissolved in ethanol to form a saturated alcoholic solution. The drug was then precipitated by the addition of water or aqueous surfactant solution. Ebian and Abugella<sup>16</sup>, have described two other methods for preparing crystals of the hydrophobic drug covered with surfactants, by soaking or shaking with aqueous surfactant solutions for one hour.

Generally, the adopted methods either by Lerk et al.<sup>13</sup> or by Ebian and Abugella<sup>16</sup> were found to be more applicable and have some advantages to that described by Chiou et al.<sup>3</sup> These methods were more economic, applied for any hydrophobic drug, no organic solvent is required for preparing the drug crystals. Moreover, the necessity of the solubility of the drug in solvent, which must be miscible with water as the requirement of Chiou et al. method, has no longer been needed.

The aim of the present work is to adopt the surface hydrophilization technique<sup>12</sup>, using different types of hydrophilic agents viz., surfactants, polymers and sugar alcohols for increasing the dissolution rate of the poorly soluble thiacetazone. The effect of carrier's solution volume, type of carrier as well as the carrier concentration was also

investigated. Moreover, isoniazid as a soluble drug companion to thiacetazone was included as a carrier in the study.

## EXPERIMENTAL

### Materials :

Thiacetazone, Isoniazid (The Nile Co. for Pharm, and Chem. Ind. Cairo, Egypt), PYP 44000, Sorbitol (BDH, Pool, England), Tween 80, Mannitol (Prolabo, Plee, Paris, France), Tween 40 (E.Merck-Darmstadt). Tween 60 (Roth, W.G.), PEG6000 (Fluka AG, Switzerland).

All other chemicals were of pharmaceutical grade and used as recieved.

### Equipments :

- 1- Dissolution apparatus (Erweka type DT, W.Germany).
- 2- Double beam spectrophotometer (U.V-150-02, Shimadzu-Japan),
- 3- Rotating bottle apparatus.

### Methods :

#### Preparation of samples :

Hydrophilized systems of thiacetazone with each of the tested carriers listed in table 1 were prepared. The drug powder was thoroughly mixed with small, specified amount of ethanolic carrier solutions (or hydroalcoholic solutions in the case of MC, CMC, acacia, sorbitol and mannitol). The treated samples were left to dry over night at room temperature. The dried product was then sieved and the fraction size between 100-90 um was selected for performing the dissolution rate studies. Physical mixtures of the same composition as those of the hydrophilized systems were prepared by simple mixing of the powdered drug and carrier, possessing the same particle size range (100-90 um). Pure thiacetazone powder (100-90 um) served as control.

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In the case of isoniazid, thiacetazone and isoniazid powders were mixed in a ratio of 1:2 (the ratio in which these two drugs are administered in tablet form). The mixture was then wetted with 5 % w/w alcoholic solution of tween 40, then treated as previously described with the other carriers.

Dissolution Rate Studies :

The USPXX dissolution method was adopted at sink condition and agitation intensity of 50 rpm. A 500 ml 0.1 N HCl at  $37^{\circ}\text{C} \pm 0.1$  was used as dissolution medium. Samples of different hydrophilized systems equivalent to 150 mg thiacetazone were used. At specified time intervals, 5 ml samples were withdrawn for analysis and were replaced with equal volumes of 0.1 N HCl maintained at the same temperature.

Dissolution rate studies of the physical mixtures were also carried out. Also, the dissolution of 150 mg of powdered drug was used for comparison.

Assay Procedure :

The amounts of thiacetazone in solution after time intervals were estimated from its U.V. absorbance at 328 nm<sup>17</sup>.

Estimation of thiacetazone in the presence of isoniazid was carried out at 328 nm without interference of isoniazid according to the method described by Deodhar et al.<sup>17</sup> At the same time isoniazid was estimated in presence of thiacetazone colorimetrically at 395 nm<sup>17</sup>, without interference of thiacetazone.

Solubility Studies :

Excess amounts of thiacetazone were placed in stoppered conical flasks containing 25 ml of an aqueous solution of each carrier in varying concentrations ranging from 0.0125 to 0.5 % w/v. The contents of each flask were allowed to rotate in a thermostatically controlled

water bath, adjusted to 37°C for two hours (suitable predetermined time for equilibration). After equilibration, samples were withdrawn by means of filter pipette and suitably diluted with water. A sample filtrate was assayed for thiacetazone content at 321 nm. A blank experiment was carried out using distilled water.

#### Determination of Wettability of Hydrophilized Thiacetazone Powder<sup>18</sup> :

The apparatus used is shown in Fig. 1. It consists of glass tube 10 cm in length. The tube was plugged at its lower end with a wrapped filter strip (2 cm height) and packed with 1 gm of hydrophilized thiacetazone powder to a constant height of 8 cm. The packing was not too loose to produce heterogeneous porosities through the powder column. The tube was dipped to 1 cm depth in a beaker 100 ml capacity containing 50 ml distilled water. The extent of water penetration through the column of powder was measured in centimeters after 5, 10, 20, 30 and 60 minutes. A blank experiment was carried out using in situ thiacetazone powder.

## RESULTS AND DISCUSSION

Alcohol was chosen as a hydrophilization solvent rather than water, since preliminary experiments utilizing either ethyl alcohol or water were performed (Table 2). The results showed better enhancement in dissolution of thiacetazone from hydrophilized systems with tween 60, PVP44000 and acacia utilizing ethyl alcohol, than those hydrophilized using water. Moreover, ethyl alcohol has the advantage of high volatility so the process of hydrophilization is extremely fast.

Hydrophilized systems of thiacetazone with different types of hydrophilic carriers were prepared. In order to assess the effect of ethyl alcohol's volume used in the preparation of the hydrophilized systems, the dissolution rates of thiacetazone treated with different volumes of ethanolic carrier solution (PVP44000) were determined and illustrated in Fig.2. It is

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evident from Fig. 2 that slight differences in drug dissolution were detected by changing the volume of ethyl alcohol. Consequently, the least amount of alcohol ( $\frac{1}{2}$  ml) can be used during this study.

The effect of surface hydrophilization of thiacetazone powder on the dissolution rate profile of the drug was investigated. Table 3, summarizes the dissolution characteristics of the physical mixtures and hydrophilized systems of thiacetazone. Significantly, higher dissolution rates were found for the hydrophilized systems than for the corresponding physical mixtures or pure drug. Moreover, the enhancement was more pronounced when the drug treated with surfactants than when treated with polymers or sugar alcohols. Generally, the enhancement in dissolution of thiacetazone from hydrophilized systems, could be attributed to the fact that the distribution of hydrophilic carrier over the surface of the drug particles leads to creation of hydrophilic surface on the drug particles allowing more rapid penetration of the dissolution fluid, which tends to increase the wettability and thereby increases the dissolution rate of the drug.

(1) Hydrophilized Systems of Thiacetazone Using Non-ionic Surfactants :

Hydrophilized systems of thiacetazone using some non-ionic surface active agents were prepared. From the group of polyoxyethylene sorbitan esters, Tween 20, Tween 40, Tween 60 and Tween 80 were used besides Myrj 53 (polyoxyethylene (50) stearate and Brij 52 (polyoxyethylene (52) cetyl ether).

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The effect of the used surface active agents on the apparent water solubility of thiacetazone at 37°C was investigated (Fig. 3). It was found that a slight enhancement of thiacetazone solubility was achieved using these agents at the concentration ranges applied (0.0125-0.5 % w/v). However, the surfactants used differ in their solubilizing efficiency towards the drug. Tween 80 (HLB = 15) exerted the highest effect while, Tween 20 (HLB = 16.7) showed the lowest, thus the solubilizing efficiency is inversely proportional to the value of HLB. This is agreed with the results of the solubilization of some barbiturates, where the solubilizing capacity of a series of polysorbates is found to increase as alkyl chain length is increased from C<sub>12</sub> (Tween 20) to C<sub>18</sub> (Tween 80)<sup>19</sup>. Moreover, Myrj 53 showed better solubilizing effect than Brij 52.

Figs. 4-6 and Table 3 represent the results of dissolution of thiacetazone from its hydrophilized systems with the selected surfactants. It is clear that a pronounced increase in the dissolution rate of the drug was observed. Moreover, the dissolution enhancement effect is proportional to the surfactant concentration, thus 5 % (w/w) surfactant solution is better than 2% which is better than 1 % w/w. The rank order relationship of dissolution enhancement effect was found to be :

Tween 80 > Tween 60 > Myrj 53 > Tween 40 > Brij 52 > Tween 20 , comparing the values of dissolution rate constant K (Table 3).

Dissolution rate enhancing effects due to non-ionic surfactants are attributed to their effect on lowering of



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interfacial tension of the hydrophobic thiacetazone powder which led to improving its wettability and consequently its dispersion and dissolution, since a rapid and homogeneous dispersion of a solid in a liquid, can only occur when sufficient wetting is achieved<sup>20</sup>.

To study the influence of increasing wettability on the dissolution rate of the drug, inclusion of different concentrations of tween 20 in the dissolution medium was performed (Fig. 7).

The presence of surfactant in the dissolution medium enhanced the dissolution rate of thiacetazone. The enhancement effect is correlated directly with the concentration of the surfactant. It is clear that a good correlation exists between the dissolution rate and increasing wettability of the drug.

The effect of the different surfactants on the wettability of the drug have been studied (Table 4). From the table, it is evident that all the surfactants tested showed an increase of the wettability of thiacetazone a prerequisite for its dissolution. At 1% Tween concentration, an inverse correlation was found between the HLB values of the Tweens and their wetting capacities. Thus, Tween 80 (HLB = 15) was more efficient than Tween 60 (HLB = 15.6) and Tween 20 (HLB = 16.7).

At higher Tween concentrations this correlation could not be obtained in all the members.

However, Myrj 53 and Brij 52 showed less effect than Tweens and showed nearly the same effect except at 2% surfactant concentration Brij 52 exhibited higher effect on the wettability of the drug.

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(2) Hydrophilized Systems of Thiacetazone Using Polymers :

Different hydrophilic polymers were used to prepare hydrophilized systems of thiacetazone. The polymers used are polyvinylpyrrolidone 44000, polyethylene glycol 6000, methylcellulose, carboxymethylcellulose and acacia.

The effect of the polymers on the apparent water solubility of the drug at 37°C was investigated (Fig. 8). The polymers tested showed very slight increase in solubility. Carboxymethylcellulose showed the highest and methylcellulose showed the lowest solubilizing effect.

However, these polymers when utilized for preparation of hydrophilized thiacetazone systems, showed moderate dissolution enhancement effect (Fig. 9-11). With respect to their dissolution enhancement effect, the polymers are ranked in the sequence of PVP44000 > acacia > carboxymethylcellulose > methylcellulose > Polyethylene glycol 6000. From the figures it is obvious that increasing the concentration of the polymers from 1 to 2% increased the dissolution enhancing effect but higher polymer concentration (5%) leads to a reduction in the dissolution enhancing effect, may be even less than the effect of 1% and 2% as in case of PVP 44000, acacia and methylcellulose or in between the influence due to 1 & 2% polymer solution as in case of carboxymethylcellulose, except in case of PEG6000, increasing the polymer concentration leads to increase the dissolution enhancing effect.

The influence of members of this group which are hydrophilic carriers on enhancement of thiacetazone dissolution is less than the group of non-ionic surfactants which possess higher surface activity. Moreover, the increase in viscosity imparted by these polymers may decrease the dissolution rate.

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It has been reported that, increasing chain length of PEGS leads to decrease in the dissolution rates of drugs<sup>21</sup>. Of all the tested polymers, only methylcellulose was used to hydrophilize systems of hexobarbital powders filled in gelatin capsules. Significantly higher release rates from capsules were found for the treated hexobarbital than for pure drug<sup>13</sup>.

Studying the effect of these polymers on the wettability of the drug (Table 5) revealed that the tested polymers increased the wettability of thiacetazone to varying extents, depending on the polymer concentration and the time of the experiment. A common observation is that a decrease in the wetting influence at a 5% polymer concentration.

(3) Hydrophilized Systems of Thiacetazone Using Sugar Alcohols:

The effect of the two sugar alcohols namely sorbitol and mannitol on the apparent water solubility of thiacetazone at 37°C was studied (Fig. 12). The two substances showed a very slight and similar solubilizing action. However, preparing hydrophilized systems of thiacetazone powder utilizing these two sugar alcohols resulted in a pronounced improvement of the dissolution of thiacetazone compared to untreated thiacetazone powder (Fig. 13). These soluble sugar alcohols would tend to increase the wetting of drug particles and thereby increase dissolution rate. Since the drug particles are very intimately encircled by the soluble carrier, which can readily dissolve and cause the dissolution fluid to come in and wet the drug particles. However, higher concentrations of the sugar alcohols would lead to decrease the dissolution enhancing effect due to the formation of more viscous solution which make it difficult for particles to leave the diffusion layer to the bulk of the dissolution medium.

Studying the influence of sorbitol and mannitol on the wettability of thiacetazone was studied (Table 6). It is clear that both sugar alcohols showed moderate effect on increasing the wettability of thiacetazone, this effect is again decreased at higher carrier concentration.

(4) Hydrophilized System of Thiacetazone-isoniazid :

Isoniazid is routinely used concomitantly with thiacetazone in the treatment of tuberculosis, thus, it is worthy to prepare thiacetazone-isoniazid hydrophilized system (in the ratio of 1:2 thiacetazone-isoniazid) and to further study the effect of isoniazid on the solubility and dissolution of thiacetazone.

The effect of isoniazid on the apparent aqueous solubility of thiacetazone at 37°C was studied (Fig. 14). Isoniazid showed good solubilizing effect of thiacetazone at the concentration range used (0.0125 - 0.5 % w/w).

The dissolution of thiacetazone from thiacetazone-isoniazid system using 5 % tween 40 was studied (Fig. 15). Pronounced enhancement of thiacetazone dissolution was observed relative to pure drug.

Studying the effect of isoniazid on the wettability of thiacetazone (Table 6) showed a good wetting action of isoniazid at the ratio used.

It could be concluded that the technique of hydrophilization is effective for improving the dissolution rate of the drug by these soluble carriers. The dissolution enhancing effect revealed itself not due to the solubilization of the drug by these carriers except in the case of isoniazid which showed a promising solubilizing effect. The effect of all the carriers could be attributed to the technique itself as revealed by increasing the wettability of the drug from the hydrophilized systems more than their corresponding physical mixtures with the drug.

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Table 1: List of Materials Tested as Carriers for  
Hydrophilized Thiacetazone systems.

Surfactants:

|          |
|----------|
| Tween 20 |
| Tween 40 |
| Tween 60 |
| Tween 80 |
| Brij 52  |
| Myrj 53  |

Polymers:

|                                 |
|---------------------------------|
| Polyvinylpyrrolidone (PVP44000) |
| Polyethylene glycol (PEG6000)   |
| Methyl cellulose (M C )         |
| Carboxy methyl cellulose (CMC)  |
| Acacia                          |

Sugars:

|          |
|----------|
| Sorbitol |
| Mannitol |

In addition, to isoniazid at 1:2 drug-isoniazid ratio.

Table 2: Effect of the Type of Hydrophilization Solvent on  
the Relative Dissolution Rate of Thiacetazone.

| Surfactant | Conc. % | Relative Dissolution Rate after 10min |        |
|------------|---------|---------------------------------------|--------|
|            |         | Alcohol<br>w/w                        | water  |
| Tween 60   | 1       | 10.849                                | 11.904 |
|            | 2       | 12.044                                | 11.626 |
|            | 5       | 13.861                                | 12.965 |
| PVP44000   | 1       | 8.045                                 | 3.235  |
|            | 2       | 6.986                                 | 4.700  |
|            | 5       | 6.217                                 | 3.965  |
| Acacia     | 1       | 7.840                                 | 0.795  |
|            | 2       | 10.336                                | 1.020  |
|            | 5       | 7.936                                 | 0.911  |

RDR\* : The relative dissolution rate: is the amount of  
of thiacetazone dissolved at any time divided by that dissol-  
uted from untreated sample at that time.

Table 3: Dissolution Characteristics of Thiacetazone Physical Mixtures  
and Hydrophilized Systems with 1% w/w of the Carrier.

| Carrier<br>used                                | Physical mixtures  |                  |      |      | Hydrophilized systems                                      |                  |       |       |
|--|--|------------------|------|------|--|------------------|-------|-------|
|  | $\frac{K}{(\text{gm}^3 \text{ min.}^{-1}) \times 10^{-3}}$ | RDR after (min.) |      |      | $\frac{K}{(\text{gm}^3 \text{ min.}^{-1}) \times 10^{-3}}$ | RDR after (min.) |       |       |
|  |  | 5                | 10   | 20   |  | 5                | 10    | 20    |
| Control  | 0.605  | ---              | ---  | ---  | 0.605  | ---              | ---   | ---   |
| <u>Surfactants</u>                             |  |                  |      |      |  |                  |       |       |
| Tween 20                                       | 3.65   | 7.33             | 8.31 | 4.30 | 4.78   | 13.60            | 9.00  | 4.54  |
| Tween 40                                       | 4.603  | 13.50            | 8.86 | 4.35 | 5.44   | 17.06            | 9.93  | 4.60  |
| Tween 60                                       | 4.33   | 12.08            | 8.31 | 4.26 | 5.80   | 16.06            | 10.85 | 5.42  |
| Tween 80                                       | 4.28   | 11.79            | 8.41 | 4.26 | 6.09   | 17.30            | 11.47 | 5.53  |
| Myrj 53  | 4.61   | 13.23            | 8.67 | 4.54 | 5.72   | 16.51            | 10.94 | 5.14  |
| Brij 52  | 3.26   | 8.19             | 6.85 | 3.25 | 4.95   | 12.82            | 10.23 | 4.95  |
| <u>Polymers</u>                                |  |                  |      |      |  |                  |       |       |
| PVP44000                                       | 2.72   | 7.33             | 4.94 | 3.04 | 4.30   | 11.29            | 8.05  | 4.10  |
| PEG6000  | 1.40   | 2.25             | 1.98 | 2.54 | 1.66   | 2.66             | 2.18  | 2.89  |
| MC   | 0.94   | 1.35             | 1.63 | 1.61 | 2.85   | 5.65             | 5.82  | 3.70  |
| CMC  | 1.49   | 2.30             | 2.58 | 2.51 | 2.95   | 6.27             | 6.08  | 3.80  |
| Acacia   | 1.42   | 1.48             | 3.08 | 2.27 | 3.39   | 5.90             | 7.84  | 4.05  |
| <u>Sugar<br/>alcohols</u>                      |  |                  |      |      |  |                  |       |       |
| Sorbitol                                       | 1.28   | 2.17             | 2.00 | 1.98 | 2.63   | 3.20             | 4.67  | 3.99  |
| Mannitol                                       | 1.89   | 4.05             | 2.95 | 2.93 | 5.54   | 16.88            | 9.97  | 4.95  |
| <u>Isoniazid<br/>(1:2 drug:<br/>isoniazid)</u> |  |                  |      |      |  |                  |       |       |
|  | 3.51   | 5.62             | 9.50 | 7.50 | 7.46   | 19.44            | 18.06 | 10.12 |

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Table 4 : Effect of Non-Ionic Surfactants on Wettability of Thiacetazone Powder.

| Surfactant | Conc. % | Mean values of penetration (cm) of water after (minutes) |     |     |     |     |
|------------|---------|--|-----|-----|-----|-----|
|            |         | 5  | 10  | 20  | 30  | 60  |
| Control    |         | ---  | --- | --  | 2.1 | 3.2 |
| Tween 20   | 1       | 2.3  | 2.5 | 3.2 | 3.5 | 6.2 |
|            | 2       | 3.0  | 3.5 | 4.2 | 4.8 | 7.0 |
|            | 5       | 3.8  | 4.6 | 5.5 | 6.2 | > 8 |
| Tween 40   | 1       | 2.8  | 3.1 | 4.0 | 4.5 | 6.7 |
|            | 2       | 3.8  | 4.6 | 5.9 | 6.4 | > 8 |
|            | 5       | 3.9  | 5.2 | 6.5 | 7.6 | > 8 |
| Tween 60   | 1       | 2.8  | 3.1 | 4.0 | 4.4 | 6.5 |
|            | 2       | 3.3  | 3.8 | 5.2 | 6.0 | 8.0 |
|            | 5       | 3.6  | 3.9 | 5.3 | 6.2 | > 8 |
| Tween 80   | 1       | 2.7  | 3.5 | 4.5 | 5.0 | 6.8 |
|            | 2       | 3.5  | 3.8 | 4.8 | 5.5 | 7.3 |
|            | 5       | 3.6  | 3.8 | 4.9 | 5.6 | 7.4 |
| Myrij 53   | 1       | 2.5  | 2.8 | 3.8 | 4.5 | 6.7 |
|            | 2       | 2.5  | 2.8 | 3.9 | 4.7 | 7.0 |
|            | 5       | 2.7  | 3.4 | 4.0 | 4.6 | 6.9 |
| Brij 52    | 1       | 2.2  | 2.8 | 3.8 | 4.5 | 6.1 |
|            | 2       | 3.0  | 3.4 | 4.2 | 4.5 | 7.5 |
|            | 5       | 3.1  | 3.4 | 4.3 | 4.8 | 7.3 |

Table 5 : Effect of Different Polymers on Wettability of Thiacetazone Powder.

| Polymer                  | Conc. % | Mean values of Penetration (cm) of water after:(minutes) |     |     |     |     |
|--------------------------|---------|--|-----|-----|-----|-----|
|                          |         | 5  | 10  | 20  | 30  | 60  |
| Control                  |         | ---  | --- | --- | 2.1 | 3.2 |
| PVP 44,000               | 1       | 2.1  | 2.5 | 3.4 | 4.1 | 5.5 |
|                          | 2       | 2.6  | 3.5 | 4.2 | 4.8 | 6.1 |
|                          | 5       | 2.6  | 3.0 | 3.8 | 4.3 | 5.8 |
| PFG 6000                 | 1       | 2.2  | 2.7 | 3.5 | 4.1 | 5.3 |
|                          | 2       | 2.4  | 3.0 | 4.0 | 4.8 | 6.2 |
|                          | 5       | 2.6  | 2.8 | 3.6 | 4.2 | 5.2 |
| Methyl Cellulose         | 1       | 2.2  | 2.8 | 3.7 | 4.0 | 5.5 |
|                          | 2       | 2.3  | 3.0 | 3.8 | 4.1 | 5.2 |
|                          | 5       | 2.1  | 2.3 | 2.7 | 3.0 | 5.3 |
| Carboxy-Methyl cellulose | 1       | 2.3  | 2.9 | 3.8 | 4.3 | 5.7 |
|                          | 2       | 2.7  | 3.1 | 4.0 | 4.5 | 6.0 |
|                          | 5       | 2.5  | 2.8 | 3.2 | 3.5 | 4.9 |
| Acacia                   | 1       | 2.5  | 2.8 | 3.3 | 3.6 | 4.9 |
|                          | 2       | 2.7  | 3.1 | 4.0 | 4.6 | 5.7 |
|                          | 5       | 2.8  | 3.0 | 3.9 | 4.3 | 5.3 |

Table 6 : Effect of Sugar alcohols and Isoniazid on Wettability of Thiacetazone Powder.

| Sugar alcohol                                     | Conc. %<br>(w/w) | Mean values of Penetration (cm) of water after (minutes) |     |     |     |     |
|---|------------------|--|-----|-----|-----|-----|
|   |                  | 5  | 10  | 20  | 30  | 60  |
| ---   | Control          | ---  | --- | --- | 2.1 | 3.2 |
| Sorbitol  | 1                | 2.4  | 2.7 | 3.1 | 3.5 | 4.5 |
|   | 2                | 2.6  | 2.7 | 3.0 | 3.4 | 4.1 |
|   | 5                | 2.2  | 2.3 | 2.9 | 3.1 | 3.8 |
| Mannitol  | 1                | 2.5  | 2.8 | 3.2 | 3.5 | 4.2 |
|   | 2                | 2.3  | 2.5 | 3.0 | 3.1 | 3.7 |
|   | 5                | 2.1  | 2.4 | 2.7 | 2.8 | 3.2 |
| Thiacetazone-isoniazid (1:2) with 5% w/w Tween 40 |                  | 3.3  | 4.0 | 4.5 | 5.3 | 8.0 |



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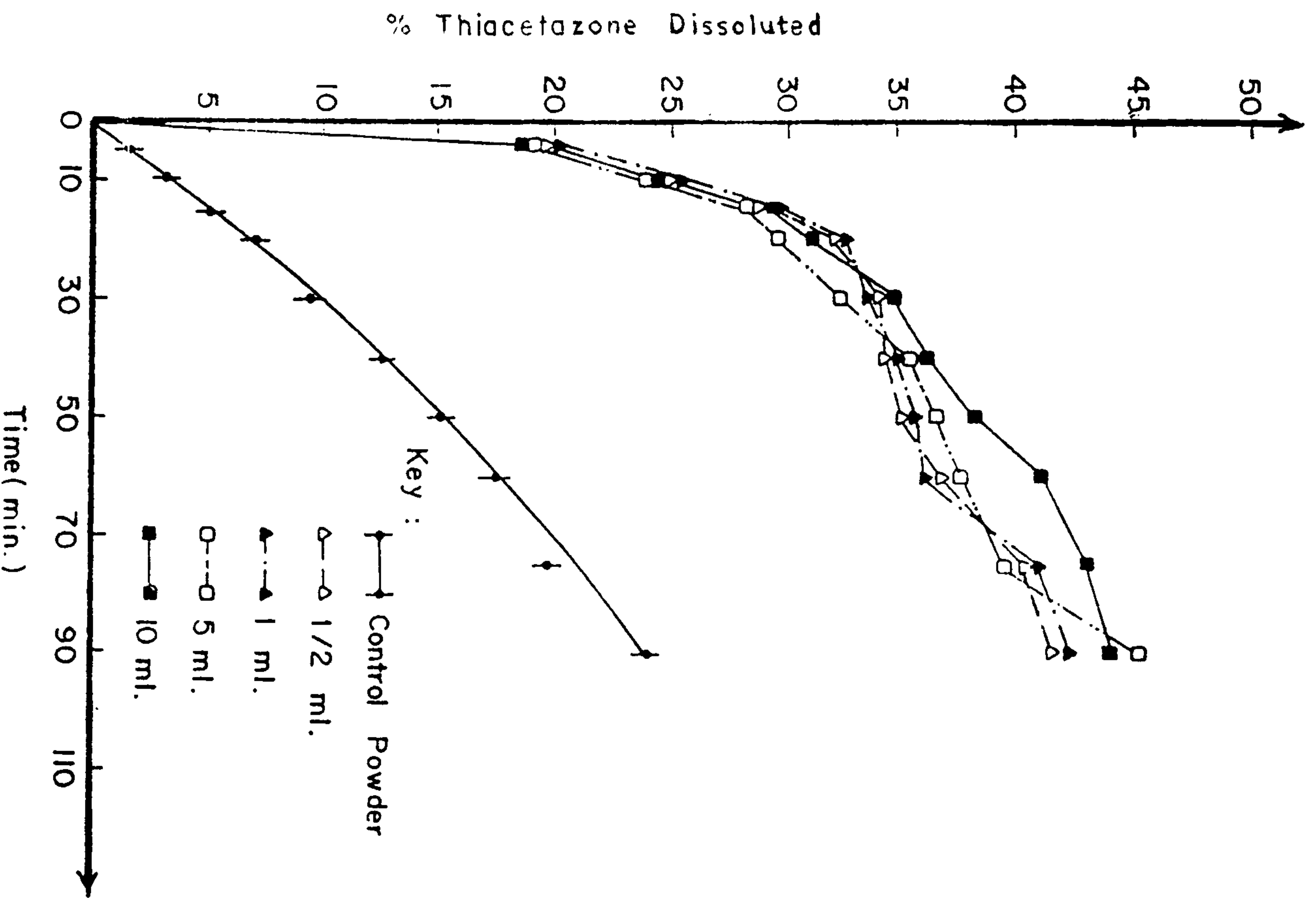
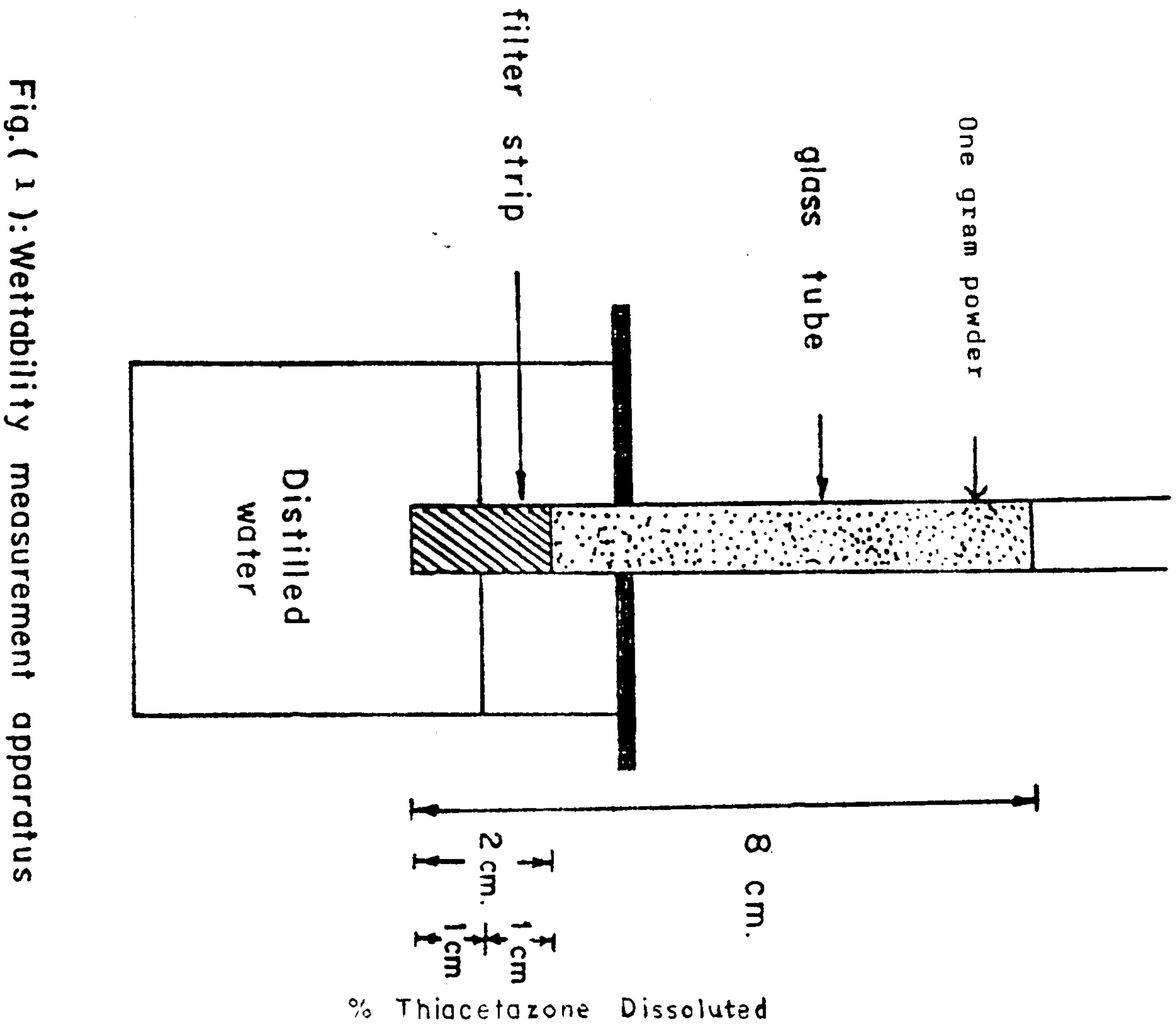


Fig. 7: Effect of the Volume of Alcohol on Dissolution of Thiacetazone from its Hydrophilized Systems with 1% (w/w) PVP 44000.

Fig. ( 1 ): Wettability measurement apparatus

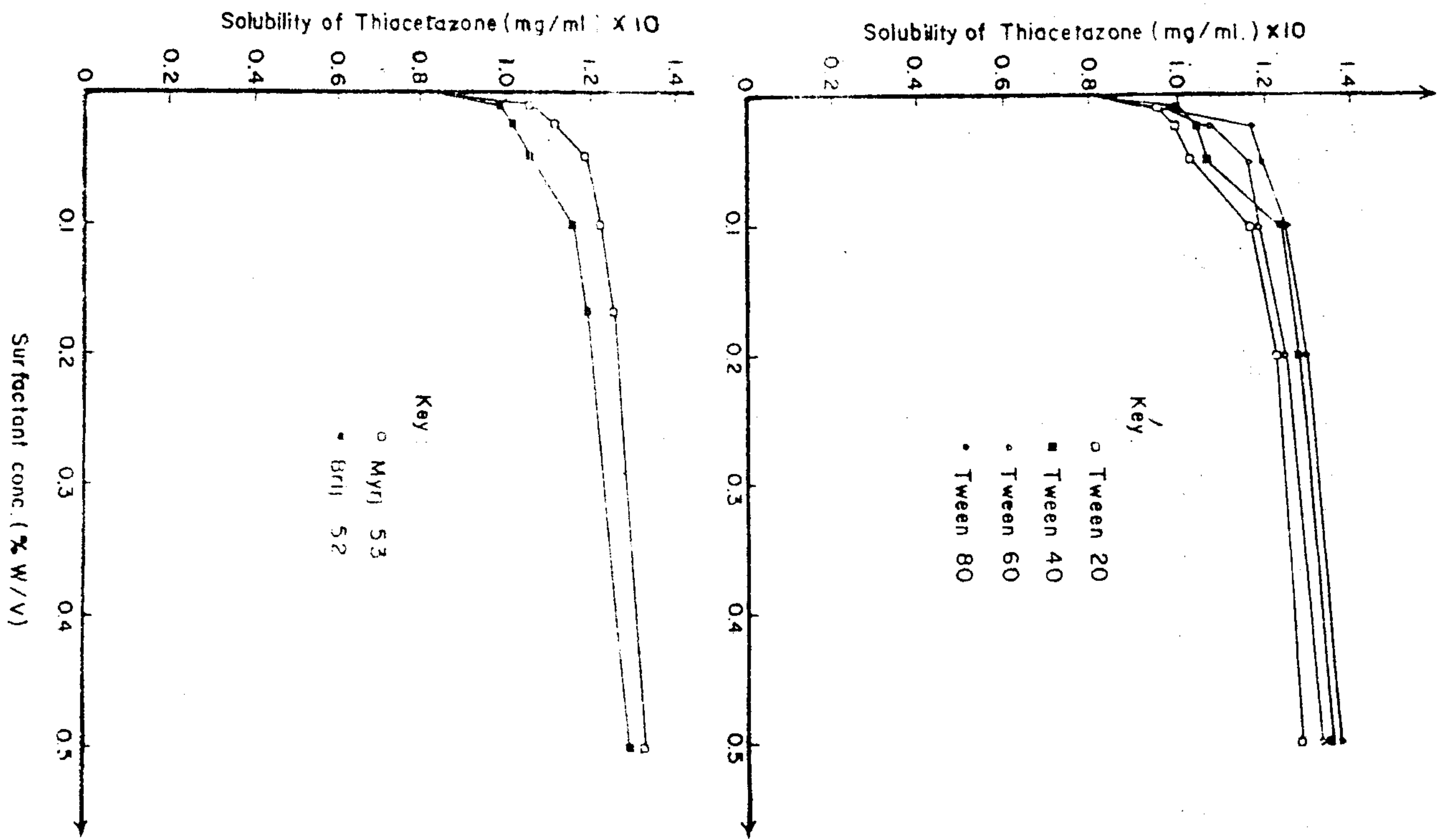


Fig. 3: Effect of some non-ionic surfactants on the solubility of thiacetazone in water at 37°C.

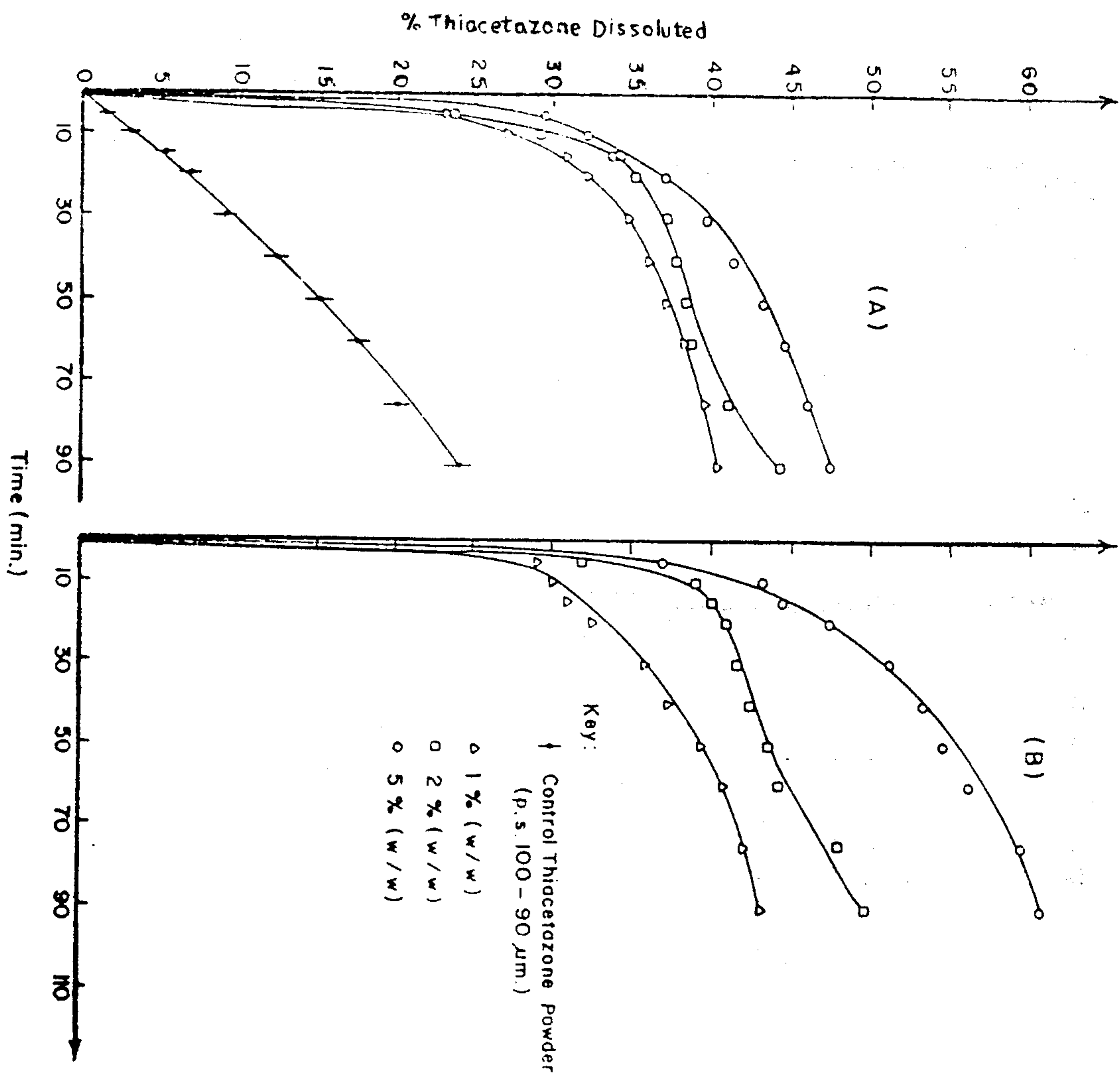


Fig. 4: Dissolution profile of Thiacetazone from its hydrophilized systems with, (A) Tween 20 and (B) Tween 40.

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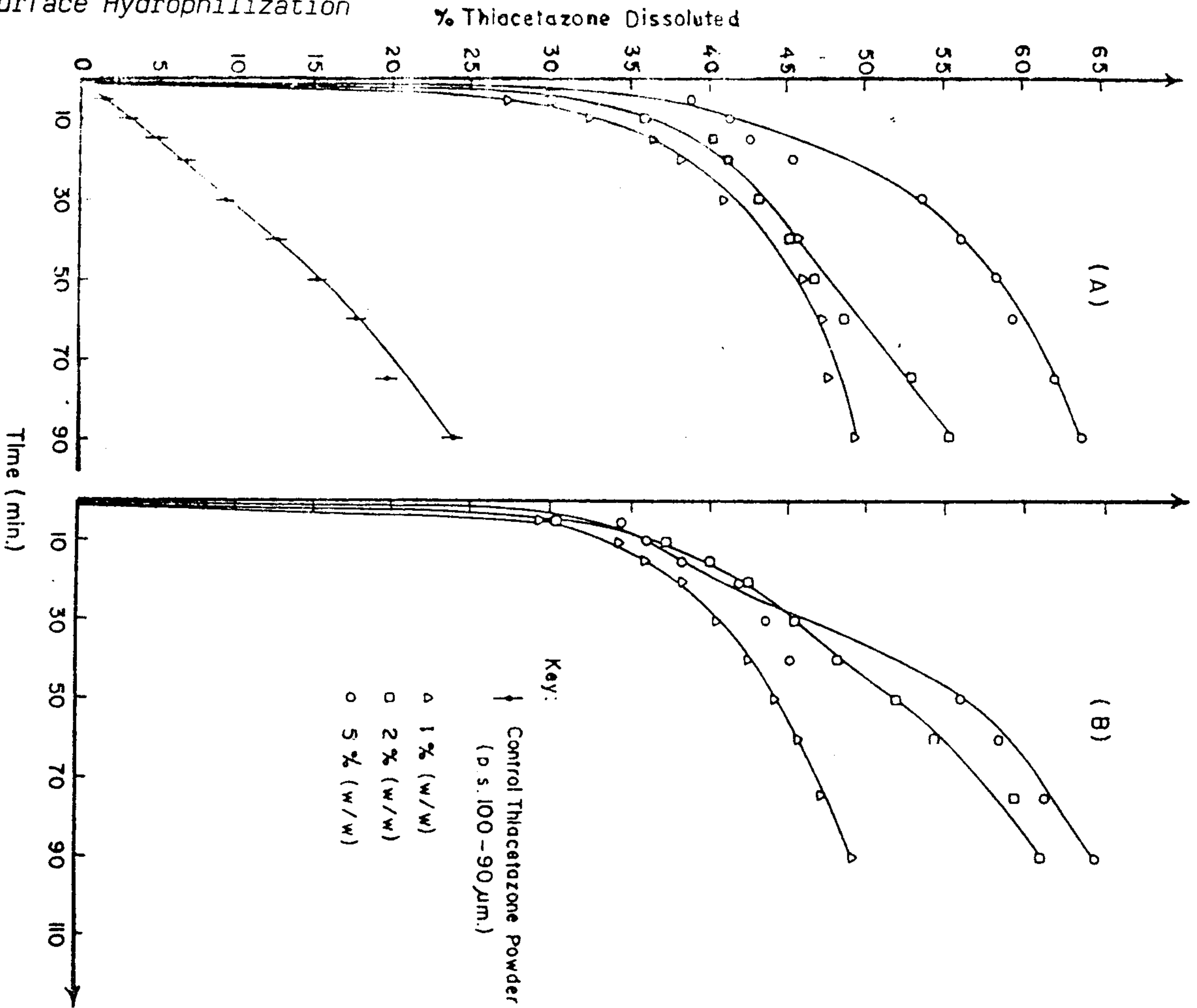


Fig. 5: Dissolution profile of thiacetazone from its hydrophilized systems with, (A) Tween 60 and (B) Tween 80.

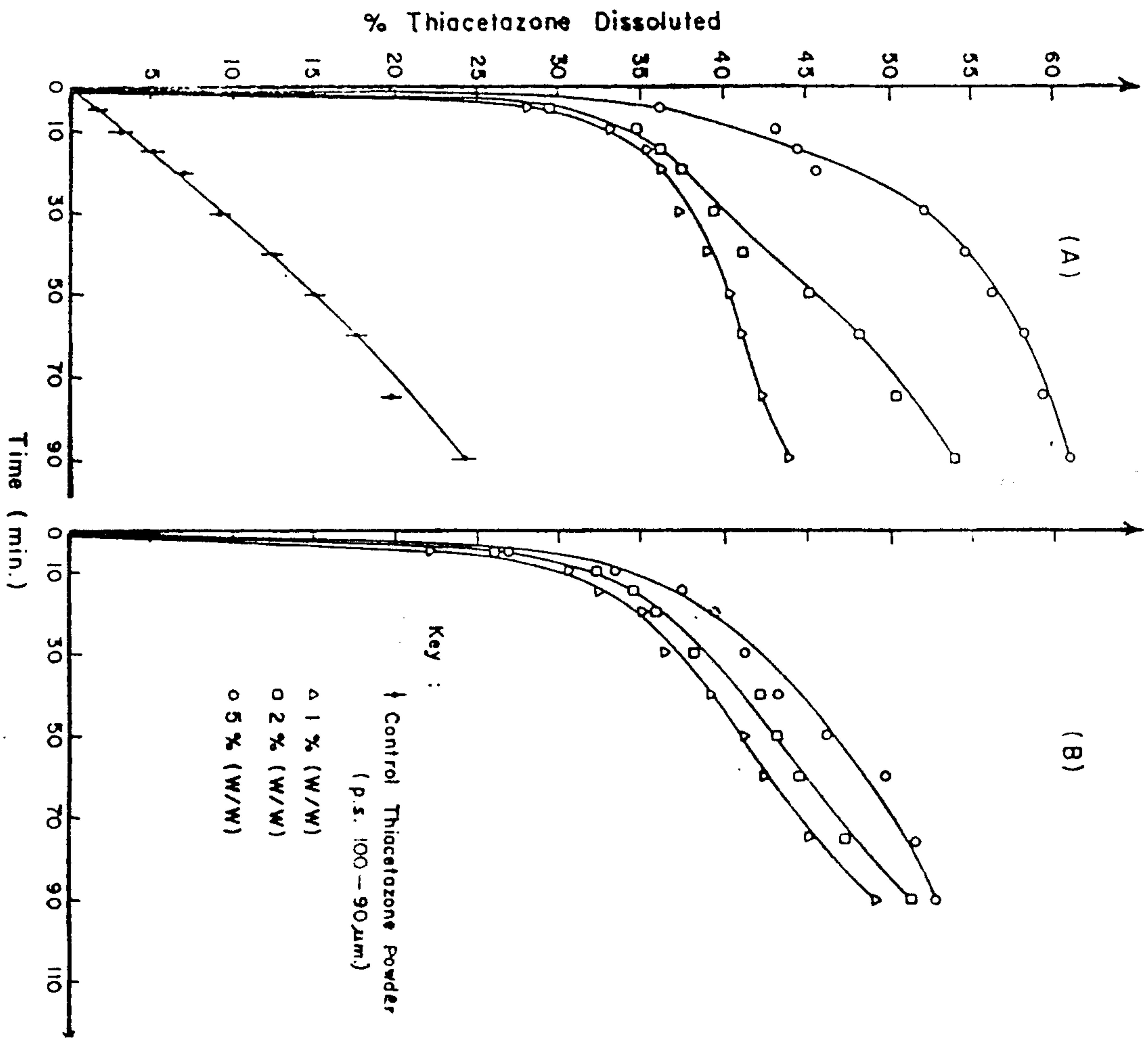


Fig. 6: Dissolution profile of thiacetazone from its hydrophilized systems with, (A) Myrij 52 and (B) Brij 52.

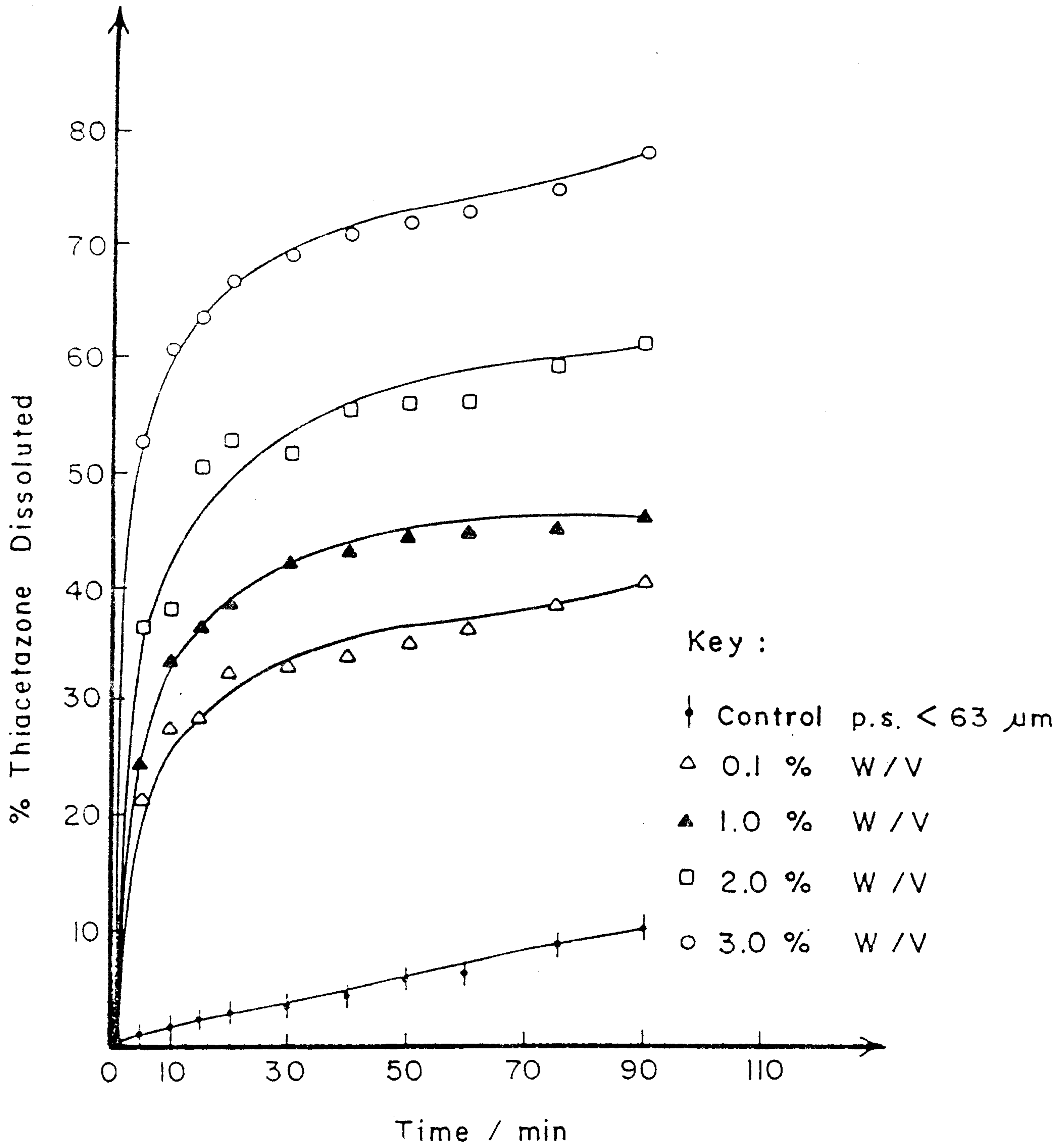


Fig. 7: Effect of Different Concentrations of Tween 20 (%w/v) on the Dissolution Profile of Thiacetazone.

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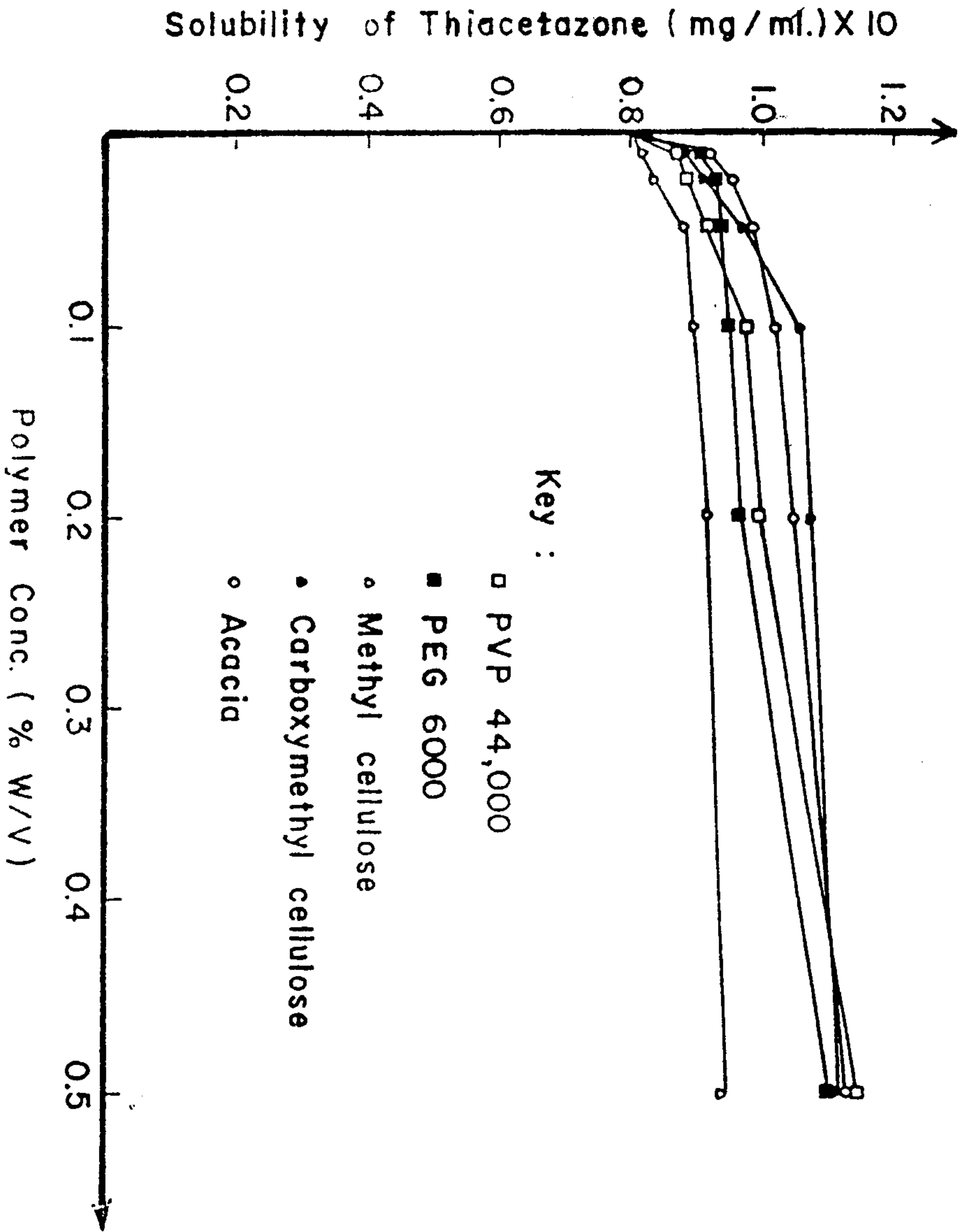


Fig. 8: Effect of some hydrophilic polymers on the solubility of thiacetazone in water at 37°C.

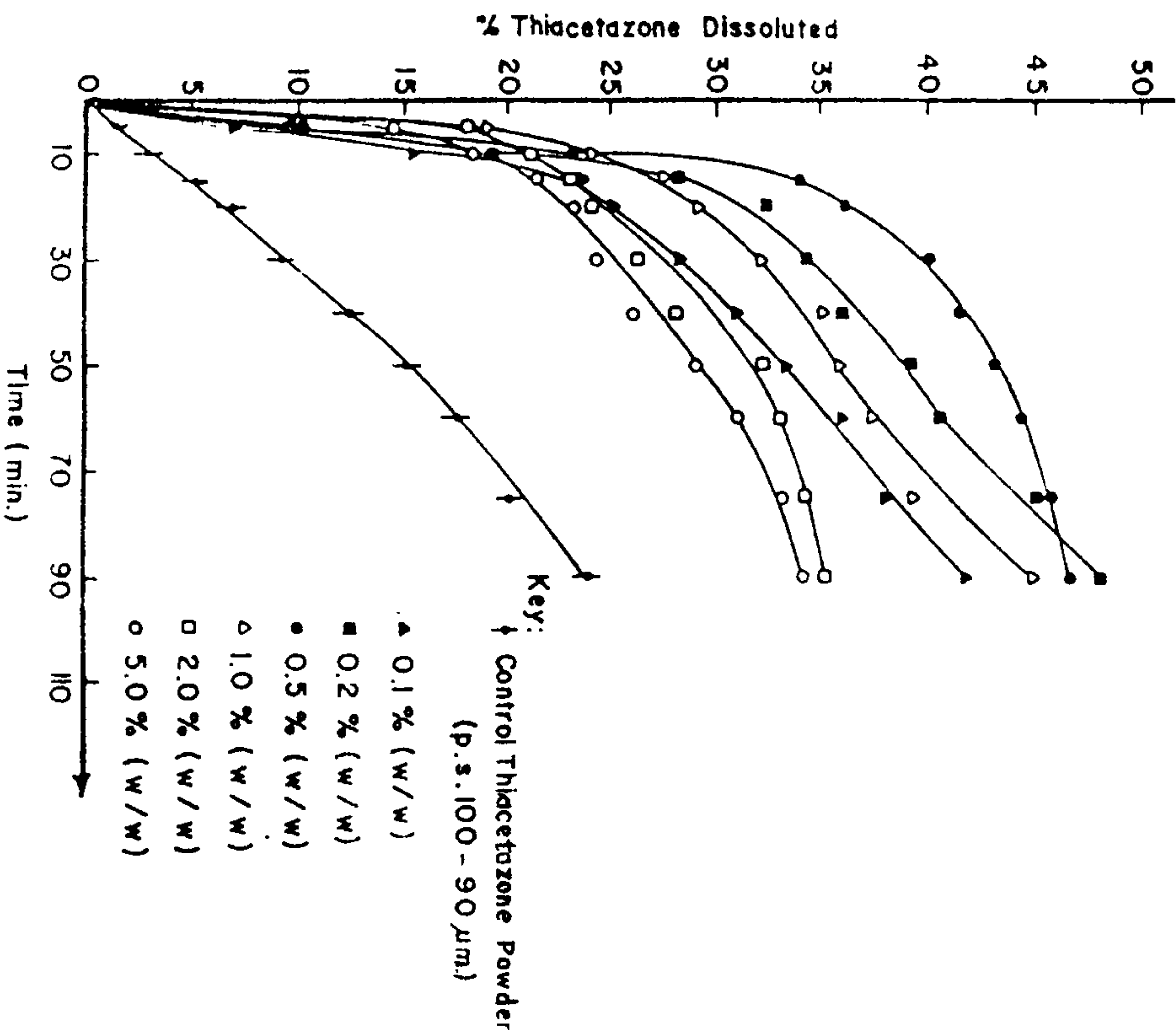


Fig. 9: Dissolution profile of thiacetazone from its hydrophilized systems with different concentrations of PVP 44000.

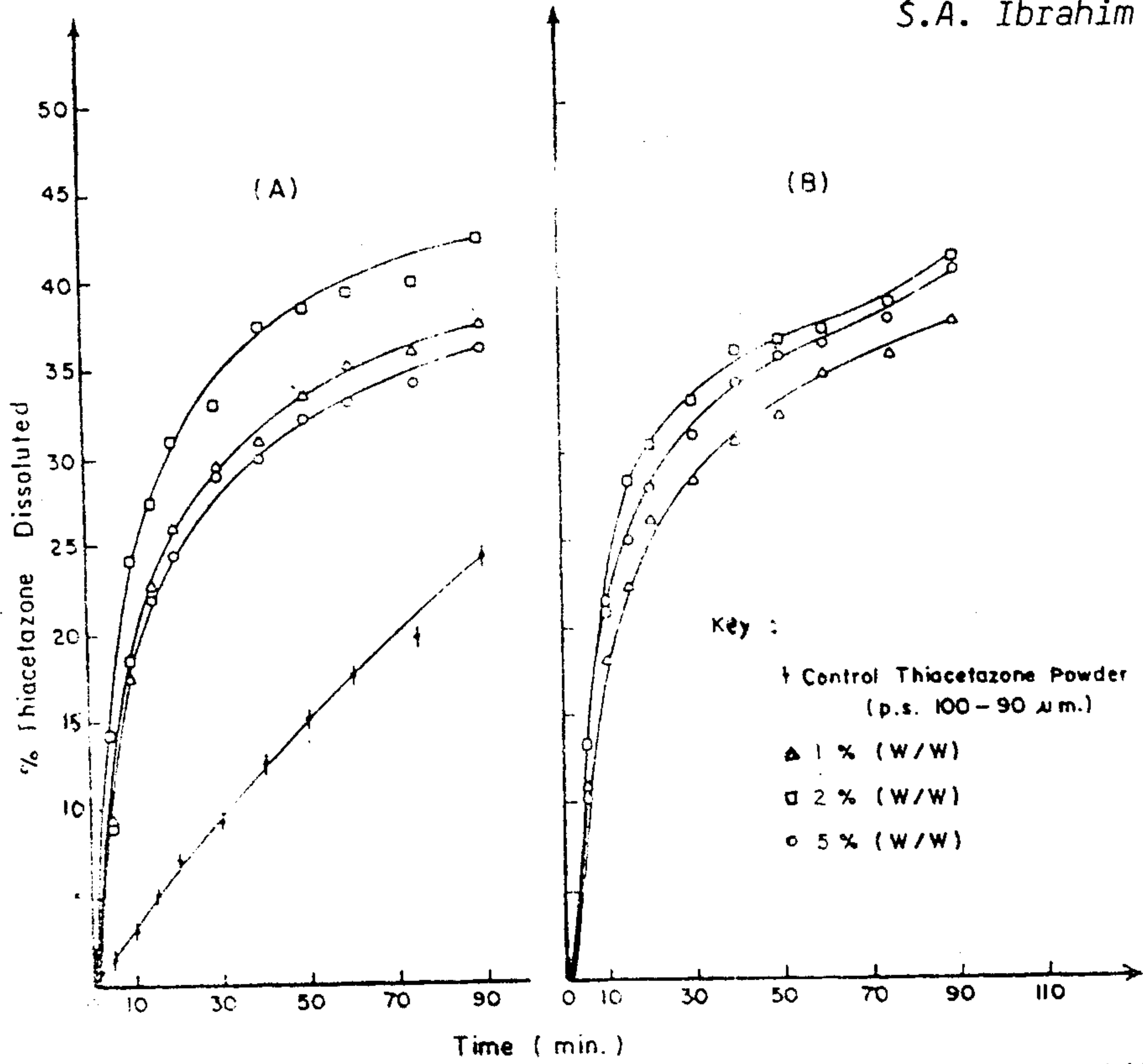


Fig. 10: Dissolution Profile of thiacetazone from its hydrophilized systems with. (A) Methylcellulose and (B) carboxymethylcellulose.

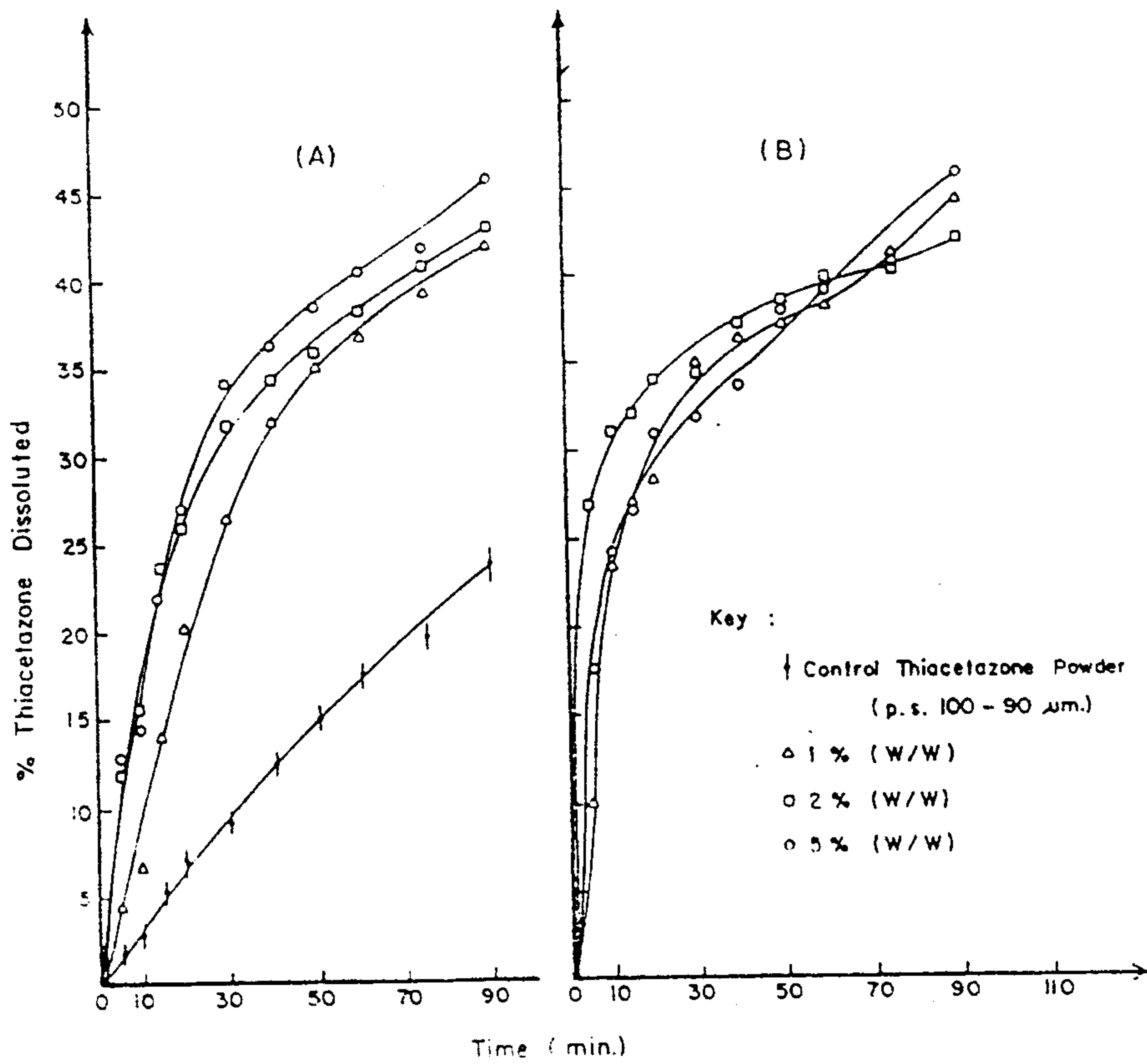


Fig. 11: Dissolution profile of thiacetazone from its hydrophilized systems with. (A) PEG6000 and (B) Acacia.

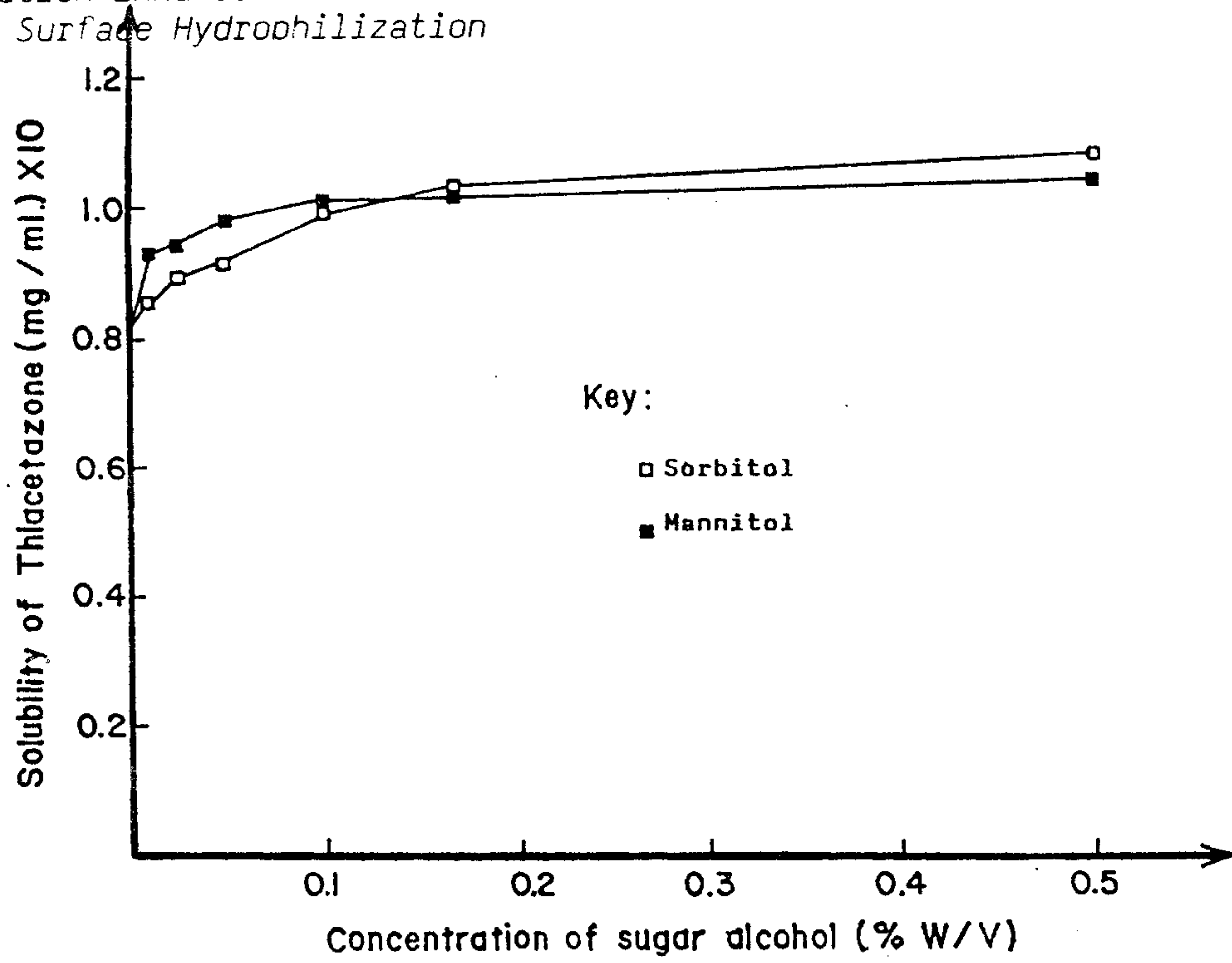


Fig. 12: Effect of sugar alcohols on the solubility of thiacetazone in water at 37°C.

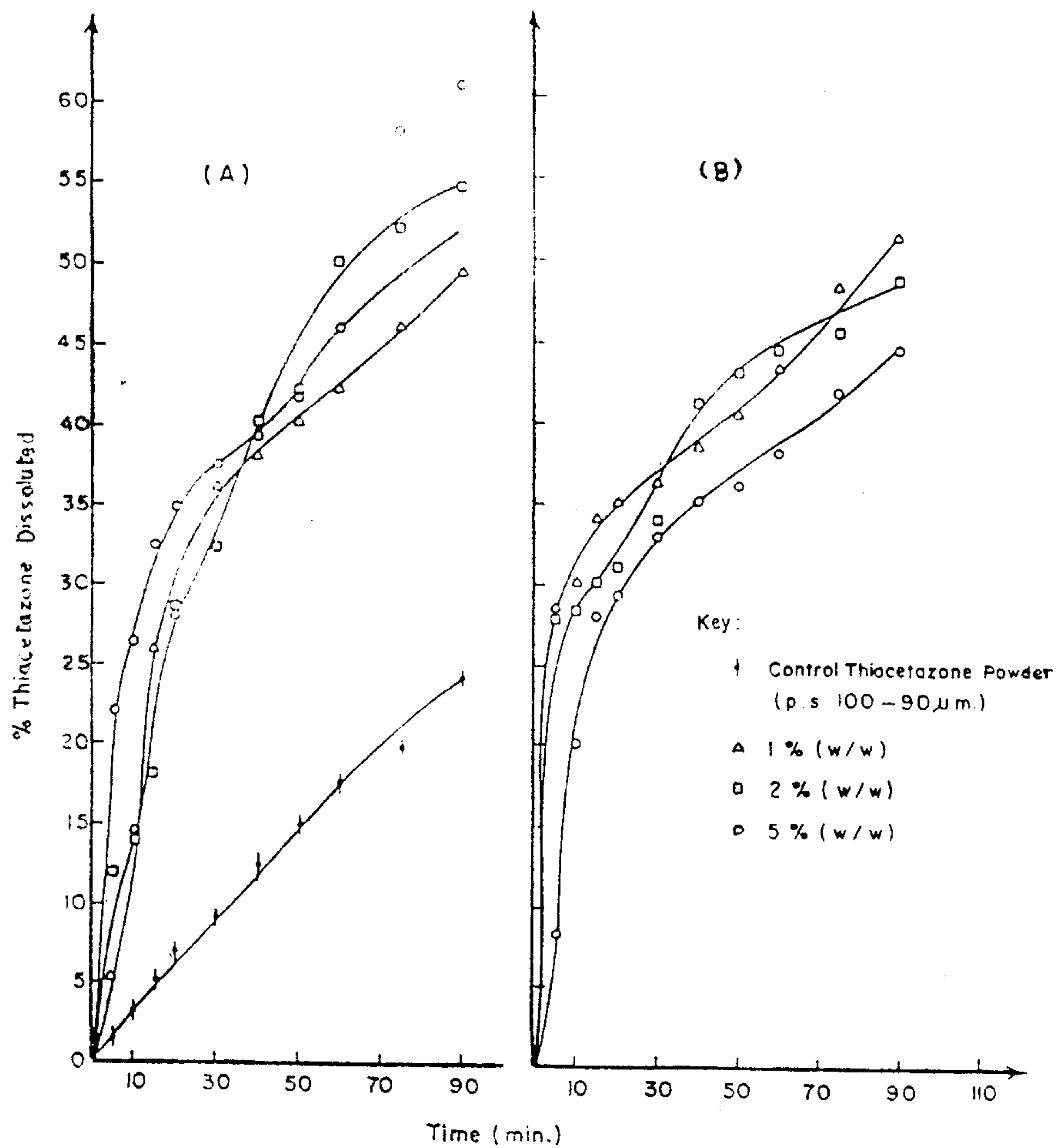


Fig. 13: Dissolution profile of thiacetazone from its hydrophilized systems with, (A) sorbitol and (B) Mannitol.

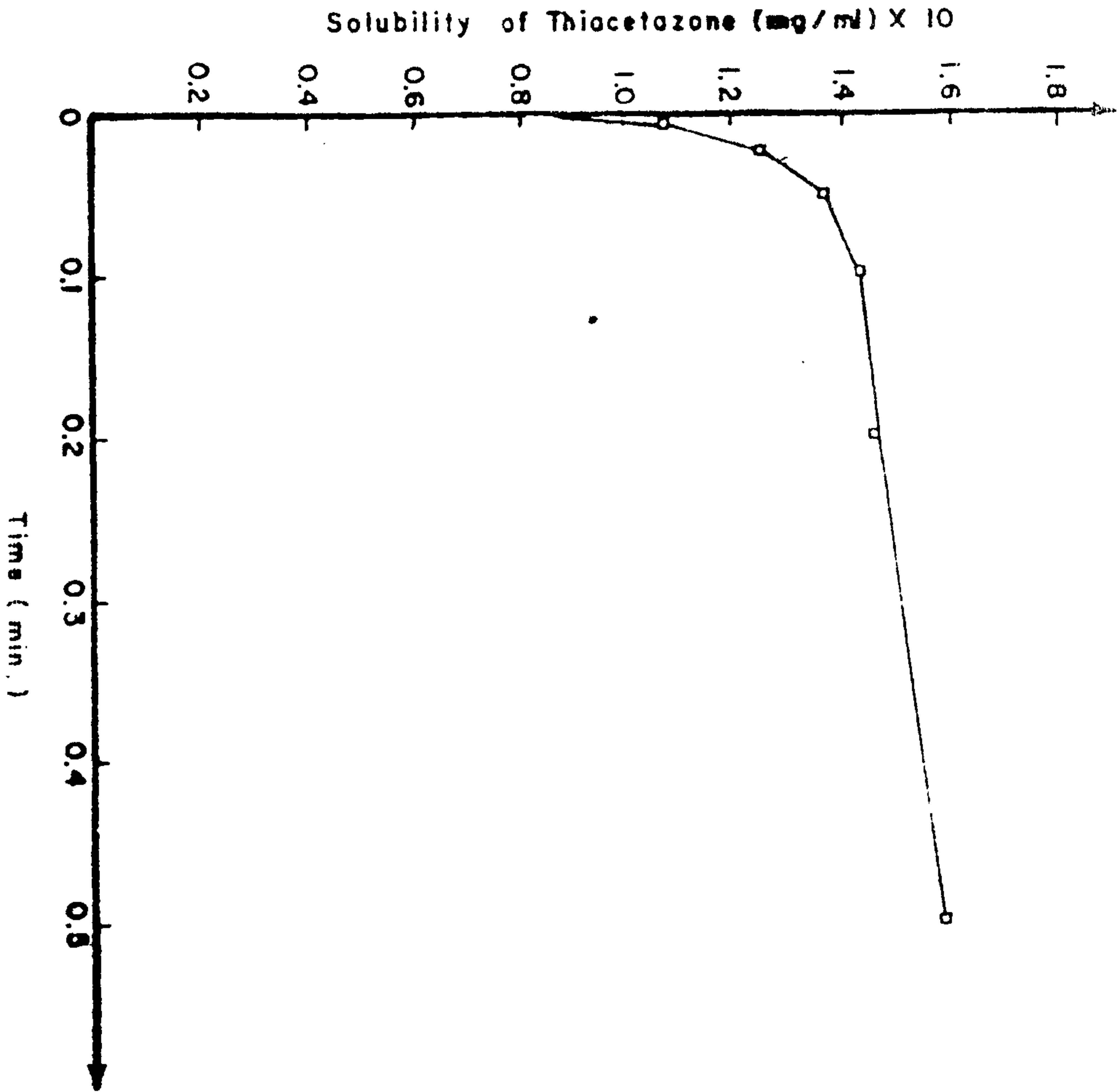


Fig. 14: Effect of isoniazid on the solubility of thiocetazone in water at 37°C.

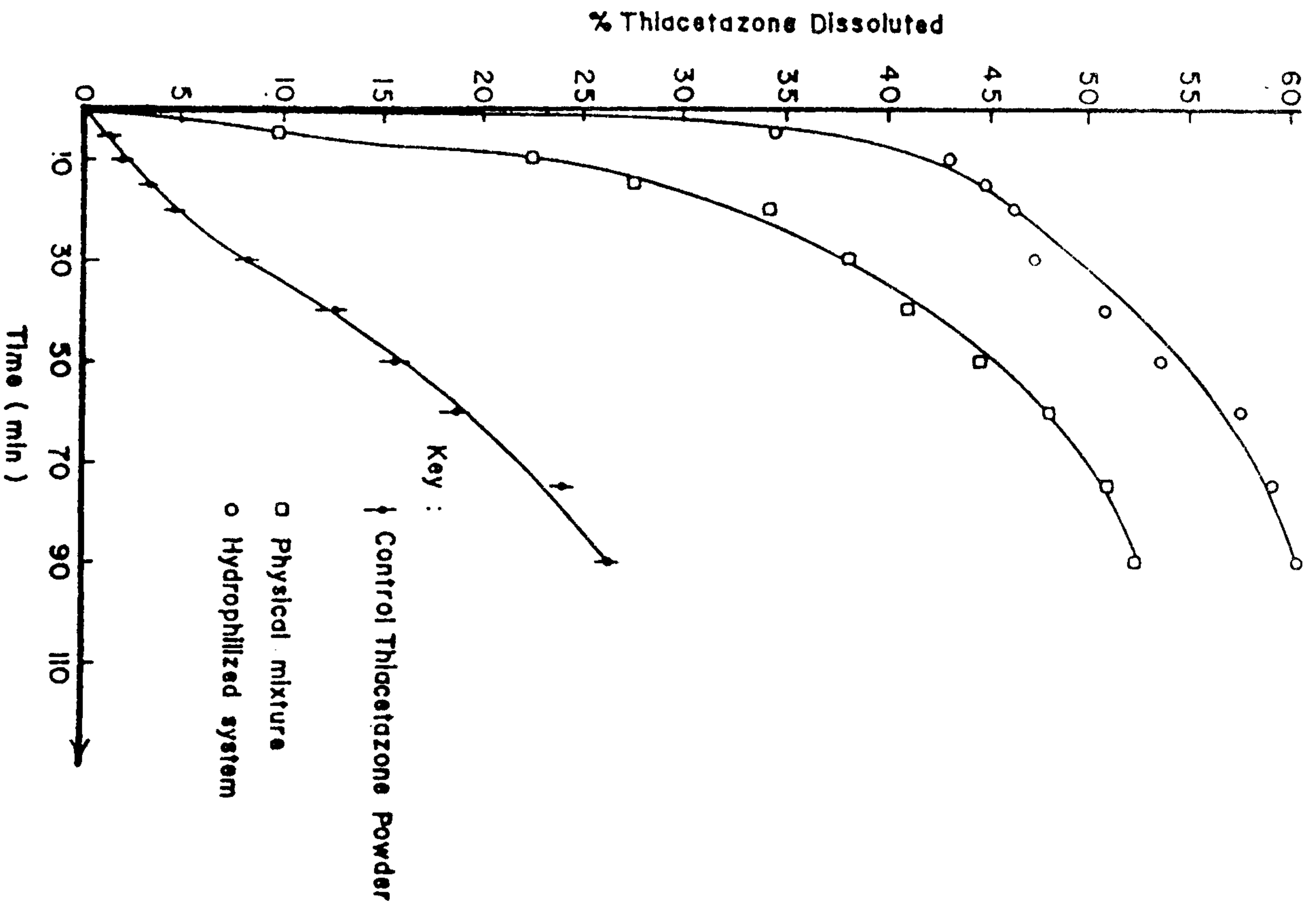


Fig. 15: Dissolution profile of thiocetazone from thiocetazone-isoniazid physical mixture and hydrophilized system.



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زيادة معدل اذابة الثياسيتازون بواسطة زيادة قابليته

السطحية للماء

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من المعروف أن عقار الثياسيتازون المستخدم فى علاج مرض الدرن شحيح الذوبان فى الماء وكذلك فى المديبات العضوية . بالاضافة الى أن هذا العقار يتكسر عند درجـة انصهاره . وبناء عليه فان العديد من الطرق المستخدمة فى زيادة ذوبان العقارات شحيحه الذوبان فى الماء لاتصلح مع الثياسيتازون .

وقد استخدمت طريقة زيادة القابلية السطحية للماء لزيادة معدل ذوبان الثياسيتازون فى الماء وفى هذه الطريقة يندى مسحوق العقار بحم قليل من المادة المحبه للماء والمذابه فى الكحول الاثيلى . ثم يترك ليحف عند درجة حراره الغرفه لمدة يوم . والمواد المحبه للماء التى استخدمت فى هذه الطريقة هى :المواد ذات النشاط السطحى الغير متآنيه ( مثل توين ٢٠ ، ٤٠ ، ٦٠ ، ٨٠ وكذلك ميرج ٥٣ ، بردج ٥٢ ، المواد المبلوره ( بيروليدون عديد الفينيل ٤٤٠٠٠ ر ، الجليكول عديد الاثيلين ٦٠٠٠ ، سليلوز المثيل وكربوكسى مثيل سيليلوز و الصمغ العربى) والسكريات الكحولية (مثل السوربيتول والمانيتول ) وقد استخدمت هذه المواد بتركيزات ١ ، ٢ ، ٥ فى المائه بالوزن بالنسبة للعقار . بالاضافة قد استخدم عقار ايزونيازيد بنسبة ١ : ٢ للعقار . وأظهرت النتائج أن اضافة عقار الايزونيازيد أظهر أعلى زيادة فى معدل زياده الذوبان بهذه الطريقة يليه المواد ذات النشاط السطحى . وتتناسب هذه الزيادة طرديا مع تركيز المواد المستخدمه وتدل النتائج على أهمية استخدام هذه الطريقة لزيادة معدل ذوبان الثياسيتازون .