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INTERACTION OF 1,4-BENZODIAZEPINES WITH HYDROPHILIC MACROMOLECULES: V-WETTABILITY OF MODIFIED TEMAZEPAM CRYSTALS

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ABSTRACT

Wettability of temazepam crystals, crystallized from different concentrations of polysorbate 80 and cetomacrogol 1000 was evaluated quantitatively by measuring the contact angles on compressed discs of the crystallized drug. Increasing the concentration of the surfactant from which the drug was crystallized leads to increase in wettability. A direct correlation was found between the wettability of the drug and its dissolution.

An agreement was observed between the values of the contact angles measured using the adopted and the photographic methods.

The effect of time on the contact angle values was also investigated.

INTRODUCTION

The wettability of pharmaceutical powders is an important property; as wetting is often the first step of dispersion or dissolution both in vitro and in vivo. Quick and homogeneous dispersion of a solid in a liquid, can only occur when sufficient wetting is achieved[1].

A good correlation was found between the dissolution rate of many hydrophobic and water-insoluble drugs and wettability, e.g.,salicylic acid[2], acetohexamide, phenylbutazone, indomethacin and sulphathiazole[3], amobarbital and paracetamol[4], phenobarbitone[5] and aspirin[6]. In general, the higher the wettability the higher the dissolution rate.

Improvement of wetting of hydrophobic drugs may have consequence in vivo. This is based on the deduction of Solvang et al[7], who stated that gastric juice exhibits considerable surface activity.

Temazepam, the 1,4-benzodiazepine derivative, used in practice as a rapidly acting hypnotic[8], was chosen as a model drug in the present work. The drug is marketed now as soft gelatin capsules containing solution of the drug in polythylene glycol From the technological point of view, the manufacture of such a dosage form is comparatively difficult. Additionally, there is the problem of leakage of soft gelatin capsule contents present in the market[9]. In a recent report based upon comparing the various formulations in the market, a fundamental difference in the drug was stated[10]. Moreover, Divoll et al[11] have reported that when temazepam is given in a solid dosage form containing dry powder the dissolution of the drug is slow and the drug is therefore poorly available to the gut mucosa for absorption. Thus, it is clear that the main problem encountered in the manufacture of temazepam in a solid oral dosage form, other than the soft gelatin capsule, is the slow rate of dissolution of this drug. These problems have pushed us to apply certain techniques for improving temazepam dissolution rate. These techniques are: coprecipitation of temazepam with some hydrophilic polymers[12], incorporation of surfactants in the dissolution media[13] and crystallization of the drug from solutions containing surfactants or hydrophilic polymers[14].

Interaction of 1,4-Benzodiazepines with Hydrophilic Macromolecules: V-Wettability of Modidied Temazepam Crystals.

An enhancement in the dissolution rate of temazepam was achieved by crystallizing the drug from solution containing cetomacrogol 1000 and polysorbate 80. The produced crystals were subjected to further investigations including solubility, computerized thermal analysis studies, electron scanning microscopic examinations and dissolution rate determinations. These investigations could declare some mechanisms which may be responsible for the enhancement of the dissolution rate of the drug using various techniques[14]. However, the possible role of the wettability cannot be ignored.

The main purpose of this research article is to clarify, in a quantitative manner, the role of the wettability as one of the major factors participated in the dissolution rate of temazepam modified crystals prepared and characterized in a previous article[14].

The following works describe techniques which permit a quantitative determination of the contact angle and thus an accurate measurment of wettability : (a) the direct method based on measuring the contact angle by observing the shape of a liquid drop deposited on the surface of a solid plane surface[15] and (b) the indirect method in which the contact angle was calculated indirectly by determining the liquid penetration rate into a powder after experimental determination of some parameters such as the drop height, bed porosity, liquid density and liquid surface tension. The accuracy of this method could be poor[16].

EXPERIMENTAL

Materials :

Temazepam (Fabrica Italiana Sintetica, Laboratori Controllo Alte Montecchio; Vicenzo, Italy).

Polyoxyethylene (20-24) monohexadecyl ether (cetomacrogol 1000), (Atlas chemical industries Ltd., England).

Polyoxyethylene (20) sorbitan monooleate (polysorbate 80), (Sigma chemical company, USA).

Apparatus :

Controlled Environment Chamber for Sessile Drop Measurment:

— The main parts of the apparatus used are shown in Fig. 1. It is mainly composed of a prespex box rested on three levelling screws. Standing in the cubic box was a pedestal on which the disc of the sample could be placed. Two heating elements, an adjustable thermostatic switch and a small fan rotating in front of a petri dish filled with water were fixed inside the cubic box in order to control the temperature and the humidity inside it to the recommended levels. A flat ended needle of a jacketed syringe is admitted in a vertical level prependicular to the surface of the compressed drug disc.

— A very strong projector lamp is aligned with the sample disc and a convex lens is placed from the other side so that the image of the drop from the syringe could be projected on a fixed white paper. A motorized camera is placed in between the lens and the screen to ensure photography of the drop image from the screen.

- CE 292 UV-spectrophotometer (instrum-NTS, Cambridge, England).
- Multipen-recorder (Rikadenki Mitsni Electronics Ltd., England).
- Dissolution apparatus (Erweka-Apparatebau, GmbH., West Germany).

Interaction of 1,4-Benzodiazepines with Hydrophilic Macromolecules: V-Wettability of Modified Temazepam Crystals.

Procedure:

a - Preparation of the modified temazepam crystals :

Temazepam was crystallized from ethyl alcohol alone or from alcoholic solutions of either polysorbate 80 or cetomacrogol 1000 (1,2.5 and 5% W/V) using the following procedure: temazepam powder (1 gm) was dissolved in a minimum volume of ethanol alone (20 ml) or ethanol containing the previously mentioned concentrations of the investigated surfactants at 50 C. The systems were allowed to cool slowly overnight at room temperature. The produced crystals were separated by filtration, thoroughly washed with fresh ethanol and dried in a vacuum desiccator over shavings of hard paraffin. The crystals were screened to a particle size of 45-200 μ and used for further investigations.

b - Preparation of temazepam compressed discs :

Seived tamazepam crystals (200 mg) as received or crystallized from ethanol containing polysorbate 80 or ethanol containing cetomacrogol were compressed at a force of 70.3 Kg cm^{-2} using stainless steel compression assembly[13].

c - Measurment of the contact angle :

The mould of the compression assembly (base plate) housing the compressed disc was horizontally positioned (using spirit level) on the pedestal inside the chamber which was kept at 37 C and 100% relative humidity so as to retard the evaporation of the drop. The system was allowed to be equilibrated for 30 minutes.

A drop (15 μl) of saturated solution of temazepam in deionized double distilled water at 37 C, was dropped on the compressed disc surface, although it was found that increasing or decreasing the drop volume did not affect the results. Saturated solution of the drug was used in order to minimize the possibility of dissolution. The contact angles (θ) of the drop on the comp-

ressed disc were measured directly from the projected images at least 5 times on a new surface each time in each case.

d - Measurment of the contact angle by photographic method :

The same steps mentioned above were adopted but the projected image was photographed with a motorized camera at zero, 25 and 50 seconds after dropping. This method was applied to one sample only (temazepam recrystallized from ethanolic solution containing 2.5% W/V polysorbate 80). The experiment was done twice and the average reading was considered.

e - Determination of the dissolution of temazepam modified crystals :

Dispersed particulate method for studying the dissolution of temazepam crystals, using deionized double distilled water as a dissolution medium, was performed as mentioned in detail in a previous article[13]. This test was applied for studying the dissolution of untreated temazepam powder, temazepam crystallized from ethanol and temazepam crystallized from ethanol containing the different investigated concentrations of polysorbate 80 and cetomacrogol 1000.

In order to check the reproducibility of the test, the dissolution of each sample was performed seven times.

RESULTS AND DISCUSSION

When a drop of a liquid is placed on a plane solid surface it assumes certain shape which corresponds to a minimum free energy of the system. The condition for free energy at equilibrium is given by Young's equation[17]:

$$\gamma_{S/A} = \gamma_{S/L} + \gamma_{L/A} \cos. \theta \qquad (1)$$

Where γS/A, γS/L and γL/A are the surface or interfacial tension at the solid/air, solid/liquid/air interfaces respectively. The angle θ is termed the contact angle wich is the angle measured between the plane solid surface and a tangent to the liquid drop surface where it touches the plane solid surface at the point of contact. When θ=0, the liquid spreads over the solid surface. As it increases, the tendency for a liquid to spread decreases. Therefore, the contact angle θ is a useful inverse measure and cos. θ is a direct inverse measure of wettability.

Upon crystallization of temazepam from the surfactant solutions investigated, an increase in its wettability was observed (Table 1 and Fig. 2). The wettability increases as the concentration of the investigated surfactant increases from 1 to 5% W/V.

Surfactants have high affinities to be adsorbed at interfaces with a resultant decrease in interfacial tension. The observed reduction in the contact angle (increase in wettability of temazepam treated crystals) was attributed to the adsorption of some surfactant molecules onto crystal surface. Equation (1) implies that the adsorbed surfactant molecules lead to change in one or more of the three interfacial tensions involved in the equation. This might indicate, that during the crystallization of temazepam from surfactant solutions, some surfactant molecules are adsorbed onto the surface of the crystals, in spite of the washing of the modified crystals with fresh ethanol after separation[14].

Increasing the wettability of temazepam crystals upon increasing the investigated surfactant concentrations would indicate that the amount of the surfactant adsorbed on the crystal surface is proportional to its concentration in the crystallization medium.

Dissolution studies (T50% values) and contact angle measurments for untreated temazepam powder and temazepam crystallized from ethanol alone revealed that ethanol has negligible effect on the drug wettability, since it has no surface activity.

The correlation between wettability of temazepam modified crystals and its dissolution rate as a function of the investigated surfactant concentration is shown in Fig. 2. The higher the concentration of either cetomacrogol or polysorbate 80 in the crystallization medium, the higher the number of the surfactant molecules adsorbed, the easier the crystals wetting and the higher their respective dissolution rate (decrease in T50% values, Table 1)

This correlation reveals that the surfactant molecules are adsorbed by their hydrophobic tails toward the hydrophobic temazepam crystals, while their hydrophilic heads projected toward the aqueous medium during dissolution, thereby increasing the hydrophilicity and dissolution of the crystals, rendering them more wettable upon exposure to the aqueous medium[1].

The photographic method was applied to follow the contact angle values as a function of time. It could be observed that a decrease in the contact angle from 56 to 50 degrees took place after 50 seconds. Thus it seems very important to measure the contact angle at zero time from dropping[16,18].

Finally, it could be concluded that a direct correlation is obtained between the wettability of temazepam modified crystals and its dissolution rate. Thus, the technique applied in the present work involving the crystallization of hydrophobic and water-insoluble drug, and finding out a quantitative relation between wettability and dissolution could be applied for similar drugs for enhancing their dissolution rate.

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The bioavailability of formulations containing the modified temazepam crystals will be subjected to further investigations recently.

Table 1. Wettability and Dissolution Rates of Temazepam Modified Crystals.

Sample	Measured values* of the contact angle (θ) Mean	Standared Error	Wettability (cos.θ)	T50%** (minutes)
Untreated temazepam powder	67.1	1.14	0.389	15.6
Temazepam crystallized from ethanol containing:				
Ethanol alone	65.1	1.12	0.421	15.2
1% W/V cetomacrogol 1000	59.4	1.19	0.509	6.0
2.5% W/V cetomacrogol 1000	55.0	1.73	0.574	5.7
5% W/V cetomacrogol 1000	20.4	1.14	0.937	4.5
1% W/V polysorbate 80	60.0	1.41	0.500	11.2
2.5% W/V polysorbate 80	56.3	0.97	0.555	6.7
5% W/V polysorbate 80	25.3	0.58	0.904	5.0

* Mean of 5 determinations.

** T 50 equals time required for 50% of the drug to go to solution.

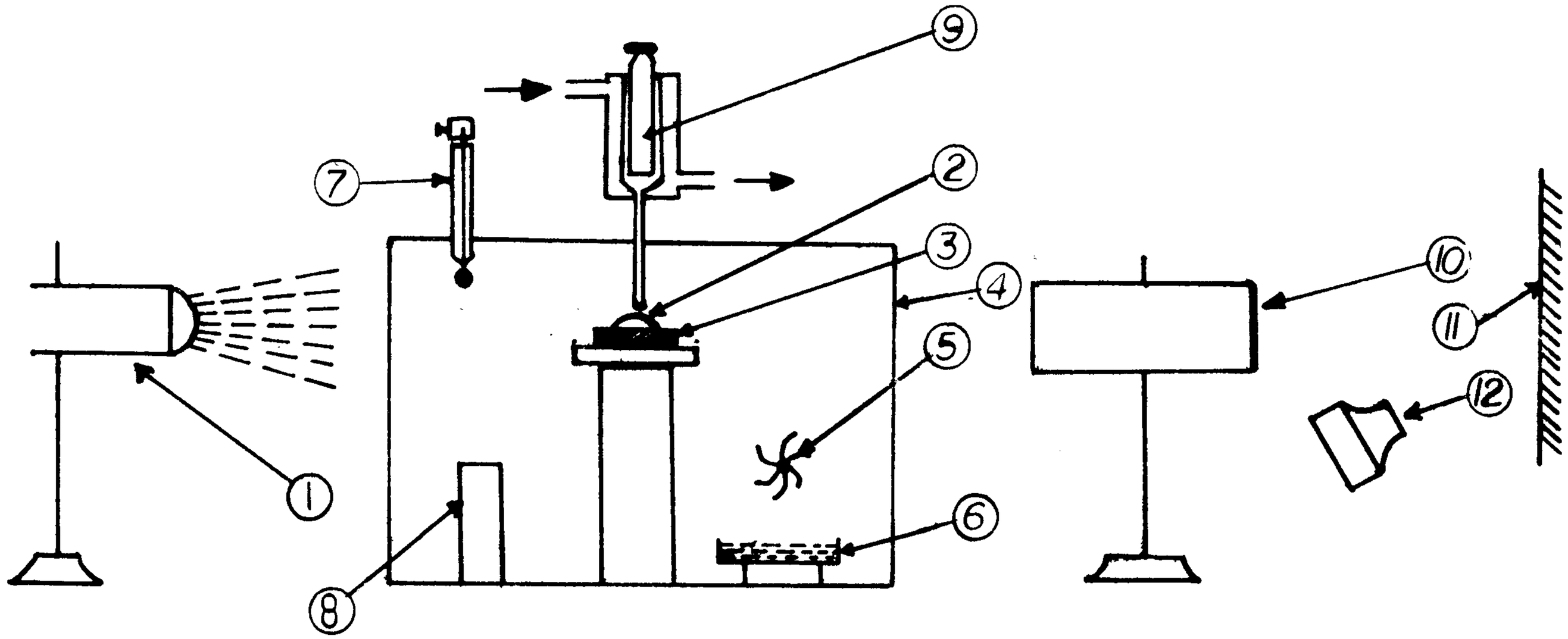
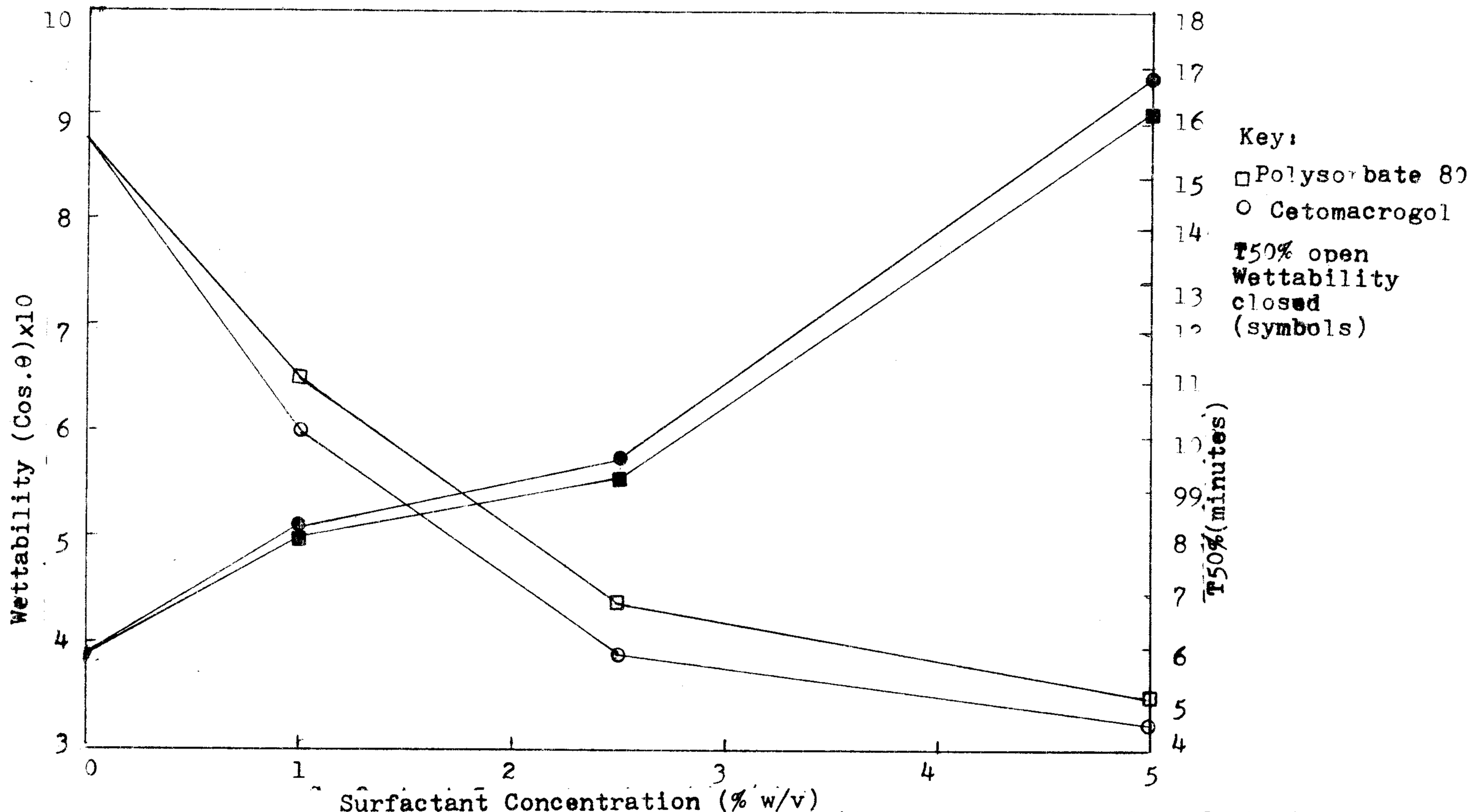


Fig 1. Schematic Diagram for the Controlled Environment Chamber for Sessile Drop Measurment Apparatus.

Key: 1- Projecter lamp, 2-One drop of temazepam saturated solution in distilled water, 3- Compressed disc of the drug treated crystals, 4- prespex box. 5- fan. 5- petri dish filled with water, 7- thermometer and thermostate. 8- heating element. 9- jacketed glass syring, 10- convex lens. 11- screen. 12- motorized camera. 13- pedestal.



Fig(2): Correlation of Temazepam release rate with wettability as a function of surfactant concentration from which the drug was crystallized.(Computer drawn)

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تفـــاعلات مجموعة ار٤ ـ بنزوديازيبينات مع جزيئات كبيرة محبة للماء

٥ ـ دراسة تأثير منشطات سطحية غير متأينة معينة على تبلل بلورات التيمازيبام

براين آرثر مللى ـ احمد السيد ابو طالب ـ على عبد الظاهر عبد الرحمن ـ سيد محمد احمد

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كلية الصيدلة ـ جامعة براد فورد ـ بانجلترا

قيمت درجة تبلل بلورات التيمازيبام المتبلرة من محاليل ستيوماجروكول ١٠٠٠ ، عديد السوربات ٨٠ بطريقة كمية وذلك بقياس زاوية التماس على اقراص مكبوسة من بلورات العقار ولقد وجد ان زيادة تركيز المنشطات السطحية غير المتأينة المذكورة آنفا فى وسط التبلر تقلل من قيمة زاوية التماس ويزيد من قيمة تبلل بلورات الدواء ويعكس ذلك ادمصاص جزئيات من المنشطات السطحية غير المتأينة على سطح البلورات .

ولقد وجد ان هناك علاقة بين اتاحة العقار ودرجة تبلله فكلما زاد تركيز المنشطات السطحية غير المتأينة كلما كان من السهل تبلل مسحوق الدواء وكلما زاد معدل الاتاحة ولقد وجد ان هناك اتفاق بين قيمة زاوية التماس المقاسة بواسطة الطريقة المتبعة وطريقة التصوير وجد انه بمرور الزمن فان زاوية التماس تقل بطريقة ملحوظة خلال ثوان قليلة .

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