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DISSOLUTION BEHAVIOUR OF PROPYLTHIOURACIL-POLYVINYLPYRROLIDONE SOLID DISPERSIONS

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ABSTRACT

The objective of the present study was to investigate the influence of variation of the molecular weight and the proportion of polyvinylpyrrolidones (PVPs) on the dissolution of propylthiouracil (Pt) as a model of sparingly soluble drugs dispersed in highly soluble polymers. Solid dispersions of Pt-PVP were prepared by the solvent method. The dissolution behaviour was determined as a function of the molecular weight of PVP and the drug-to-carrier ratio. Three PVP molecular weight fractions were used, namely, PVP 10,000, PVP 40,000 and PVP 360,000. The drug-PVP percentages used were 10, 20, 40, 60 and 90% w/w. Enhancement of dissolution rate was observed for all solid dispersion systems compared to the drug alone or the physical mixtures. The dissolution rate was increased with increasing the proportion of PVP to the drug. Generally, the enhancement of the dissolution rate was decreased in the order: PVP 10,000 > PVP 40,000> PVP360,000. Differential scanning calorimetry (DSC) reveals a decrease in the melting point of Pt due to retardation of drug nucleation in the PVP matrix. X-ray diffractometry of the highest dissolution rate solid dispersion indicates the presence of Pt in an amorphous state in the carrier.

INTRODUCTION

In the last two decades, the dispersion of poorly soluble drugs in highly soluble carriers in order to improve their dissolution rates has received a considerable attention. Many workers have used PVPs to increase the dissolution of various

drugs, e.g., sulfathiazole[1], chlorpropamide[2], indomethacin[3], prednisolone[4], ibuprofen[5], nifedipine[6], and benzodiazepines[7]. The enhancement of dissolution has oftenly been attributed to the presence of the drug in a finely subdivided form or in an amorphous state in the PVP matrix. Some authors have also proposed complex formation between the drug and the carrier[4,5].

In the present work the dissolution behaviour of Pt from its solid dispersions in PVPs was investigated. Although this drug is the mediçament of choice in treatment of hyperthyrodism because of its relatively rapid absorption and excretion in comparison with other antithyroids, patients need long time to achieve a steady metabolic state[8]. Therefore, it was also the aim of this study to improve the dissolution rate of this sparingly soluble drug by dispersing it in PVPs which may lead to enhancement of its bioavailability.

EXPERIMENTAL

Materials :

- Propylthiouracil (Sigma Chemical Company, St. Louis, MO, USA).
- Polyvinylpyrrolidones of molecular weights 10,000,40,000 and 360,000 referred hereafter as PVP 10, PVP 40 and PVP 360, respectively (General Aniline and Film Corporation, Charlotte, NC, USA).
- Ethanol was analytical grade.

Methods :

Known weights of both Pt and each of PVPs were dissolved in a minimum volume of ethanol in a round-bottomed flask to prepare 10,20,40,60 and 90% Pt-PVP solid dispersions. The flask was fitted to a rotary vacuum evaporator with its bottom immersed in a water bath at 45°C. After evaporation of the solvent, the resulting residue was forced through No.50 sieve and the fraction retained on No. 60 sieve (particle size range

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250-297 um) was dried in a desiccator over phosphorous pentoxide. Complete dryness was ensured by weighing the residue at different time intervals until a constant weight was obtained.

The dissolution rate studies of Pt alone, in physical mixtures or solid dispersions in PVPs were carried out in a standard U.S.P. XXI paddle dissolution apparatus. The dissolution medium consisted of 500 ml degassed double distilled water to which 0.5 ml of 5% Tween 80 aqueous solution was added to ensure similar wettability of the powders throughout the dissolution study. The dissolution apparatus was run at 37°C and 40 R.P.M. An equivalent of 25 mg Pt was sprinkled on the surface of the dissolution medium and 1 ml samples were withdrawn with a syringe fitted with a filter tip at suitable time intervals. One-half ml was diluted ten fold and the Pt content was assayed spectrophotometrically at 272 nm using the appropriate blank. The presence of PVPs in the dilution range employed did not interfer with the assay of Pt. The dissolution experiments were performed in triplicates and the mean was taken as the dissolution value. The results were reproducible for all experiments.

DSC investigations were carried out using a Perkin-Elmer differential scanning calorimeter Model DSC-IB.Samples (Fig. 5) of about three mg were examined using aluminium pans and covers at a heating rate of 10°C per min. in an atmosphere of static air. Tin was used as a standard to calibrate the differential temperature.

The equilibrium solubility of Pt was determined in water and 0.05-4 M aqueous PVP solutions using a rotating wheel assembly (rotation at 10 R.P.M.) immersed in a water bath at 37 ± 0.5°C. Excess amounts of solute were suspended in 20 ml of solvent in screw-capped tubes which were rotated for 36 hrs. to attain equilibrium. Samples were withdrawn, filtered through No.3 sintered glass funnels and assayed spectrophotometrically at 272 nm after suitable dilution and using the appropriate blank.

The X-ray diffractogramms were obtained on Philips diffractometer, Holland, with Cu-Kα radiation. Samples of the pure drug, 1:9 Pt-PVP 10 solid dispersion and PVP 10 were investigated.

RESULTS AND DISCUSSION

The dissolution profiles of Pt-PVP solid dispersions, physical mixtures and Pt alone are shown in (Figs 1-3). The time required for 50% Pt to be dissolved for different systems is also shown in (Table 1). The dissolution of Pt from the solid dispsrsions was enhanced in comparison with the drug alone or the physical mixtures. The enhancement the the dissolution rate of drugs dispersed in water soluble polymers is often attributed to the formation of a multi-layer system of swollen or gel like layers of increasing solvent uptake located between the solid polymer and the diffusion layer. The dissolution kinetics of glassy state polymers (the polymers which give glassy appearance and are amorphous after evaporating the solvent in which they are dissolved, e,g, PVPs) has been extensively reviewed by Ueberreiter[9] and Merkle[10]. The enhancement of dissolution rate has also been attributed to complex formation between the drug and PVP[3,5], as well as the presence of the drug in a very finely subdivided form or in an amorphous state in the polymer matrix[11].

Increasing the drug percentage in the solid dispersion from 10 to 90% w/w decreased the dissolution rate as shown in (Figs 1-3). This appears to be due to the establishment of a solid hydrophobic drug layer at the dissolution boundary which minimizes the solvent penetration and results in high supersaturation levels in the surface layer as the preparation was exposed to the dissolution medium. This may lead to retardation of the solvent uptake by the polymer and subsequently

the dissolution of both the polymer and the drug is expected to decrease as the drug proportion in the solid dispersion is increased.

The results indicate that an increase in the mean molecular weight of the PVP lead to decreased dissolution rate of Pt from the solid dispersion as shown by comparing the dissolution profiles of Pt in (Figs. 1-3) and the time required for 50% drug to be dissolved (T 50), Table 1. Assuming that the dissolution of Pt is a diffusion controlled process and the dissolution rate is inversely proportional to the viscosity of the diffusion layer, it would be expected that the difference in the viscosity of the diffusion layer of the different polymers would lead to differences in the dissolution rates of the drug from the solid dispersions. The intrinsic viscosity of PVP 10, PVP 40 and PVP 360 at 25°C is 7.3, 22.5 and 160 $cm^3\ g^{-1}$, respectively[12]. Accordingly, lower dissolution rates of the drug might be expected on increasing the molecular weight of PVP in the solid dispersion system. The differences in T 50 between PVP 40 and PVP 360 systems are greater than the differences between the former and PVP 10 systems. This may be due to the relatively large difference in viscosity between either PVP 10 or PVP 40 and PVP 360. The previous results may also be supported by the fact that the hydrophilicity of the PVP is increased as the molecular weight is decreased[13].

The solubility curves of Pt in PVPs (fig. 4) reveal that the solubilizing effect of the polymers is in the order : PVP 360 > PVP 40 > PVP 10 on molar basis. Considering the slopes of these curves as a measure of the solubilizing effects, the solubility of Pt will be 3.31, 2.01 and 0.125 gM^{-1}

of PVP 360, PVP 40 PVP 10, respectively. Despite more work is required to investigate the binding affinities of PVPs toward Pt, these results are not unexpected since the higher molecular weight polymer has more binding sites for drug moleculues[12]. Apparantly, strong binding between drug and polymer is unfavourable to high drug release rates because of its negative effect on the polymer dissolution[10]. This may also interpret the dissolution results in the previous section. Increasing the PVP molecular weight has also been reported to decrease the dissolution rates of drugs like indomethacin[3] and ibuprofen[5].

DSC studies were performed on Pt,PVP and Pt-PVP solid dispersions. The results obtained are shown in (Fig. 5). The Pt thermogram shows one endothermic peak at 224°C which corresponds to the melting point of Pt as confirmed by hot stage microscopy. No peaks due to PVP either alone (not shown in the figure) or in the solid dispersions were obser ved. The endothermic peak appears in 90% drug-PVP at 220°C for all three systems. A shallow broad endothermic peak at about 216°C appears in the 60% Pt-PVP 40 system. The decrease in the melting point of Pt in presence of PVP may be attributed to the retardation of the drug nucleation caused by the polymer matrix. The disappearance of the endothermic peaks at lower drug percentages may be attributed to the presence of the drug in an amorphous form or in solid solution in the PVP which prevents the drug nucleation.

A study of the relationship between the degree of crystallinity and dissolution rates of drugs in solid dispersions using X-ray diffraction has been reported[14]. Solid dispersion of Pt-PVP 10 (1:9) was investigated because it gives the highest dissolution rate in comparison with other preparations, Table 1 and Figures 1-3. The X-ray spectrum of the aforementioned solid dispersion lacks the characteristic diffraction peaks of Pt which confirms the amorphous state of the drug in the polymer matrix(Figure 6

& Table 2). This explains the enhancement of the drug dissolution rate from its dispersion in PVP.

In conclusion, the dissolution of Pt was enhanced by dispersing it in PVPs. This enhancement was more pronounced for the lowest molecular weight PVP and the lcwest drug percentage in the range 10-90% Pt in PVP. From DSC and X-ray diffraction it was found that Pt was distributed in an amorphous form in PVP matrix. Taking in account the formulation factors, percentages of drug lower than 10 % were not investigated because of the relatively large dose of Pt. Further in vivo studies will be useful to elucidate the corresponding changes on Pt bioavailability.

Table 1: Time Required for 50% Propylthiouracil to be Dissolved (T 50) from its Solid Dispersions and Physical Mixtures in PVPs.

Pt (%w/w) in the Solid Dispersions	T 50 (Minutes)		
	PVP 10	PVP 40	PVP 360
10	1.5	2.0	5.5
20	2.5	3.0	9.0
40	5.5	5.0	10.0
60	7.0	7.0	12.0
90	9.0	8.5	14.0
10% physical mixture	20.0	26.0	22.0
40% physical mixture	21.0	25.0	22.5

T 50 of Pt alone was 33 minutes

Table 2: X-ray Diffraction Data of Propylthiouracil

2θ	d (A°)	I	2θ	d (A°)	I
10.344	8.5516	2724	24.482	3.6359	396
12.324	7.1819	332	24.756	3.5963	442
16.148	5.4887	162	25.825	3.4498	4050
16.667	5.3190	150	29.313	3.0467	228
17.049	5.2005	112	29.426	3.0353	226
18.729	4.7377	214	29.747	3.0033	232
19.421	4.5704	356	31.325	2.8555	170
20.720	4.2869	704	32,074	2.7905	182
21.701	4.0952	368	33.631	2.6648	428
21.830	4.0713	674	37.338	2.4083	108
22.505	3.9506	58	37.486	2.3991	158
23.902	3.7227	452			

2θ:Scanning Angle, d(A°)Interplanar Distance, I:Intensity

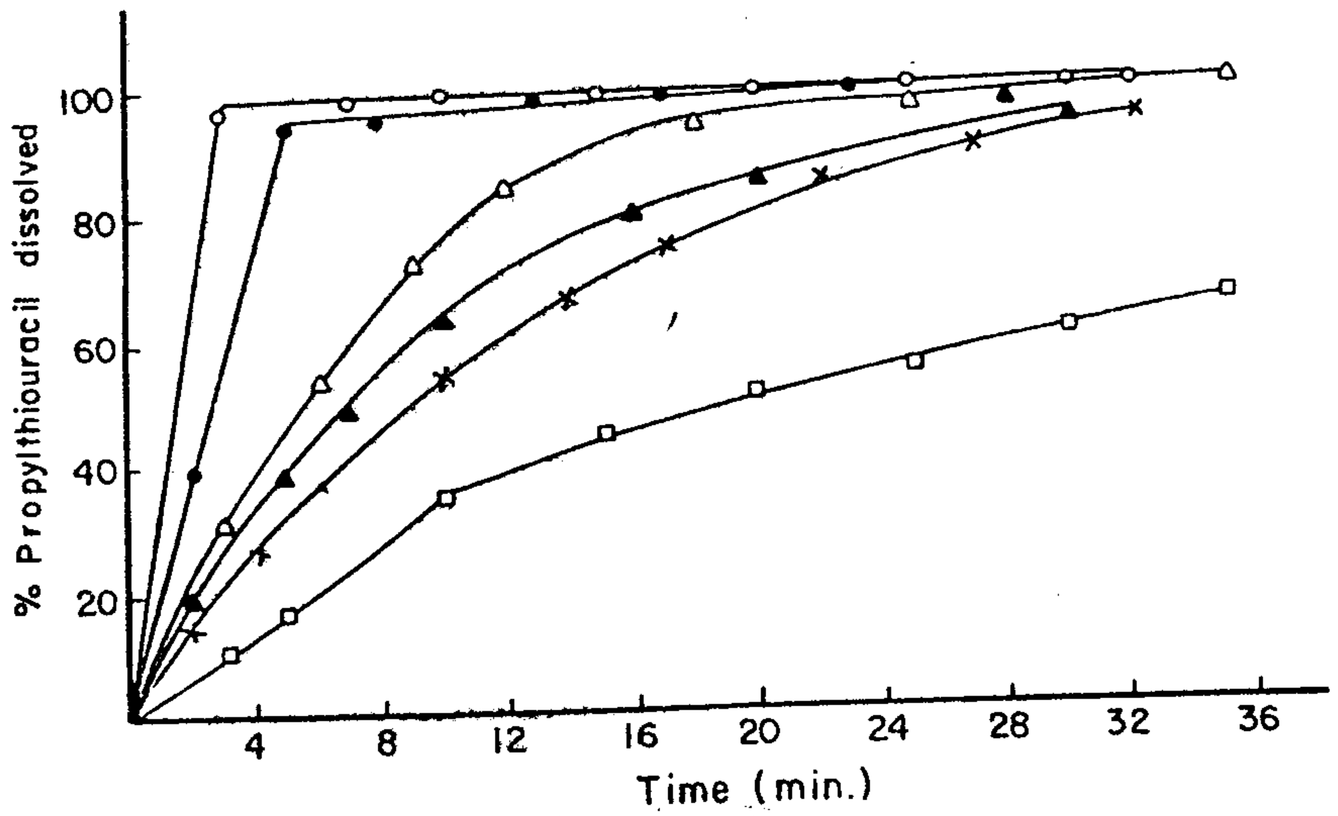


Fig. 1: Dissolution Profiles of Solid Dispersions of Propylthiouracil in PVP 10.

○ 10%, ● 20%, △ 40%, ▲ 60%, and X 90% Pt in PVP 10, □ 10% Physical Mixture.

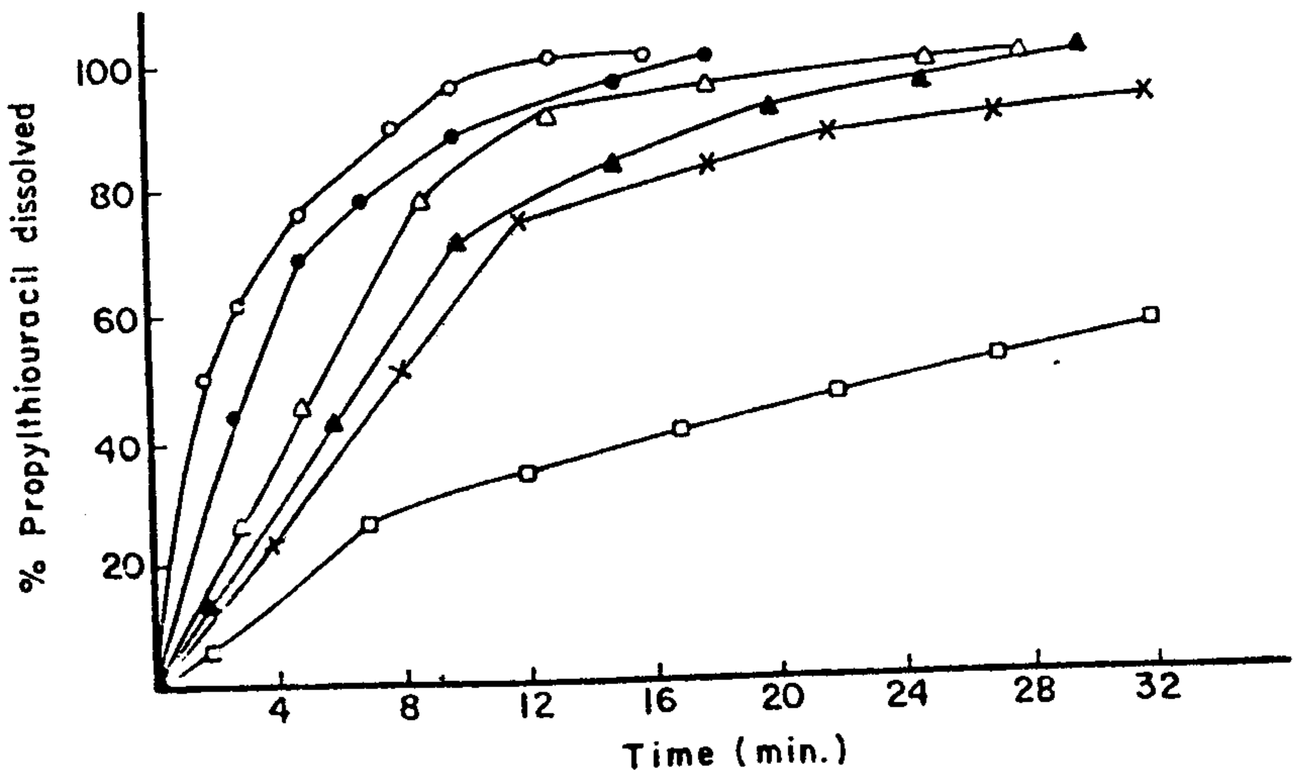


Fig. 2: Dissolution Profiles of Solid Dispersions of Propylthiouracil in PVP 40 . ○ 10%, ● 20%, △ 40%, ▲ 60% and * 90% Pt in PVP 40 □ 10% Physical Mixture

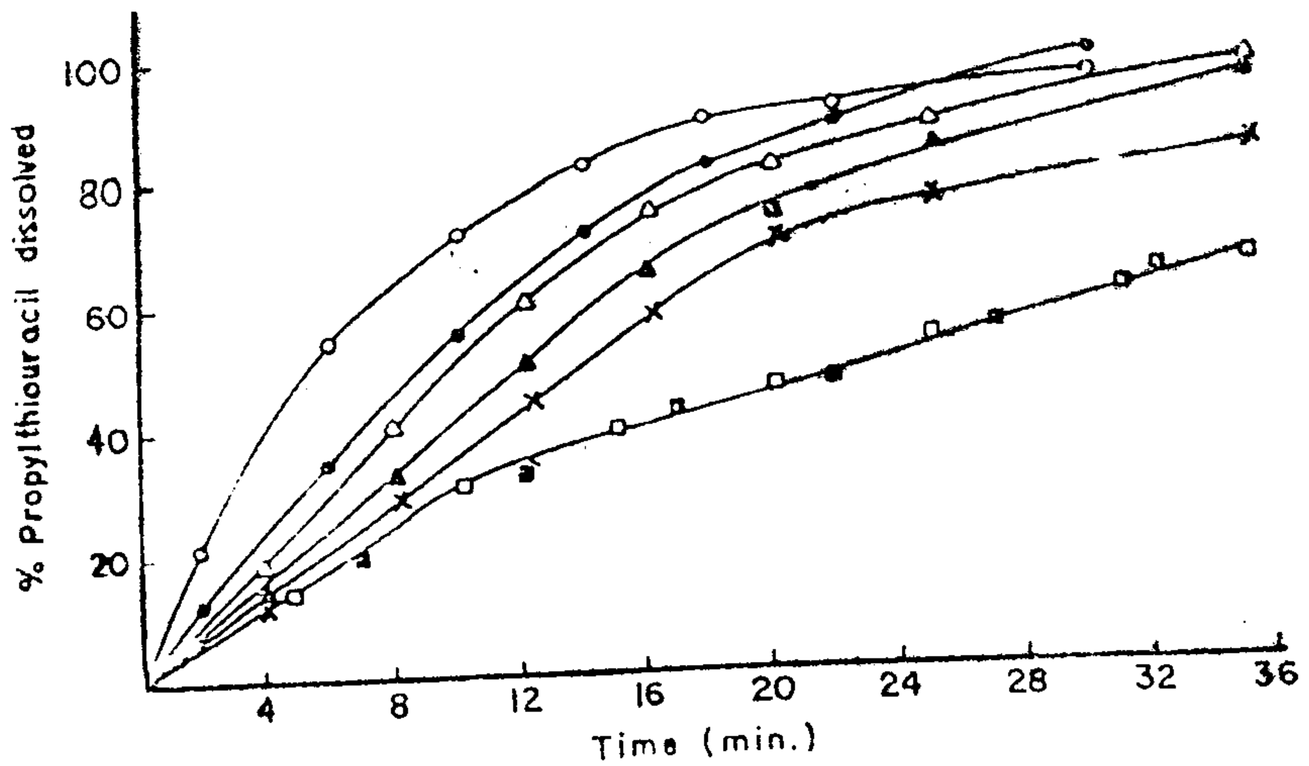
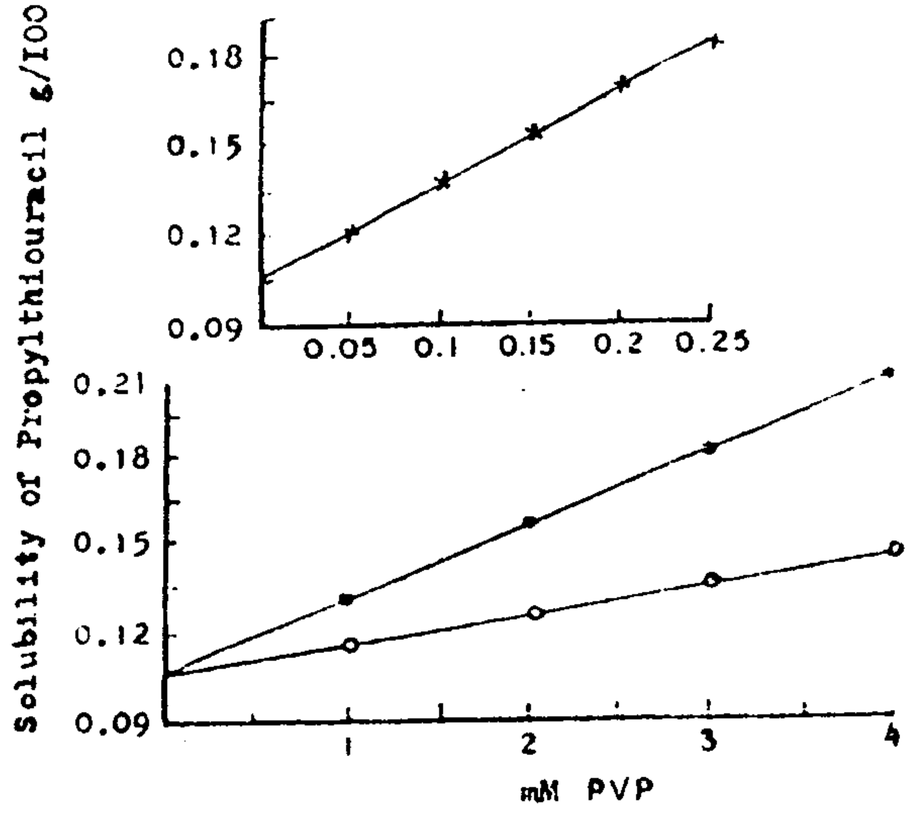


Fig. 3: Dissolution Profiles of Solid Dispersions of propylthiouracil in PVP 360. ○ 10%, ● 20%, △ 40%, ▲ 60% and X 90% Pt in PVP 360□ 10% Physical Mixture and ■ 40% Physical Mixture.



.4: Solubility of Propylthiouracil in Different Concentrations of Aqueous PVP Solutions at 37 °C:

X: PVP 360, ●: PVP 40, ○: PVP 10.

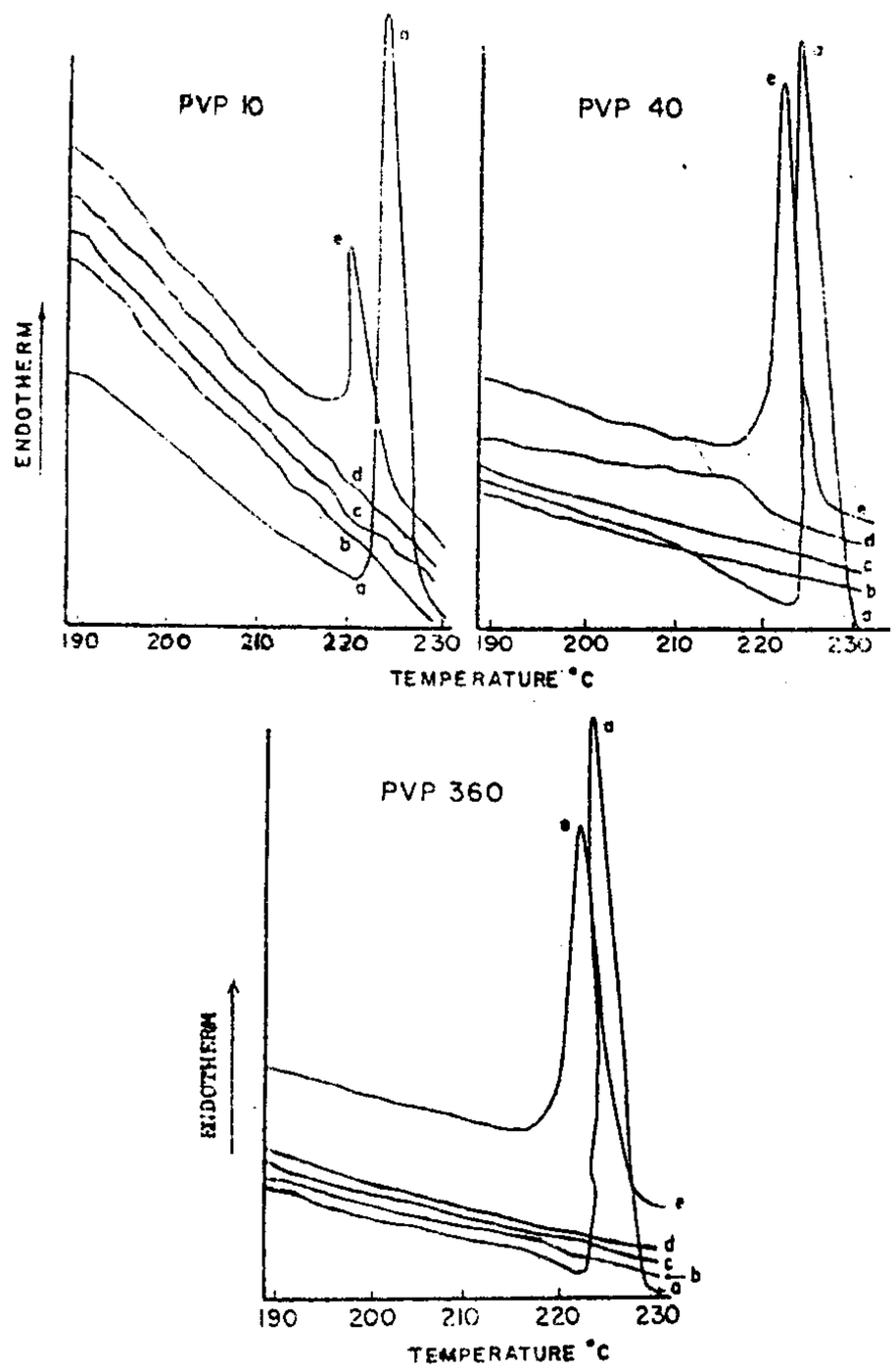


Fig. 5: DSC Thermograms of Pt and Pt/PVP Solid Dispersions. a: Pt, b: 10%, c: 20%, d: 60% and e: 90% Pt/PVP Solid Dispersions.

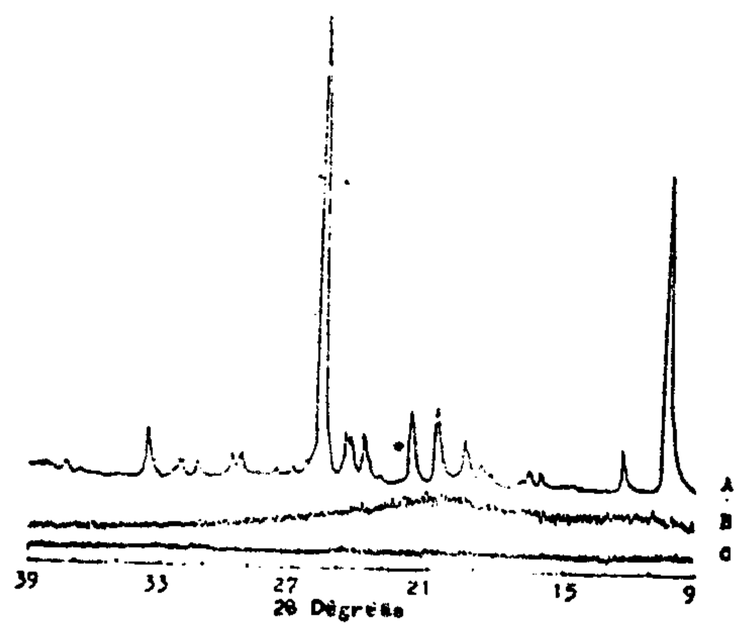


Fig. 6: X-ray Spectra of A: Pt, B: 10% Pt in PVP 10 Solid Dispersion and C: PVP 10.

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اتاحة البروبايل ثيوراسيل من مشتقاته الصلبة في متعددى فنيل البيروليـــــدون

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هدف هذة الدراسة هو زيادة اتاحة البروبايل ثيوراسيل عن طريق وضعه فى مشتقات صلبة مع بوليمرات متعددى فينيل البيروليدون وكذلك دراسة تأثير كل من نسبة البوليمر ووزنه الجزيئى على معدل الاتاحه .

أعدت المشتقات الصلبة بطريقة الاذابة باستخدام ثلاثة بوليمرات ذات أوزان جزيئية مختلفة هى : ١٠ر٠٠٠ـ ٤٠ر٠٠٠ـ ٣٦٠ر٠٠٠ ،وكانت نسبة العقـــار الى البوليمر فى كل منها ١٠ ، ٢٠ ، ٤٠ ، ٦٠ ، ٩٠ / وزنا لوزن .

وقد لوحظ زيادة معدل اتاحة البروبايل ثيوراسيل من كل آنظمه المشتقات الصلبه بالمقارنه بمعدل اتاحته بمفرده آو من مخاليطه الطبيعية مع هـــــذه البوليمرات وفسر ذلك بوجود العقار فى صورة جزيئات دقيقه آو فى صورة غيـــر بللوريه فى مادة البوليمر استنتاجا من نتائج التحليل السعرى التفاضلى وطريقة انعكاس الاشعة السينية .

وقد وجد أن زيادة نسبة العقار الى البوليمر فى كل المشتقات الصلبه قد آدى الى الاقلال من معدل اتاحة العقار وفسر ذلك بتكون طبقة من العقار كارهه للماء على السطح الفاصل بين جزيئات المشتت الصلب ومحلول الاتاحه وتزايد هذة الطبقـــة بزيادة نسبة العقار مما قلل من قدرة البوليمر على امتصاص الماء وأدى بالتالى الى تناقص معدل اتاحة العقار .

ولوحظ أن الزيادة فى معدل الاتاحة كانت أكبر للبوليمر ذى الوزن الجزيئى الاصغر وقد عللت هذه النتائج على آساس اختلاف درجة زوبان العقار فى هـــــذه البوليمرات وكذلك اختلاف درجة لزوجتها وامتصاصها للماء تبعا لاختلاف أوزانها الجزيئية .

وباستخدام الاشعة السيينية وجد أن العقار موجود فى صورة غير بلوريـــة فى المشتت الصلب الذى يعطى أعلى اتاحة .

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