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ENHANCEMENT OF DISSOLUTION RATE OF CARBAMAZEPINE I- *IN VITRO* STUDIES

Ahmed Shaker Ali

Department of Pharmaceutics, Faculty of Pharmacy Assiut University, Assiut, Egypt

يستخدم عقار الكاربامازيبين لعلاج أنواع متعددة من التشنج وقد بينت بعض الدراسات أن معدل امتصاصه من الجهاز الهضمى متفاوته تبعا لمكونات الأقراص وذلك يعزى إلى الذوبان الشحيح للعقار. فى هذا البحث أستخدمت ثلاث إتجاهات لتحسين ذوبانه (١) الترسيب من المحلول على السلكا (٢) الطحن مع السلكا أو زلال البيض أو عديد فينيل البيروليدون (٣) أو تغيير سطح العقار ليصبح محبا للماء بواسطة المواد ذات النشاط السطحى وجليكول البروبيلين. وقد تمت دراسة خواص العقار الجزيئية فى تلك المستحضرات بإستخدام التحليل الآلى مثل تشتت الأشعة السينية والتحليل السعرى التفاضلى بالإضافة إلى قياس معدل الذوبان فى الوسط الحامضى (الأس الهيدروجينى ١,٢). وقد أثبتت التجارب تحول العقار إلى الصورة الغير بلورية فى حالة تحميله على السيلكا بواسطة المذيب أو الطحن ، وقد أدى ذلك إلى زيادة معدل الذوبان بصورة واضحة. كذلك فإن تغيير طبيعة السطح العقار أدى أيضا إلى تحسين معدل ذوبانه كما أمكن تحضير أقراص منه أعطت نتائج جديدة من حيث معدل الذوبان والمعايير المختلفة لتقييم الأقراص. وقد بينت النتائج الأولية التى أجريت على الأرانب لقياس التأثير المضاد لتشنج العقار المحسن وجود تحسن ملحوظ فى سرعة التأثير بالمقارنة مع العقار العادى.

Carbamazepine (CBZ) is an antiepileptic drug which shows variable absorption and variable bioavailability due to poor solubility. Three approaches were utilized to enhance the dissolution rate namely, solvent deposition onto porous silica, co-grinding with porous silica, egg albumin or polyvinylpyrrolidone and surface hydrophilization with non-ionic surfactant or propylene glycol. The molecular behavior of CBZ in the investigated systems were studied using X-ray diffraction analysis and differential scanning calorimetry. The dissolution rate of the drug was also investigated. The obtained results indicated that CBZ was transformed to the amorphous state in both the ground and loaded mixtures with porous silica. This transformation resulted in significant enhancement of the dissolution rates of the drug. Surface hydrophilized drug using 1% w/w polyoxyethylene sorbitan monolaurate (polysorbate 20) showed higher dissolution rate and good compliance with respect to tablet characteristics according to BP 1993 limits.

INTRODUCTION

The absorption of several poorly soluble drugs in the gastro-intestinal tract is dissolution rate limited. Several techniques have been successfully adopted to improve the dissolution rates of these drugs including solid dispersions with various carriers,[1-3] solvent deposition,[4] solid solution,[5] co-grinding with certain carriers,[6] lyophilization[7] and surface hydrophilization.[8] The use of bile salts,[9] phosphatidylcholine,[10] polyvinylpyrrolidone,[11] gelatin,[12] egg albumin,[13] cyclodextrins[14,15] and hydroxypropylmethyl-cellulose[16] has been reported to enhance the dissolution of variety of poorly soluble drugs.

Carbamazepine, (CBZ) {5 H-dibenz [b,f] azepine-5-carboxyamide} is a first line drug in the treatment of most forms of epilepsy and also the drug of choice to control trigeminal neuralgia. Furthermore, it is now frequently used in bipolar depression, excited psychosis and alcohol withdrawal syndrome.[17] The rate of absorption of the drug from gastro-intestinal tract is slow and variable and its bioavailability

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can differ markedly from different pharmaceutical formulations. The main causes appear to be related to poor solubility and poor wettability of the drug.[18] Several techniques have been made to enhance the drug dissolution rate.[19,20] The present work aimed to enhance the dissolution rate of CBZ using simple and economic techniques.

EXPERIMENTAL

Materials

Carbamazepine (CBZ), (Wako Pure Chemical Industries Ltd., Japan). Porous silica Florites (a gift from Tokuyama Soda, Co., Japan) was used after drying at 120°C for 3 hr. Polyoxyethylene sorbitan monolaurate (polysorbate 20) (Atlas Chemical Co., Wilmington, USA), egg albumin (BDH Poole, England); polyvinylpyrrolidone (PVP) average molecular weight 40000, (Janssen Chimica, Belgium). All other materials and solvents were of analytical grade.

Methods

Preparation of the physical mixtures

The physical mixtures of the drug (90-125 μm) and various investigated carriers were prepared by simple blending for 5 min., using a mortar and pestle avoiding any grinding effect.

Preparation of the ground mixtures

The ground mixtures were prepared using a vibrational mill (TI-200 Heiko Seisakusho Co., Japan). The weight of each sample was about 2 grams.

Preparation of the loaded mixtures

CBZ solutions in absolute ethanol at specified concentrations (8, 12, 16, & 20 mg/ml) were prepared. Fifty ml of the drug solution was added to specified weight of the dried florite (1.6, 1.4, 1.2 and 1.0 g) to give the desired drug / florite ratio (20,30,40 & 50% w/w CBZ) respectively. Ethanol was evaporated at 35°C using a rotary evaporator.

Differential Scanning calorimetry (DSC)

A Schimadzo DSC-50 (Japan) was used for carrying out the DSC of the investigated samples. The measurements were performed using solid sample pans at a heating rate of 10°C/min., under N_2 gas flow of 50 ml/min. The sample weight was about 5 mg.

Preparation of tablets

The tablets formulations of CBZ are listed in Table 1. All materials were passed through 125 μm sieve and retained by 90 μm sieve and mixed together for 5 min. in a high speed mixer (Erweka Terbula system S27, Germany). The tablets were prepared by direct compression using single flat-faced punch (13 mm diameter) [Erweka - AR 400 E, Germany].

Table 1: Composition of the prepared carbamazepine tablets.

Ingredients	Formula I	Formula II
Pure drug	200 mg	---
Surface hydrophilized drug*	---	202.02 mg
Talc	4 mg	4 mg
Avicel PH101	50 mg	50 mg
Emcompress	96 mg	93.98 mg

* With 1% polysorbate 20

Evaluation of the prepared tablets

- Uniformity of weight and drug content were determined according to B.P 1993 procedures.[21]
- Hardness and friability were determined using Erweka hardness tester and Erweka friabilator respectively.
- Tablet disintegration was performed at 37°C in simulated gastric fluids without enzyme, using an Erweka disintegrator [Erweka-Apparatebau, ZT4, Germany].

Dissolution studies

The dissolution rate of the drug from different mixtures or the prepared tablets were determined using Hanson dissolution test station

(Hanson Research Co. USA). The dissolution medium was 500 ml of pH 1.2 HCl solution maintained at 37°C and stirred at 100 rpm. A quantity of 100 mg of the drug or an equivalent amount of the mixture was placed on the surface of the dissolution medium. Samples of 5 ml were periodically withdrawn by a syringe fitted with membrane filter and replaced with an equal volume of the dissolution medium equilibrated at 37°C. The samples were analyzed spectrophotometrically at 284 nm (Perkin Elmer UV/ViS spectrometer, USA) and it was found that non of the additives interfered with the assay. In case of tablets the baskets were used instead of paddles and the volume of the same dissolution medium was 900 ml. The mean of three determinations was reported.

RESULTS AND DISCUSSION

Silicas are of outstanding importance as carriers in solid, semisolid and liquid dosage forms due to their excellent physicochemical properties.[22] Florite is a novel porous calcium silicate. It has extensive surface area (140 m^2/g), good flowability and excellent mouldability. Moreover it is a pure synthetic inorganic unabsorbable material so that it is considered safe for oral administration.[23] Molecular dispersions of drugs onto the extremely large surface of porous silica has been utilized for improving dissolution rates and absorption of several poorly soluble drugs.[23&24]

Fig. 1 shows the X-ray diffraction patterns of the physical and loaded mixtures of CBZ onto porous silica in various ratios. The physical mixtures demonstrate the X-ray diffraction peaks of the drug crystals (α form).[25] The loaded mixtures of 20-30% CBZ show halo patterns indicating its transformation to the amorphous state. In case of the loaded mixture of 40% CBZ the characteristic peaks of the drug of low intensities are observed indicating that complete amorphization of the drug was not achieved.

Grinding is a common process used for size reduction. Grinding of the crystalline drugs with certain carriers having extensive surface area has been utilized for reducing drug crystallinity or inducing drug transformation to the amorphous state. It has been recently reported that grinding causes change in the molecular behavior of the drug in solid state.[6,25] Fig. 2 shows the X-ray diffraction patterns of the physical and ground mixtures of CBZ and porous silica in 1: 1 ratio. The intensity of the diffraction peaks of CBZ crystals were reduced with increasing grinding time. A halo pattern was observed after grinding for 10 min. indicating complete transformation of the drug to the amorphous state.

The effect of grinding of CBZ with various carriers was investigated by using DSC. DSC studies allow characterization of the molecular state of the drug and rapid evaluation of possible drug-carrier interaction according to appearance, shift or disappearance of endothermic or exothermic peaks and/or variation of the corresponding enthalpy.[26] Figure 3 shows the DSC curves of the physical and 10 min. ground mixtures of CBZ and various carriers. The drug as well as the physical mixtures show two endothermic peaks at about 177°C & 192°C due to phase transition of ß form of CBZ to α form and melting of α form respectively.[25] The ground mixtures with porous silica show no endothermic peaks confirming complete transformation of CBZ to amorphous state. The ground mixtures with either PVP or egg albumin show broad endothermic peaks in the phase transition and melting region of the drug. However, the calculated values of enthalpy (ΔH) were less than the corresponding values in case of the physical mixtures. These results indicate that CBZ partially exists in the amorphous state in the ground mixtures with PVP or egg albumin. It is obvious that porous silica had the greatest tendency to induce transformation of the drug to the amorphous state in a relatively shorter grinding time. Nakai *et al.*[6] studied the molecular behavior of crystalline medicinals in the ground mixtures with various carriers. The phase transformation of crystalline CBZ to the amorphous state in the loaded or the ground mixtures with porous silica was explained in view of the physical adsorption phenomena associated with drug silanol interaction within the inner pores of the silica matrix. Adsorption may take place via hydrogen bonding between silanol groups and amide group of the drug in addition to van der Waal forces.

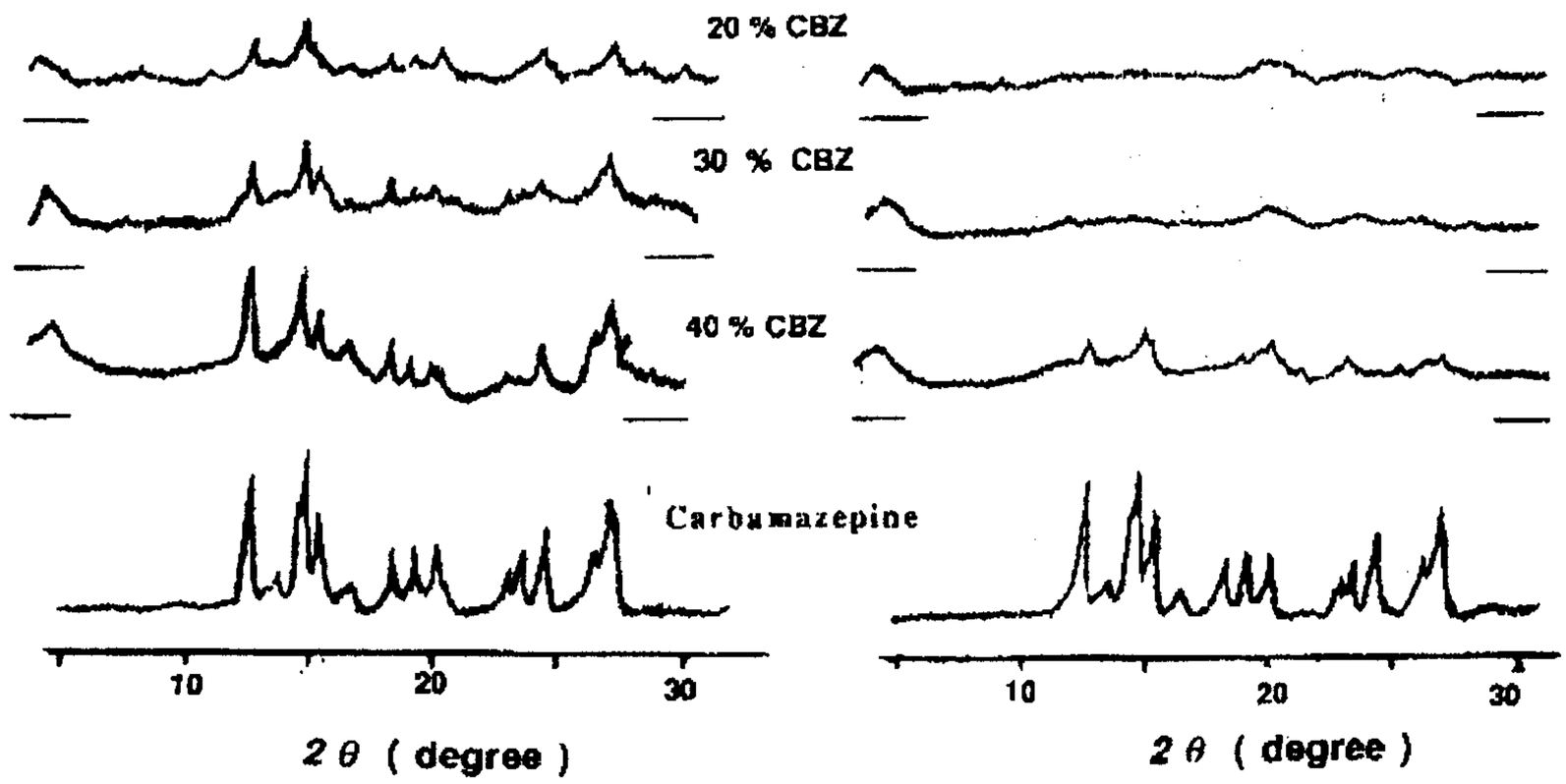

Fig. 1: Powder x-ray diffraction patterns of the physical and the loaded mixtures of CBZ onto porous silica in various ratios (% w/w CBZ).

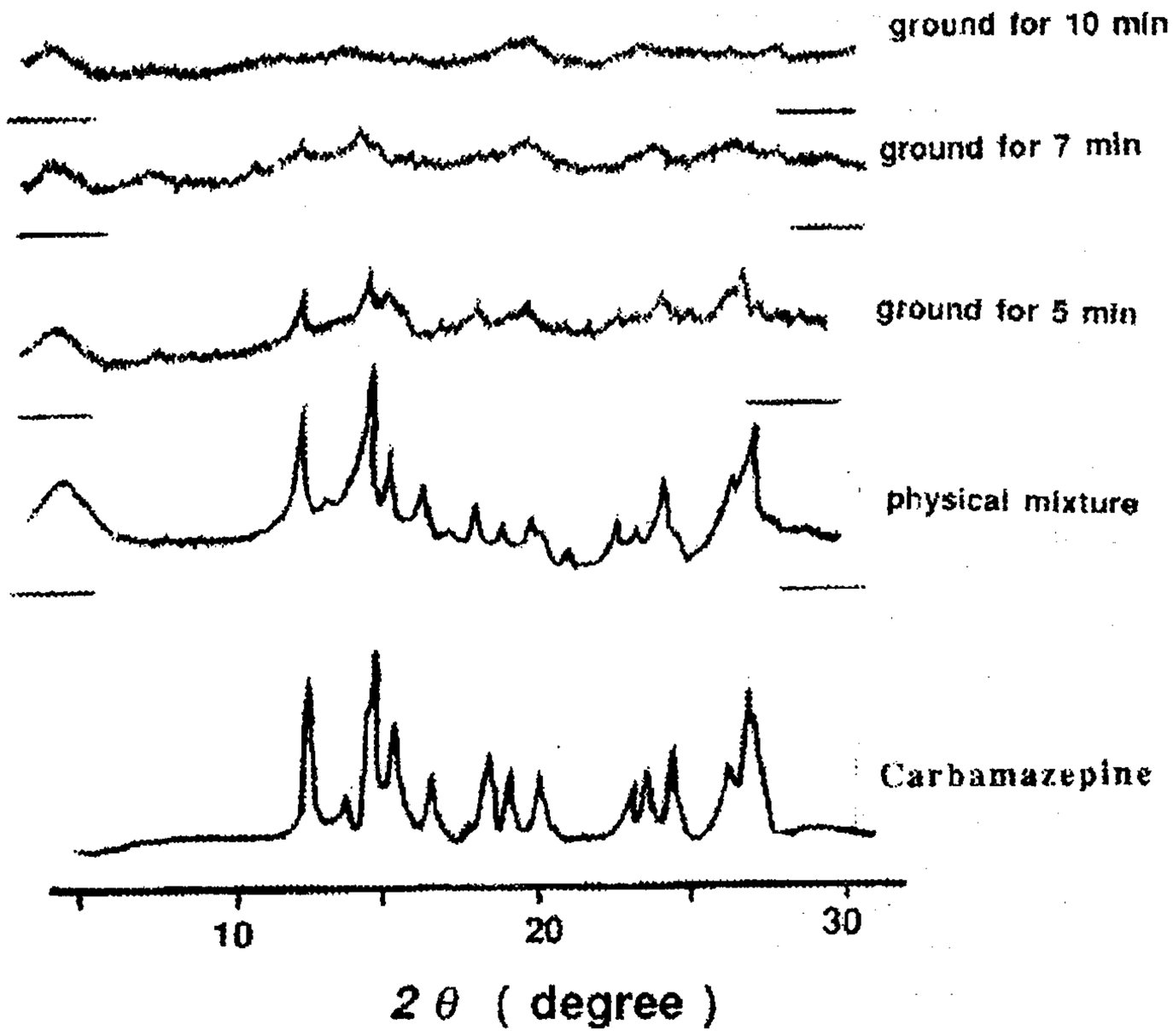

Fig. 2: Powder x-ray diffraction patterns of the ground mixtures of CBZ and porous silica (in 1:1 ratio).

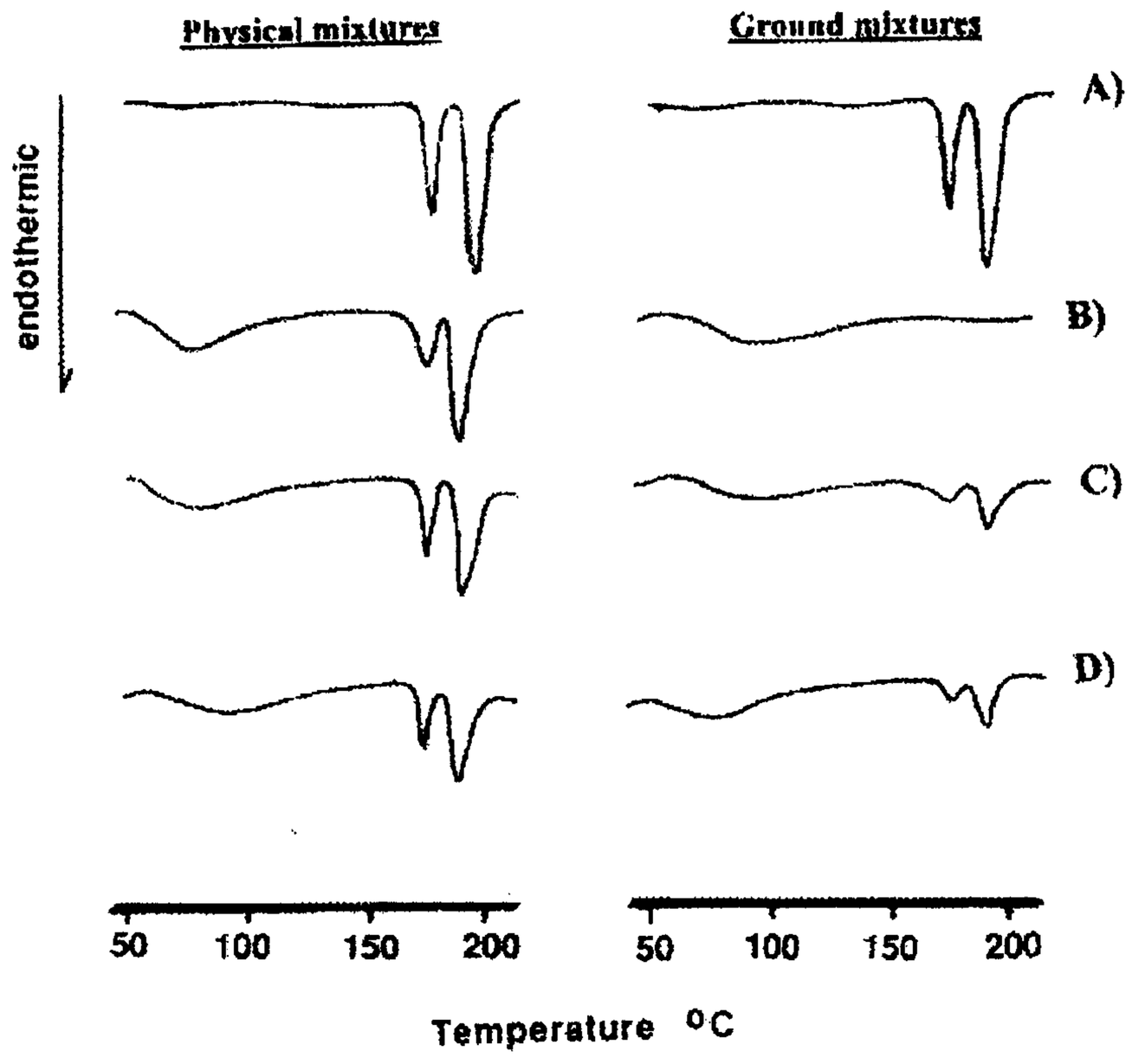

Fig. 3: DSC curves of the physical and 10 min ground mixtures of CBZ and different carriers (in 1:1 ratio).
A) Carbamazepine B) Mixture with porous silica
C) Mixture with PVP D) Mixtures with egg albumin.

The dissolution behavior of CBZ from the loaded mixtures with porous silica in pH 1.2 HCl solution is shown in Fig. 4. The dissolution rate of CBZ from the loaded mixtures with porous silica in all ratios were significantly enhanced. However, the dissolution rate in case of the loaded mixture of 40% w/w CBZ was slightly lower than that from the loaded mixtures of either 20% w/w or 30% w/w CBZ. The obtained results clearly indicate good correlation between the dissolution rate of the drug and its molecular state. The present results are in good agreement with those reported by Liao *et al.*[27] demonstrating that the dissolution rates of corticosteroids-silica dispersions were more rapid than those from micronized powders of the investigated drugs.

The dissolution profiles of CBZ from the ground mixture with various carriers are shown in Fig. 5. The dissolution rate of the drug was significantly enhanced from all the ground

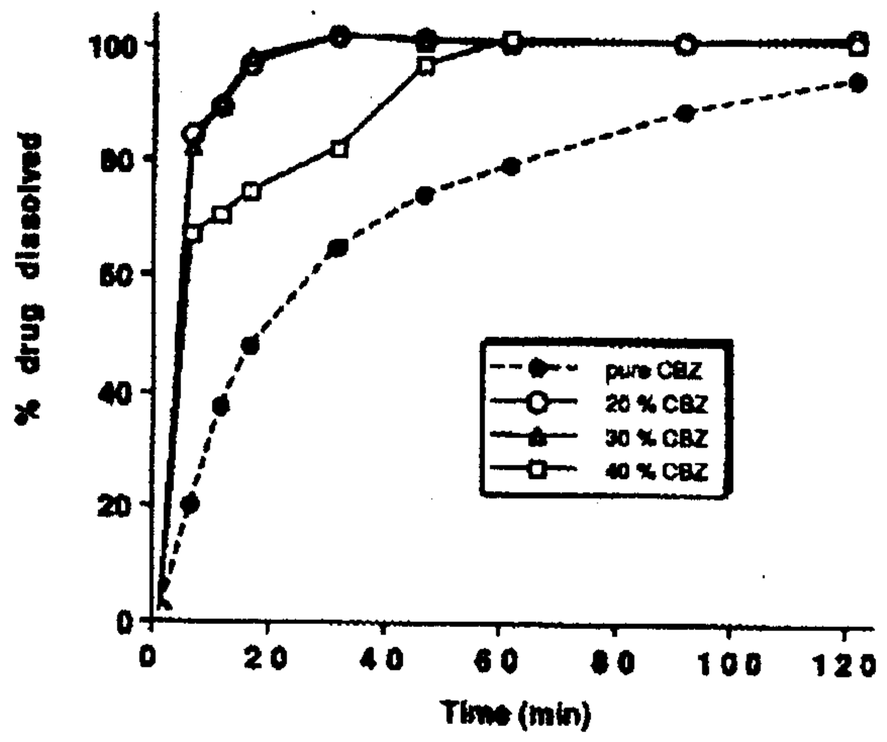

Fig. 4: Dissolution profiles of CBZ from the loaded mixtures onto porous silica in various ratios (% w/w CBZ) in pH 1.2 HCl buffer at 37°C.

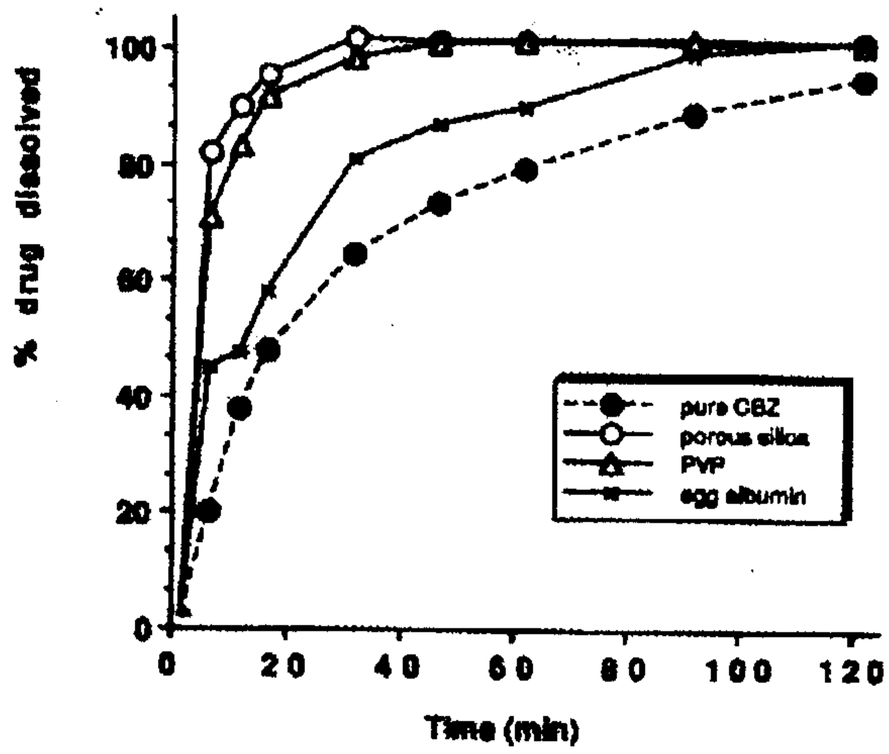

Fig. 5: Dissolution profiles of CBZ from the ground mixtures with various carriers (1:1 w/w) in pH 1.2 HCl buffer at 37°C.

mixtures. In this respect the ground mixture with porous silica showed the greatest enhancement in the dissolution rate. The high dissolution rate of CBZ in case of the loaded or ground mixture with porous silica could be explained in view of the rapid desorption of the physically adsorbed drug molecules when these mixtures are placed onto the dissolution medium (oxygen is more electronegative than silicon). Thus the drug molecules released simultaneously onto the dissolution medium. The dissolution mechanism is therefore different from that of pure drug where dissolution occurs from the surface of the drug crystals according to concentration gradient.

Surface hydrophilization is known to improve the dissolution of drugs of poor wettability. Fig. 6 demonstrate that surface hydrophilization of the drug with polysorbate 20 effectively enhanced the dissolution rate of the drug due to improved wettability. Almost complete dissolution of the drug was attained after about 30 min. Addition of 1% w/w polysorbate 20 was shown to be satisfactory to enhance the dissolution rate of the drug. On the other hand surface hydrophilization with propylene glycol only slightly enhanced the dissolution of CBZ (Fig. 7). In view of the previous results surface hydrophilized drug with

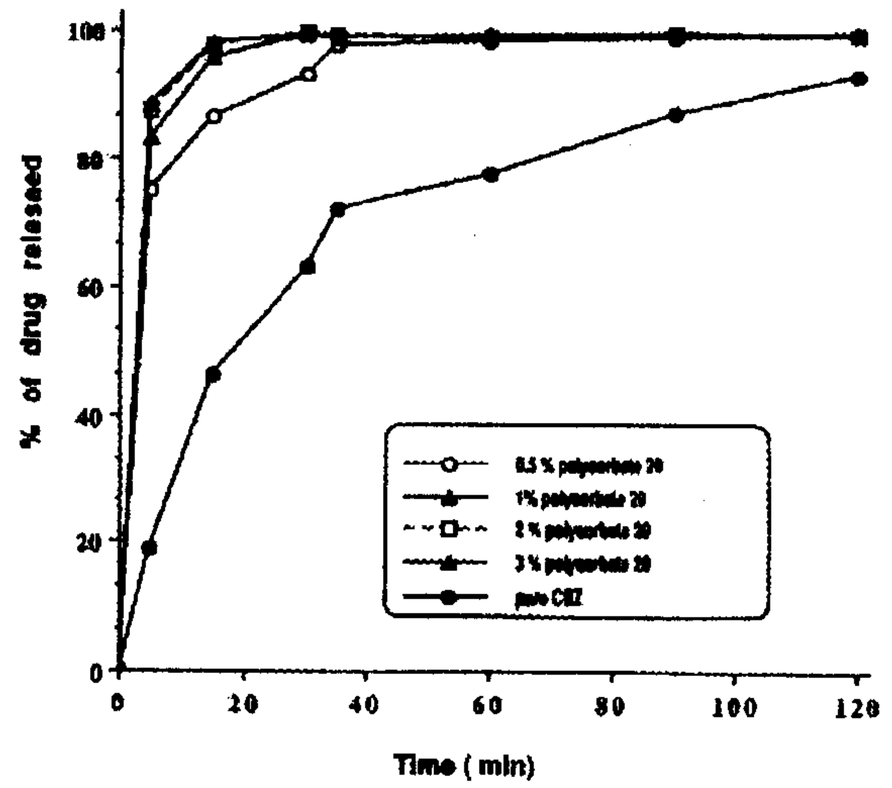

Fig. 6: Dissolution profiles of CBZ from the surface hydrophilized samples containing different ratios of polysorbate 20 (% w/w) in pH 1.2 HCl buffer at 37°C.

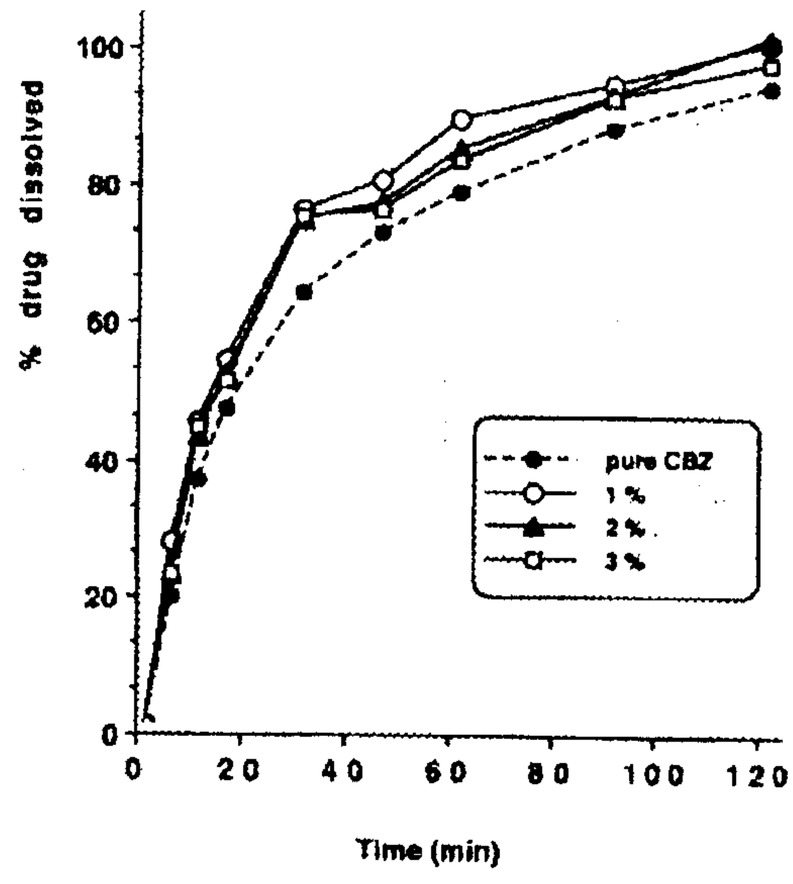

Fig. 7: Dissolution profile of CBZ from surface hydrophilized samples containing different ratios of propylene glycol (% w/w) at pH 1.2 HCl buffer at 37°C.

1% w/w polysorbate 20 was selected for tablets preparation.

Direct compression was adopted to prepare tablets containing 200 mg of the pure drug or

Table 2: Physical characteristics of the two different formulations of carbamazepine tablets.

	Weight (mg) mean (C.V.%)	Drug content (mg) mean (C.V.%)	Disintegration time (min.) mean (C.V.%)	Hardness (Kg) mean (C.V.%)	Friability (%) mean (C.V.%)
Formula I	350 (2.47)	200 (1.16)	6.33 (4.12)	4.63 (2.96)	1.07 (2.41)
Formula II	350 (2.26)	200 (0.93)	6.04 (3.79)	4.81 (2.84)	0.97 (2.25)

equivalent amount of surface hydrophilizd drug. The formulations of the tablets are presented in Table 1. The prepared tablets complied with BP 1993[21] requirements for uniformity of weight, uniformity of drug content and disintegration time. The hardness and friability values of the prepared tablets were acceptable (Table 2).

Fig. 8 demonstrates the dissolution profile of CBZ from the prepared tablets at pH 1.2 HCl solution. The tablets of the pure drug show slightly higher dissolution rate than that from tegretol tablets. The tablets containing surface hydrophilized drug show significantly higher dissolution rate. The obtained results indicated the effectiveness of surface hydrophilization for improving the dissolution rate of the drug.

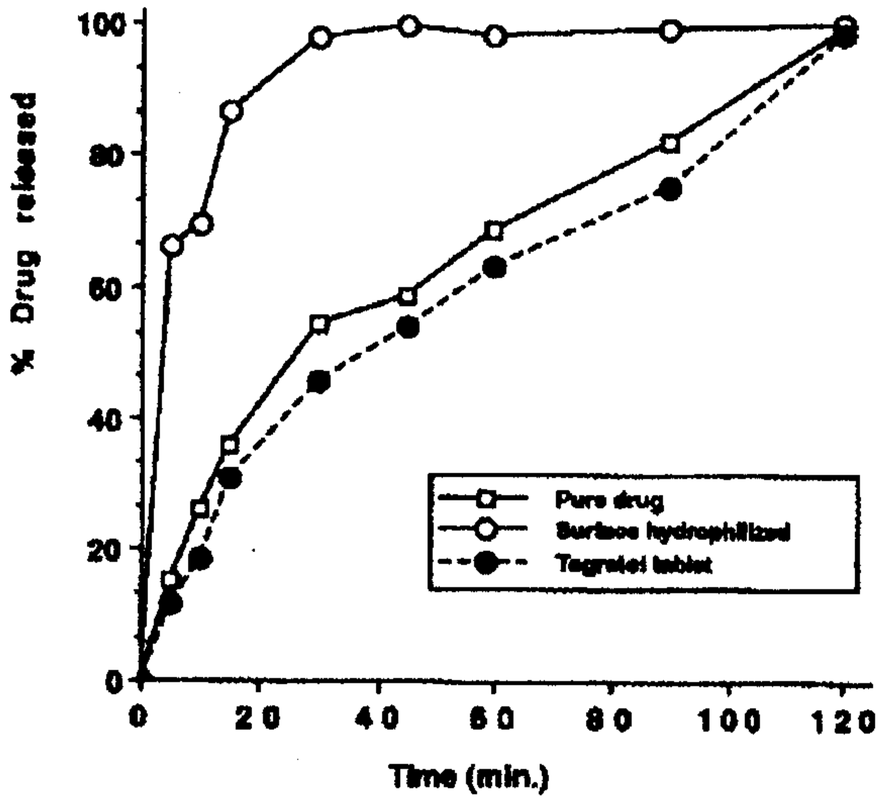

Fig. 8: Dissolution profiles of CBZ from tablets containing either pure drug or surface hydrophilized drug (1 % w/w polysorbate 20) in pH 1.2 HCl buffer at 37°C.

The results of the bioavailability study will be the subject of next publication.

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