THE EFFECT OF SOLVENT AND CRYSTALLIZATION CONDITIONS ON HABIT MODIFICATION OF CARBAMAZEPINE

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ABSTRACT

Physical characteristics of carbamazepine crystals grown from pure ethanol or acetone under different conditions were studied for the morphology of crystals by scanning electron microscope, x-ray powder diffraction and FT-IR, and for thermodynamic properties by differential scanning calorimeter. Also the dissolution behavior and compaction properties of crystals were studied. The results showed that crystallization of carbamazepine using watering-out method produced needle shape crystals while by the other methods such as reducing temperature or solvent evaporation produced polyhedral crystals in alcohol and thin plate-like crystals in acetone. The crystals which were grown from acetone were larger than those from alcohol. Differential scanning calorimetery and x-ray powder diffraction showed no evidence of polymorphism for carbamazepine crystallized by reducing the temperature or by the solvent evaporation in contrast with the crystals produced by the watering out technique. Crystallization of carbamazepine by different methods especially watering-out technique improved its dissolution rate and compactibility and produced high crushing strength compacts without capping.

Key words: Carbamazepine, Crystallization, Crystal habit, Crystal shape, Dissolution rate, Compaction

INTRODUCTION

Crystallization from solvents is commonly used for the purification of drugs during their final stages of manufacturing and it has been demonstrated that under certain conditions, crystals with completely different appearance are produced (1). The crystallization technique can change the crystal properties such as habit, polymorphism and size. The nature and extent of these changes depend on the crystallization conditions including type of solvent and cooling rate as well as the presence of impurities. Several studies have used alternative solvents (2-4) or low level additives (5-13) in order to modify crystal properties. Crystal engineering of pharmaceuticals provides an enormous potential for preparation of powdered materials with desired chemical, physical and/or mechanical properties (14). Carbamazepine (5H-dibenzazepine-5-carboxamide), is widely used in the treatment of epilepsy and trigeminal neuralgia. Variations in absorption and dissolution rates have been reported for two crystalline forms of carbamazepine (15). Physical stresses, like applied milling during manufacturing, affect transition of one crystalline form to another (16).

Crystal habit (i.e., shape) and crystal imperfections (e.g., point defect and dislocations) arise during and/or after crystallization and could play important roles in the processability of pharmaceutical raw materials as well as the efficacy and performance of the final solid dosage forms (17). Thus, modification of carbamazepine's crystal structure to obtain crystals suitable for direct compression becomes highly necessary and desirable.

In the present work, carbamazepine crystals were modified, by different crystallization techniques. The effects of solvent and crystallization temperature on

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the crystal habit were studied. The solid state characteristics and compaction properties of the modified crystals were also investigated.

MATERIALS AND METHODS

Materials

Carbamazepine was obtained as a gift from Sobhan Pharmaceutical Co., Iran. Ethanol, acetone and sodium lauryl sulfate were purchased from Merck, (Germany).

Crystallization Procedures

Carbamazepine (3 g) was dissolved in 30 ml of ethanol at 65 °C or 90 ml of acetone at 55 °C. The solutions were then treated under different conditions as follows:

1: The solution was immediately transferred to a freezer (-10°C) and stored for a period of 48 h.

2: The solution was kept at room temperature until its temperature was reached to 25°C (with the rate of 1.5 ± 0.3°C) and then stored at 7±1°C for a period of 48 h. The precipitated crystals from two methods were collected by filtration through a sintered glass funnel vacuum.

3: The solution was kept at room temperature until the solvent was completely evaporated.

4: The solution at 55-60 °C was rapidly added to 200 ml of cold water (+10 °C) and the resulting solution was stirred with a glass rod and then was left at 10-15 °C for 2 h. The precipitated crystals were collected by filtration through a sintered glass funnel vacuum, spread on a petri dish, air-dried for 2 days and stored in a dessicator at room temperature before use.

Scanning Electron Microscopy

The morphology of crystals (their habits and surface features) was examined with a scanning electron microscope (Leica Cambridge S360, UK) operating at 12 kV. The samples were mounted on a metal stub with double-sided adhesive tape and coated with gold under vacuum in an argon atmosphere prior to observation.

Differential Scanning Calorimetry (DSC)

DSC thermograms of the samples (3-6 mg) were recorded by a thermal analysis system (Polymer Laboratories, UK). Following calibration with indium and lead as standards, samples were heated at 10 °C/min in aluminum pans under a nitrogen atmosphere. The enthalpy of fusion, melting point and onset temperatures were recorded automatically.

Fourier Transform Infrared Spectroscopy (FT-IR)

The spectra of the potassium bromide discs which were made by compressing a mixture of samples and KBr powder under a hydraulic pressure of 10 tons for 30 s, were recorded on a FT-IR spectrophotometer (Magna-IR, 550 Nicolet, USA) at 4 cm^{-1} resolution for scans.

Powder X-Ray Diffraction (XRD)

A Seimens x-ray diffractometer (Model D5000, Germany) at 40 kV, 30 mA and a scanning rate of 6°/min over a range of 5-70 2 θ, using $CuK_{\alpha 1}$ radiation of wavelength of 1.5406 A° was employed for this purpose.

Dissolution Studies

A USP dissolution test apparatus No.2 (Erweka, Germany) was used to monitor the dissolution profiles of 25 mg carbamazepine powder (90-425 µm). The dissolution medium was 900 ml of phosphate buffer (pH 7.4) containing 1% sodium lauryl sulfate equilibrated at 37±0.2 °C. The paddles were rotated at 50 rpm. 5 ml samples were withdrawn from the dissolution vessel at determined time intervals and the concentration of carbamazepine present was determined, by a UV spectrophotometer (Shimadzu, Japan) at 280 nm. The amount of dissolved carbamazepine was calculated from the concentration after correction for the change in volume of the dissolution medium. At least three determinations for each sample were carried out.

Preparation of Carbamazepine Crystals Compacts

Crystals were ground by a mortar and pestle to achieve a similar particle size distribution for each batch (90-425 µm). Compacts were prepared directly from the ground crystals, using 8mm flat-faced punches fitted on a hydraulic press (Riken Seiki Co., Japan). The compaction surfaces were lubricated with 2% w/v magnesium stearate in acetone before each experiment. Tableting materials were individually weighed (120 mg) and introduced into the die and compacted at various pressures of 12.5, 25 and 37.5 MPa for 30 s. The prepared compacts were then stored in screw-capped sample bottles for 24 h before use to allow possible hardening and elastic recovery.

Tablet Crushing Strength

Tablet crushing strength was determined from the force required to fracture compacts on a motorized tablet hardness tester (Erweka, Germany). Crushing strength was employed instead of tensile strength because it was not possible to obtain idealized diametral tablet fracture as a result of the fragile nature of the compacts. Tests were carried out 24 h after ejection.

RESULTS AND DISCUSSION

Morphology of Crystals

Figure 1 shows the scanning electron micrographs (SEM) of untreated and treated carbamazepine crystals from alcohol by different methods of crystallization.

Table 1. DSC thermograms data for carbamazepine crystals

Type of crystals	Fusion temperature of first peak (°C)	Heat of fusion (mcal.mg^{-1})	Onset temperature of main peak (°C)	Fusion temperature of main peak (°C)	Heat of fusion (mcal.mg^{-1})
Untreated sample	160.6	1.49	186.0	190.9	11.36
Alcohol[1]	162.6	1.37	186.1	190.7	11.10
Acetone[1]	166.7	1.38	185.1	189.4	7.87
Alcohol[2]	150.8	1.43	188.8	192.4	12.06
Acetone[2]	165.6	1.44	187.4	190.0	11.07
Alcohol[3]	---	---	189.7	192.0	12.89
Acetone[3]	---	---	185.6	190.8	9.38
Alcohol[4]	---	---	186.7	189.7	9.86
Acetone[4]	---	---	187.1	190.6	11.48

[1,2,3,4] represent different methods used for samples.

As can be seen the crystal shape of untreated carbamazepine was flaky or thin plate-like (Figure 1a). The shape of crystals obtained from alcohol by methods 1, 2 or 3 were polyhedral or hexagonal prism (Figures 1b-1d), whereas, those prepared by method 4 were acicular or needle-like (Figure 1e).

Crystallization of carbamazepine from acetone by the same methods as alcohol, produced different shapes of crystals. The scanning electron micrographs of carbamazepine crystals obtained from acetone (Figures 2f-2i) show that while the crystals grown from this solvent by methods 1, 2 and 3 were long tabular, those obtained by the method 4 were needle-shaped. The later was similar to the crystals obtained from alcohol by method 4, but with much longer size (about 10 folds). The results also show that the size of crystals obtained from acetone or alcohol under different conditions are as follows: method 3 > method 2 > method 1 (considering the magnification of the SEM in Figures 1 and 2). Therefore, it can be concluded that the crystal size generally decreases at fast cooling (method 2) due to incomplete growth of a large number of small crystals. On the basis of the results, the solvent type and crystallization conditions have a significant effect on carbamazepine crystal habit modification. The changes in morphology of crystals in different solvents could be due to variations in face dimensions or the appearance or disappearance of some faces (18). Under certain conditions of crystallization one set of crystal faces may be induced to grow faster than others, or the growth of another set of faces may be retarded. For example by the same method (1 or 2 or 3) but with different solvents the pattern of crystal growth changed from polyhedral crystals in alcohol to long tabular crystals in acetone. This observation may be explained by the interaction (adsorption) between the solvent molecules and the different crystal faces, which is believed to change the crystal morphology (1). Berkovitch-Yellin (19) proposed a method for predicting the habits of crystals grown from various solvents. He suggested that polar solvents are preferentially adsorbed by polar faces and non-polar solvents by non-polar faces. Davey et al. (20) demonstrated that crystallization of succinic acid from water or isopropanol produced plate and needle habits, respectively. They suggested that the carboxylic acid groups of succinic acid interact more strongly with isopropanol than water and as a result the growth rates of faces containing carboxylic acid groups reduces, leading to modifications in the crystal habit.

In method 4, in which the crystals are formed after addition of cold water, interaction of water through strong hydrogen bonds with the carbamazepine amide group, reduces the growth rates of faces containing these groups which leads to needle shape crystals.

Differential Scanning Calorimetry

It has been reported that carbamazepine can be present in different polymorphs mainly form I (USP grade material; m.p. of 176°C) and form III (m.p. of 189°C) (21). The DSC thermograms (Figure 3) of untreated and some treated carbamazepine samples (from methods 1, 2 and 3) showed two endotherms. The first weak endotherm was present in the range of 155-165 °C and the second one occurred in the range of 189-192 °C, indicating form I. The first endotherm has been shown (22-24) for some carbamazepine powder samples at about 170 °C. It has been reported that this weak endothermic effect could be due to the transition of the form I (β) to the form III (α) (24). The DSC thermograms for the crystals by method 4 did not show the first endothermic peak and this is in agreement with the published thermogram of form III (21). DSC data for the carbamazepine samples recrystallized from each solvent system at different conditions are shown in Table 1. Generally, The onset melting point of treated carbamazepine samples increased in comparison with the untreated samples. Decrease in enthalpy of fusion and melting point may be attributed to the presence of amorphousness in the particles, or due to weakening and disrupting of the crystal lattice and order.

FT-IR

The KBr disc spectra of untreated and treated carbamazepine samples are shown in Figure 4. The samples recrystallized from ethanol or acetone solutions as well as the untreated samples exhibited identical IR spectra, indicating that there is not any changes at the molecular level.

X-Ray Diffraction of Powder

The untreated carbamazepine crystals used in the present study was form I. The XRD spectra showed that the crystals produced from alcohol and acetone by methods 1, 2 and 3 are also present as form I (Figures 5 and 6). On the other hand, the XRD spectra of the samples crystallized by method 4, showed some peaks of lower intensity with different pattern, which might be due to the less crystal perfection or polymorphism. This is similar to the reported XRD spectra of form III (21). The Figures also show that x-ray powder diffraction pattern of the carbamazepine crystals from method 4 is relatively broad at 30-70 2 θ indicating higher degree of amorphousness. These patterns are quite distinguishable from the other samples which gave sharp and defined diffraction patterns. It is suggested that the samples crystallized by method 4 are less crystalline in comparison with other samples.

By comparing Figures 5a-5e and 6f-6i, it appears that the intensity of the samples crystallized from ethanol is significantly higher than those obtained from acetone, indicating the greater crystal perfection.

Dissolution Studies

Figure 7 compares the dissolution profiles of untreated carbamazepine with crystals obtained from alcohol or acetone respectively. This figure indicates that there is a marked enhancement in the dissolution characters of carbamazepine crystallized from alcohol (figure 7A) and acetone (figure 7B). The lowest dissolution rate was observed for untreated carbamazepine samples, while crystals obtained by method 4 (from either alcohol or acetone) showed the highest dissolution rate. It has been reported that at the first 10 min form III exhibited higher dissolution rate than that of form I (21), due to the higher solubility of form III. The intrinsic solubility of form I and III at 37°C are 460.2 and 501.9 μg/ml respectively, and this is one of the reasons for the higher dissolution rate of the form III (crystals by method 4). In addition these crystals have small particle size and as a result higher surface area. Statistical analyses showed no significant difference between the amount of the drug dissolved by crystals from ethanol or acetone after 20 min ($P_r > 0.05$). Kobayashi et al. have reported (21) that both form I and III were thoroughly transformed to dihydrate during the dissolution test and the rate of transformation of form III was higher than that of form I. This could be the reason why there was no significant difference between the percentage of drug dissolved in dissolution medium after 20 min.

Compaction studies

Compression of untreated carbamazepine crystals at all compaction pressures produced weak compacts with a high tendency to cap (about 78%). The needle crystals obtained by method 4 (watering-out technique) showed improvement in compressibility (Figure 8). Tablets made from needle shape crystals exhibited very good hardness with no tendency to cap at all compression pressures probably due to greater amor-phousness of the crystals. Crystallinity or amorphous-ness had significant effect on the mechanical proper-ties of materials. Amorphous materials showed ten-dency to exhibit plastic deformation rather than elas-tic and compact deformations (25). It seems possible that differences in the crystallinity or amorphousness of the different crystals of carbamazepine would cause difference in the hardness of the tablets.

Particles obtained from method 1, 2 or 3 showed little improvement in their compaction properties. The tablets made from these crystals exhibited a tendency to cap. Figure 8 also shows that there is no linear relationship between compact crushing strength and upper punch pressure. The reduction in the crushing strengths beyond 25 MPa in some samples is due to higher elastic recovery of the compacts.

CONCLUSION

The results of this investigation show that the type of solvent can modify crystal habit of carbamazepine particles and crystallization temperature only altered the size of the crystals. Different crystal shapes of carbamazepine (thin plate-like, polyhedral, tabular, acicular and needle crystals) obtained from different solvents by various methods. The x-ray powder diffraction and DSC studies show that watering out technique leads to polymorphism. The needle crystals obtained by this method produced compacts with higher crushing strengths but with no tendency to cap as compared to untreated and other treated samples, due to greater amorphousness of the crystals. The highest dissolution rate was observed with treated carbamazepine crystals by method 4.

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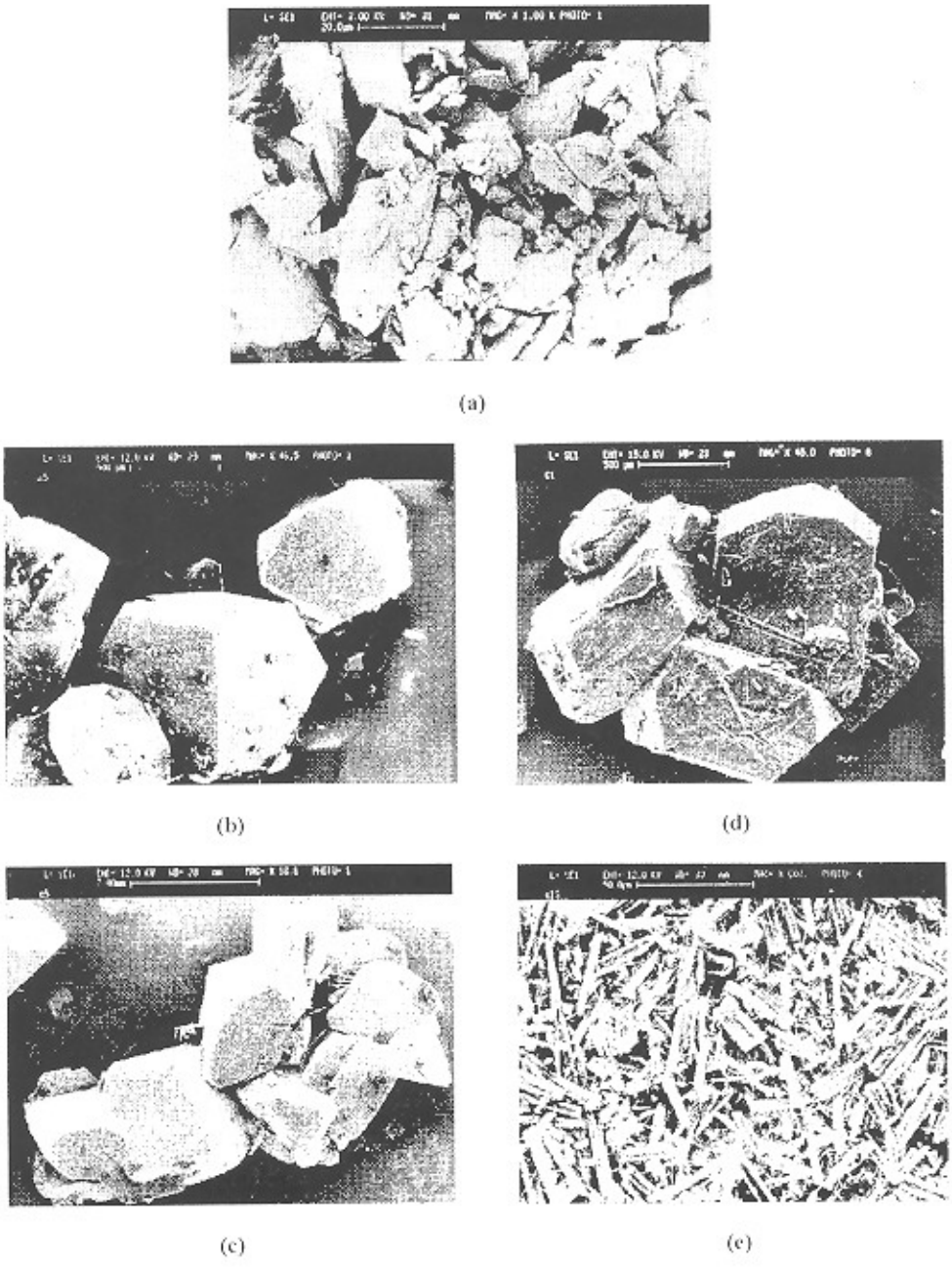


(a)

(b)

(d)

(c)

(e)

Figure 1. Scanning electron micrographs of (a) untreated carbamazepine, (b) carbamazepin crystallized from alcohol by method 1, (c) method 2, (d) method 3 and (e) method 4.

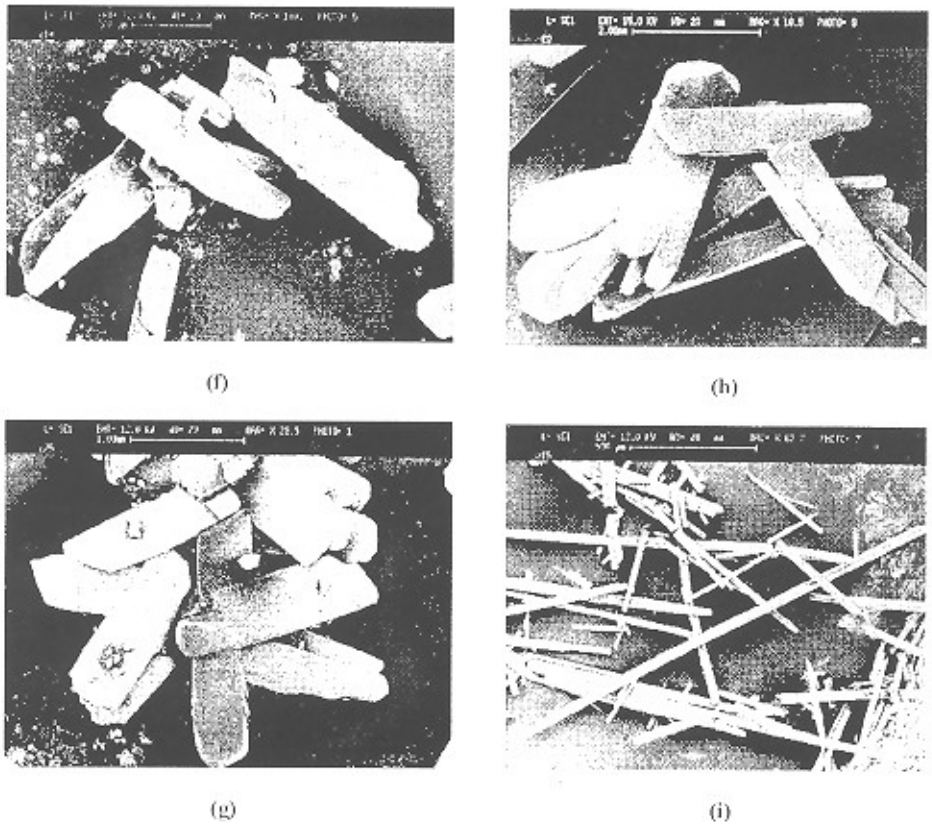


Figure 2. Scanning electron micrographs of carbamazepine crystallized from acetone by (f) method 1, (g) method 2, (h) method 3 and (i) method 4.

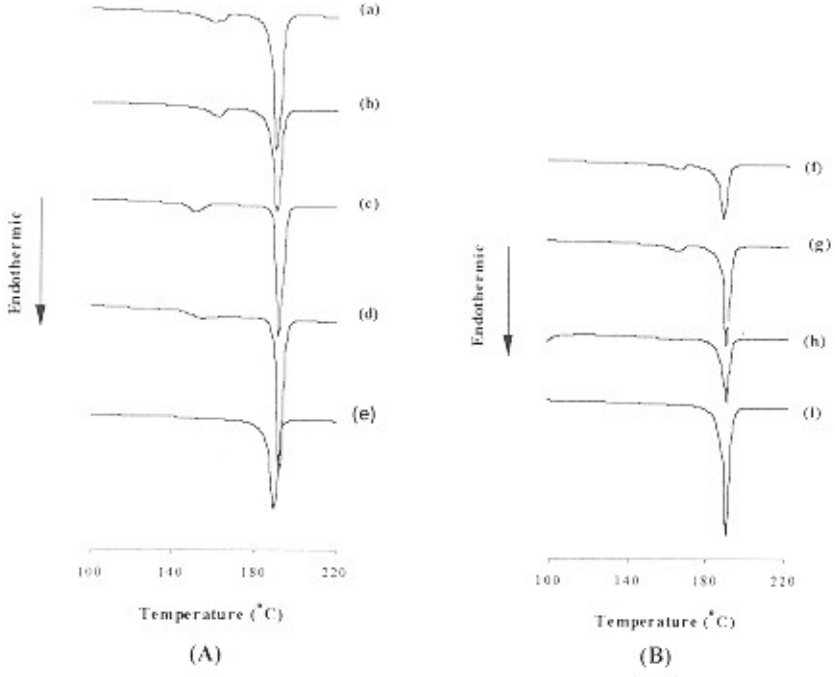


Figure 3. DSC thermograms of untreated carbamazepine and carbamazepine crystallized from alcohol (A) and acetone (B) (legends are the same as mentioned in Figures 1 and 2)

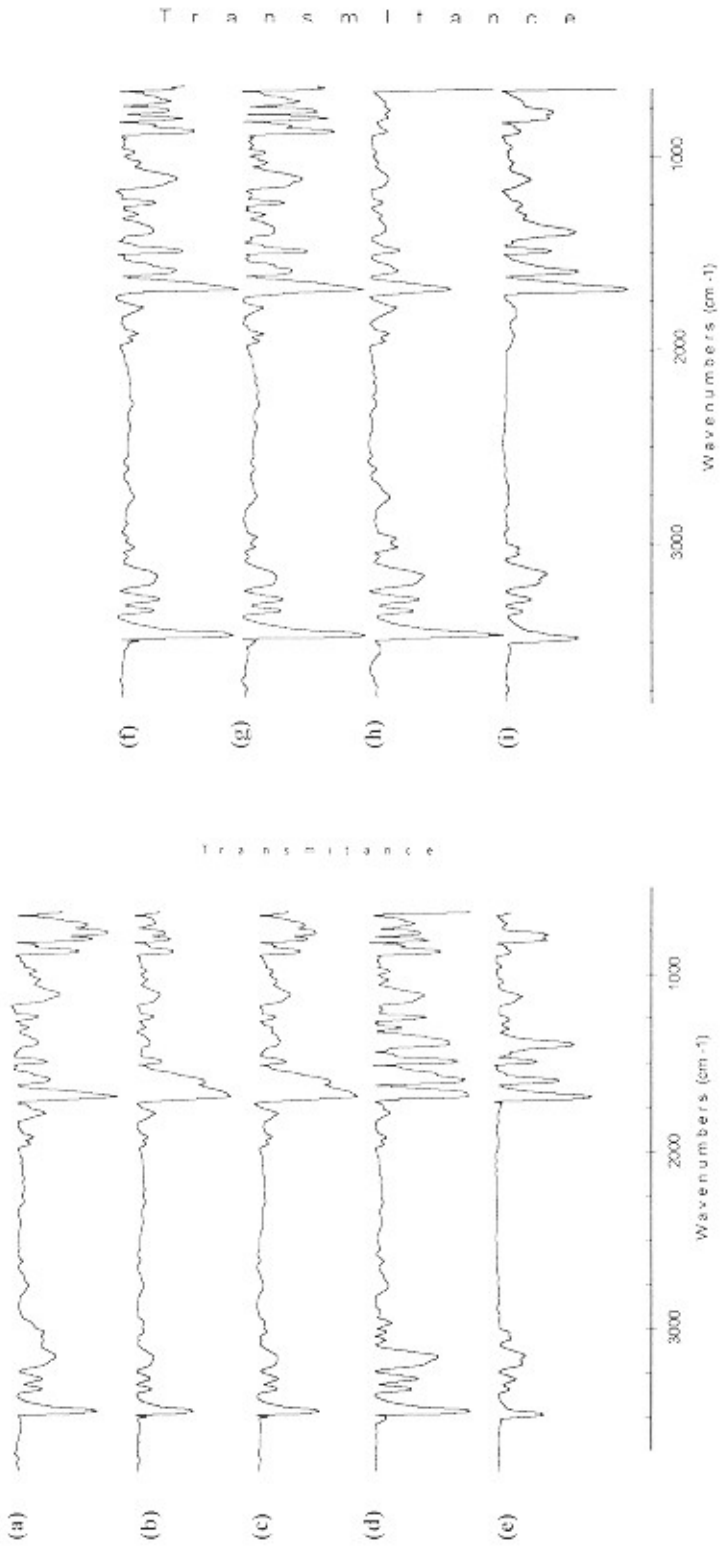


Figure 4. FT-IR spectra of untreated and treated carbamazepine crystals (legends are the same as mentioned in Figures 1 and 2)

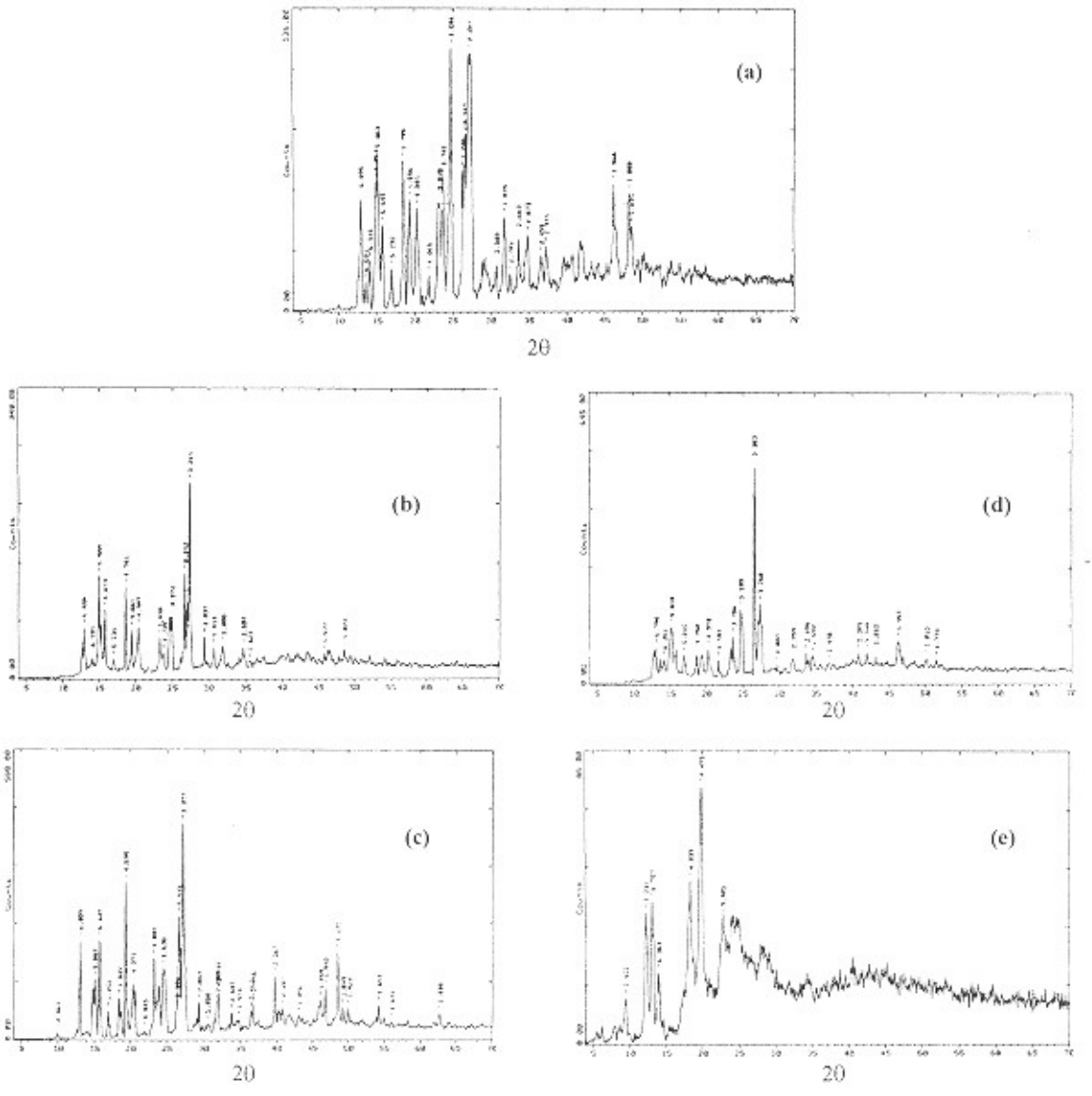


Figure 5. X-ray powder diffraction patterns of untreated carbamazepine and carbamazepine crystallized from alcohol (legends are the same as mentioned in Figure 1)

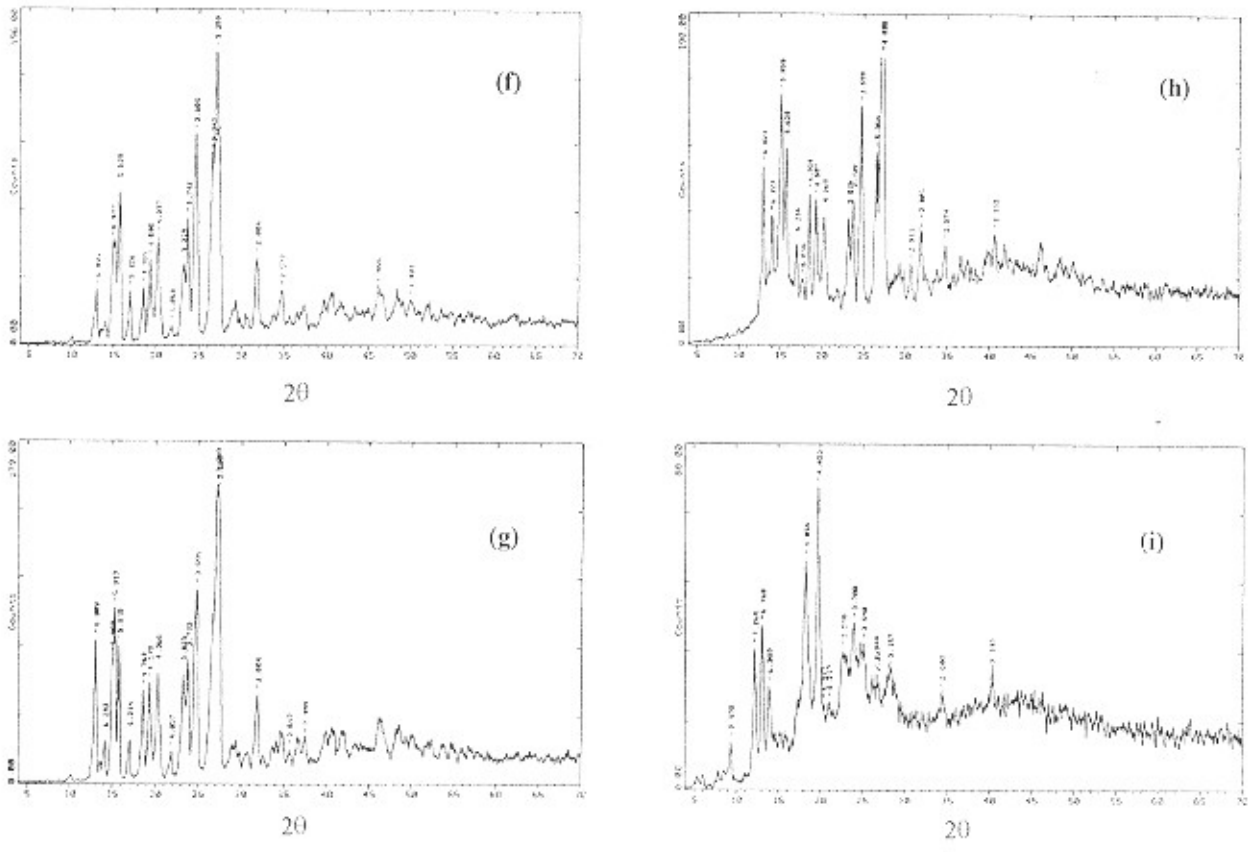
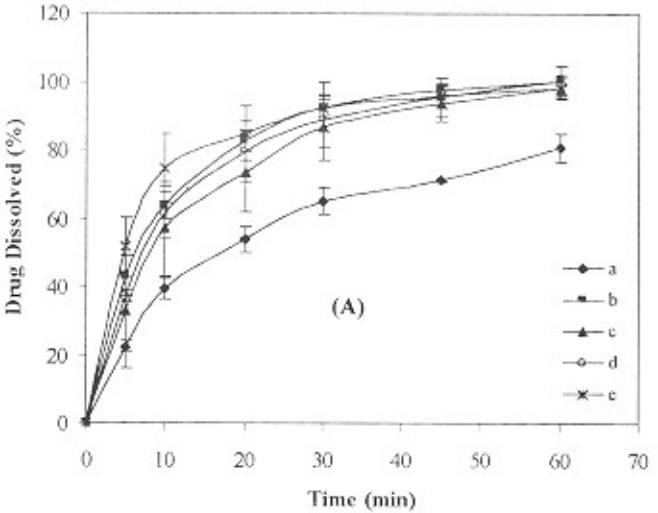


Figure 6. X-ray powder diffraction patterns of carbamazepine crystallized from acetone (legends are the same as mentioned in Figure 2)



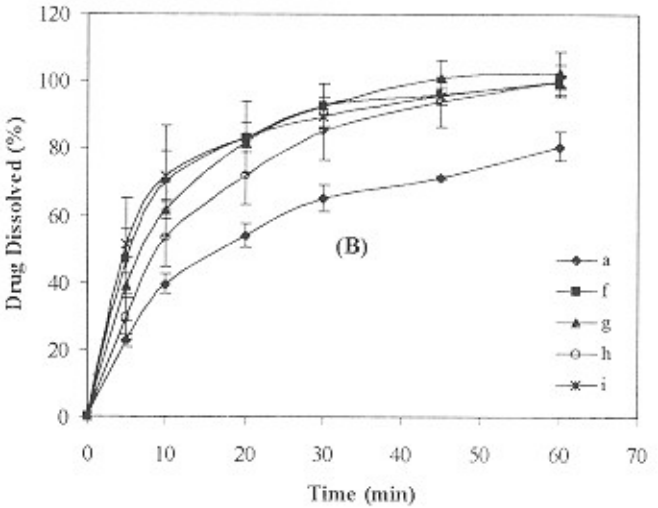
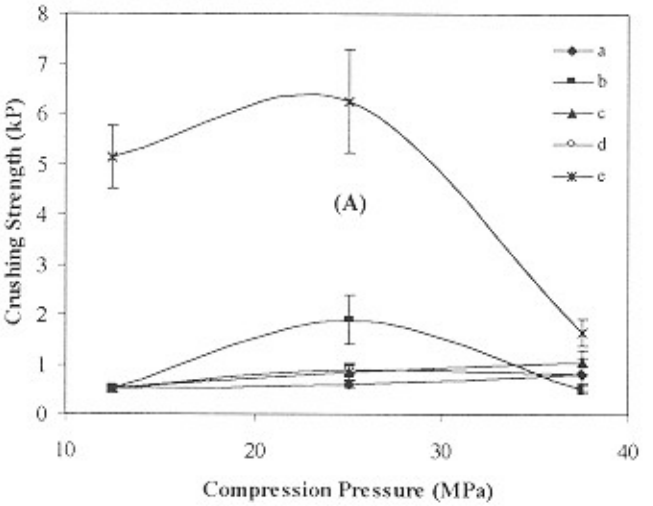


Figure 7. The dissolution profile of untreated carbamazepine and carbamazepine crystallized from alcohol (A) and acetone (B) (n=3) (legends are the same as mentioned in Figures 1 and 2)



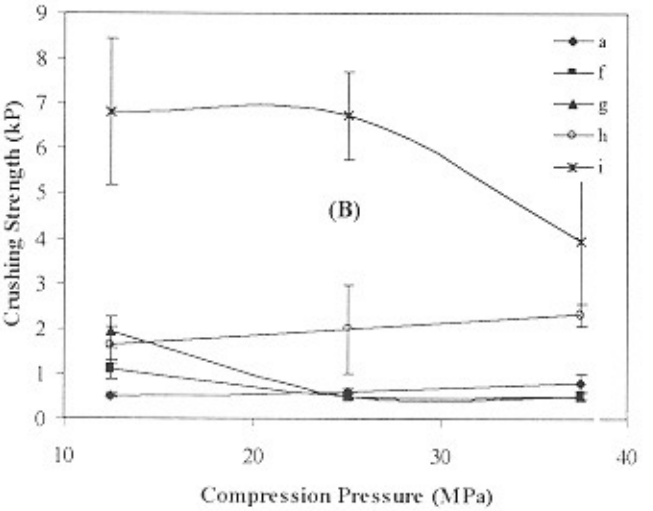


Figure 8. The effect of compression pressure on the crushing strengths of compacts made from untreated and treated carbamazepine crystals obtained from alcohol (A) and acetone (B) (n=3) (legends are the same as mentioned in Figures 1 and 2)

REFERENCES

1. Mullin, J. W. (ed) (1993) Crystallization, 3rd edn. Butterworth-Heinemann, Oxford. pp: 203-257.
2. Garti, N., Tibika, E. (1980) Habit modification and nitrofurantoin crystallized from formic acid mixtures. Drug Dev. Ind. Pharm. 6: 379-398.
3. Marshall, P. V., York, P. (1989) Crystallization solvent induced solid-state and particulate modifications of nitrofurantoin. Int. J. Pharm. 55: 257-263.
4. Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R. (1999) Formation and compression characteristics of prismatic polyhedral crystal and thin plate like crystals of paracetamol. Int. J. Pharm. 187: 77-89.
5. Chow, A.H.L., Chow, P.K.K., Wang, Z., Grant, D.J.W. (1985) Modification of acetaminophen crystals: influence of growth in aqueous solutions containing p-acetoxyacetanilide on crystal properties. Int. J. Pharm. 24: 239-258.
6. Chow, A. H. L., Hsia, C. K. (1991) Modification of phenytoin crystals: influence of 3-acetoxymethyl-5,5-diphenylhydantoin on solution-phase crystallization and related crystal properties. Int. J. Pharm. 75: 219-230.
7. Gordon, J. D., Chow, A. H. L. (1992). Modification of phenytoin crystals: influence of 3-propanoyloxymethyl-5, 5-diphenylhydantoin on solution-phase crystallization and related crystal properties. Int. J. Pharm. 79:. 171-181.
8. Femi-Oyewo, M. N., Spring, M. S. (1994) Studies on paracetamol crystals produced by growth in aqueous solutions. Int. J. Pharm. 112: 17-28.
9. Mackellar, A. J., Buckton, G., Newton, J. M., Chowdhry, B. Z., Orr, C. A. (1994) Controlled crystallization of a model powder: I: effect of altering the stirring rate and the supersaturating profile and the incorporation of a surfactant (poloxamer 188). Int. J. Pharm. 112: 65-78.
10. Mackellar, A. J., Buckton, G., Newton, J. M., Orr. C. A. (1994) Controlled crystallization of a model powder: II: investigation into the mechanism of action of poloxamers in changing crystal properties. Int. J. Pharm. 112: 79-85.
11. Kachrimanis, K., Ktistis, G., Malamataris, S. (1998) Crystallization conditions and physicomechanical properties of ibuprofen-Eudragit S100 spherical crystal agglomerates prepared by the solvent-change technique. Int. J. Pharm. 173: 61-74.
12. Garekani, H. A., Ford, J. L., Rubinstein, M. H., Rajabi-Siahboomi, A. R. (2000) Highly compressible paracetamol: I: crystallization and characterization. Int. J. Pharm. 208: 87-99.
13. Garekani, H. A., Ford, J. L., Rubinstein, M. H., Rajabi-Siahboomi, A. R. (2000) Highly compressible paracetamol: II: compression properties. Int. J. Pharm. 208: 101-110.
14. Marshall, P. V., York, P. (1987) Crystal engineering of nitrofurantoin. J. Pharm. Pharmacol. (Suppl.) 39: 88P.
15. Kahela, P., Aaltonen, R., Lewing, E., Anttila, M., Kristoffersson, E. (1983) Pharmacokinetics and dissolution of two crystalline forms of carbamazepine. Int. J. Pharm. 14: 103-112.
16. Villafuerte-Roberts, L. (1982) Zur polymorphic and mechanischen earbeitung des carbamazepine. PhD Thesis, Hamburg University, Hamburg.
17. York, P. (1983) Solid-state properties of powders in the formulation and processing of solid dosage forms. Int. J. Pharm. 14: 1-28.
18. Khamskii, E. V. (1976) Some problems of crystal habit modification. In: Mullin, J. W. (ed) Industrial Crystallization, Plenum, New York, pp: 203-214.
19. Berkovitch-Yellin, Z. (1985) Toward an ab initio derivation of crystal morphology. J. Am. Chem. Soc. 107: 8239-8253.
20. Davey, R. J., Mullin, J. W., Whiting, M. J. L. (1982) Habit modification of succinic acid crystals grown from different solvents. J. Crystal Growth. 58: 304-312.
21. Kobayashi, Y., Ito, S., Itai, S., Yamamoto, K. (2000) Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. Int. J. Pharm. 193: 137-146.
22. Dugue, J., Ceolin, R., Rouland, J.C., Lepage, F. (1991) Polymorphism of carbamazepine: solid-state studies on carbamazepine dihydrate. Acta Pharm. Helv. 66: 307-310.
23. Lowes, M. M., Caira, M. R., Lotter, A. P., Van Der Watt, J. G. (1987) Physicochemical properties and x-ray structural studies of the trigonal polymorph of carbamazepine. J. Pharm. Sci. 76: 743-752.
24. Katzhendler, I., Azoury, R., Friedman, M. (2000) The effect of egg albumin on the crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets and in aqueous solutions. J. Controlled Release. 65: 331-343.
25. Wray, P. E. (1992) The physics of tablet compaction revisited. Drug Dev. Ind. Pharm. 18: 627-658.