Drug Development and Industrial Pharmacy, 27(8), 803–809 (2001)

RESEARCH PAPER

Crystal Habit Modifications of Ibuprofen and Their Physicomechanical Characteristics

H. A. Garekani,[1] F. Sadeghi,[1] A. Badiee,[1]
S. A. Mostafa,[2] and A. R. Rajabi-Siahboomi[2,*]

[1]*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, UK*

ABSTRACT

Ibuprofen was crystallized from methanol, ethanol, isopropanol, and hexane at similar conditions. Marked differences in crystal habit of the samples obtained from these solvents were observed. The samples crystallized from methanol and ethanol had a polyhedral crystal habit, while those from hexane were needlelike. Those from isopropanol were elongated crystals. X-ray powder diffraction (XPD) and differential scanning calorimetry (DSC) studies confirmed that these samples were structurally similar; therefore, polymorphic modifications were ruled out. The results showed that crystal habit modification had a great influence on the mechanical properties (compressibility, flow rate, and bulk density) of ibuprofen crystals. Samples obtained from methanol and ethanol exhibited the highest bulk density and the best flow rate, while those from hexane showed the lowest bulk density and the worst flow rate. The samples obtained from ethanol exhibited the best compression force/hardness profiles, and those obtained from hexane produced the softest tablets.

*Corresponding author. Current address: Dr. Ali R. Rajabi-Siahboomi, Technical Director, Colorcon Limited, Flagship House, Victory Way, Crossways, Dartford, Kent, DA2 6QD, UK. Fax: +44 (0) 1322 627200; E-mail: asiahboomi@colorcon.co.uk

Key Words: *Bulk density; Compression; Crystal habit; Crystallization; Flow rate; Ibuprofen*

INTRODUCTION

Crystallization from a solution is widely used for the purification of drugs during their final stages of manufacture. The crystallization technique can change such crystal properties as habit, polymorphism, and crystal size. The extent of these changes depends on the crystallization conditions, such as the presence of impurities, type of solvent, and cooling rate (1).

The crystal habit of a drug is an important variable in pharmaceutical manufacturing. Different crystal forms of a particular drug possess different planes and thus differ not only in their specific surface, but also in their free surface energy. Therefore, they may exhibit different physicomechanical properties (2). Properties such as dissolution rate, powder flow, and compressibility, which are of pharmaceutical interest, can differ for different habits of the same drug (3–5). Attempts to change the morphology and the workability of drugs using alternative crystallization procedures include modification of the crystal habits of drugs such as paracetamol (5), hexamethylmelamine (6), and nitrofurantoin (4,7).

The aim of this study was to investigate the influence of controlled crystallization of ibuprofen from different solvents on crystal habit and the physicomechanical properties of the different crystal habits.

EXPERIMENTAL

Ibuprofen powder was obtained from Boots Limited (UK). Analytical grades of absolute ethanol BP, methanol, isopropanol, and hexane were obtained from Merck Limited (Germany).

Crystallization Procedures

Different quantities of ibuprofen powder, 100 g, 80 g, 70 g, or 17 g, were added to 50 ml of methanol, ethanol, isopropanol, or hexane, respectively, in a 200-ml round-bottom flask. The flasks were placed in a water bath at 45°C ± 1°C and stirred until a clear solution was produced; then, the temperature of the water bath was reduced to 40°C. When the flasks were cooled to 40°C, 100 mg of ibuprofen powder (< 60 μm particle size) were added to all flasks to act as nuclei (seeds). Then, the flasks were placed in a water bath at 25°C, and the temperature was gradually reduced to 0°C over 200 min (Fig. 1) while stirring. For maximum crystal recovery, the samples were allowed to stand at 0°C for 2 h. The cooling rates for all flasks were the same. The crystals were then collected by filtration using a sintered glass No. 3 funnel under vacuum and dried at 40°C for 24 h. The dried crystals were stored in a desiccator at room temperature before use.

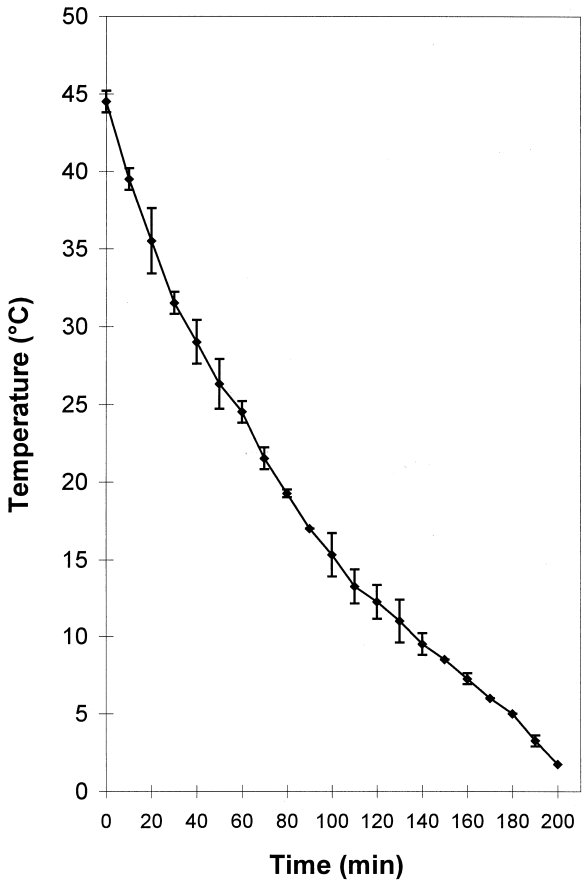

Figure 1. Cooling curve of crystallization medium over 200 min.

Crystal Shape and Size

The particle shape and size of the crystals were studied using an optical microscope (Olympus model BX60, Japan) and a scanning electron microscope (Jeol model JSM T200, Tokyo, Japan). The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. For all crystals, the length and the width of a minimum of 100 crystals were determined, and their distributions were reported.

Differential Scanning Calorimetry

A differential scanning calorimeter (DSC) model DSC7 (Perkin Elmer, Baconsfield, UK), controlled by a Perkin Elmer TAC7, was used. The equipment was calibrated using indium and zinc. Samples of ibuprofen crystals (4–6 mg) were heated at $10^{\circ}C\ min^{-1}$ in crimped aluminum pans under nitrogen atmosphere. The melting point onsets, the melting point peaks, and the enthalpies of fusion of the samples were determined.

X-ray Powder Diffraction

For X-ray powder diffraction (XPD), X-ray diffraction spectra of ibuprofen samples were obtained using an X-ray diffractometer (Siemens, Germany). The cavity of the metal sample holder was filled with the ground sample powder and then smoothed with a spatula. The spectra of samples were obtained using a scanning rate of $1^{\circ}\ 2\theta\ min^{-1}$ over the range 10° to $42^{\circ}\ 2\theta$.

Measurement of Powder Flow

The flow rate of ibuprofen crystals was determined using a flow meter (Flowdex, Erweka, GDT,

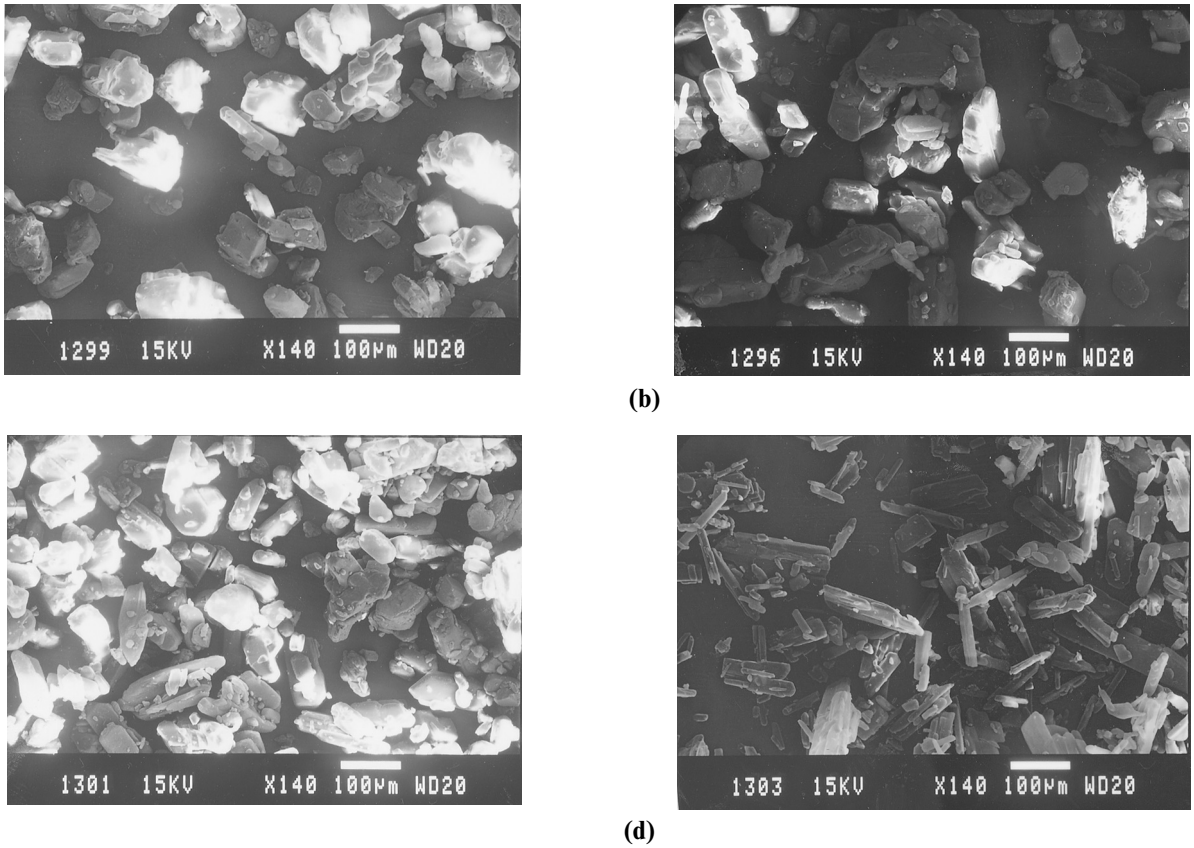

Figure 2. Photomicrographs of ibuprofen crystallized from (a) methanol, (b) ethanol, (c) isopropanol, and (d) hexane (magnification 140×).

Germany). For each sample, 10 g were poured through the funnel of the flow meter; the time required for all the sample to pass from the funnel was automatically measured by the instrument. The results are reported as grams per second.

In addition, the bulk densities of the crystals were determined by gently placing equal weights of each crystal in a volumetric cylinder, and their volumes were measured. Their bulk densities were calculated by dividing the weights by their volume.

Compression

Compression of the crystals was carried out using an instrumented single-punch tableting machine (Korsch, EK-72, Germany) fitted with 10-mm flat-faced punches. The die wall was prelubricated with 4% w/w magnesium stearate in acetone before each compression. Sieved fractions (> 250 μm) of ibuprofen samples were hand filled into the die. Four tablets (400 mg) were produced at compression forces of 5, 10, 15, 20, 25, 30, or 35 kN.

The crushing strength of the tablets was measured using an Erweka tablet hardness tester (Erweka, GDT).

RESULTS AND DISCUSSION

Figure 2 shows the micrographs of ibuprofen crystals obtained from different solvents. The morphology of the crystals obtained may be described as follows: From methanol or ethanol, polyhedral or grainlike crystals were obtained; from isopropanol, we obtained elongated crystals; and from hexane, needlelike crystals were the result.

Marshal and York (7) and Garti and Tibika (8) reported that nitrofurantoin particles crystallized from formic acid were tabular, while those crystallized from a mixture of formic acid and water were needlelike. Davey et al. (9) demonstrated that crystallization of succinic acid from water or isopropanol produced platelike and needlelike habits, respectively. Garekani et al. (5) reported that paracetamol crystallized from water or ethanol produced prismatic polyhedral crystals, while those obtained from a mixture of water and ethanol were thin and platelike. In this study, the influence of crystallization solvent and crystallization method on habit modification of ibuprofen crystals was clearly shown.

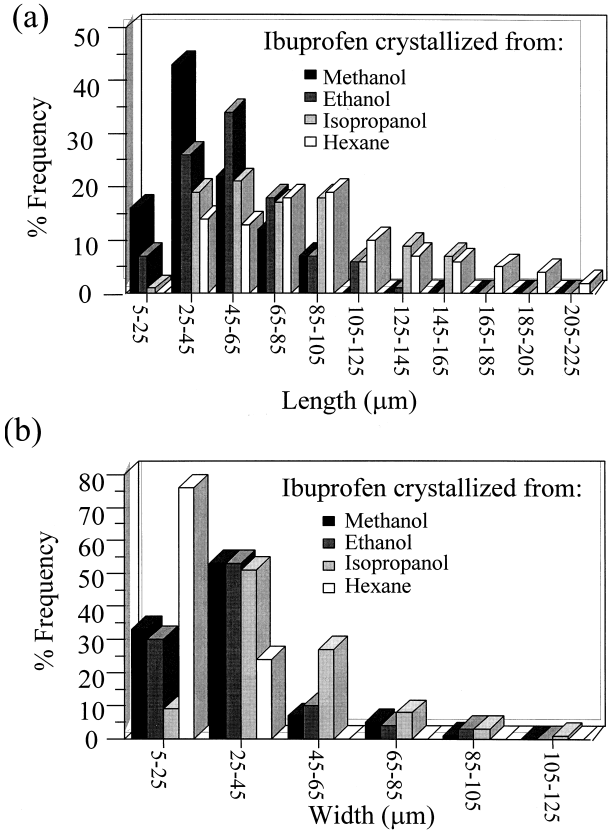

Figure 3. Size distributions of ibuprofen crystallized from different solvents: (a) length of particles; and (b) width of particles.

The solvent influences crystal growth from dissolved drug molecules through various mechanisms. Solvent properties such as its polarity, molecular weight, and interaction with the dissolved drug are factors that may influence the direction in which crystals grow on the nuclei. The formation of different habits of ibuprofen crystals, therefore, may be attributed to interactions of ibuprofen and these crystallization solvents.

Figure 3 shows the particle size distributions of ibuprofen crystals obtained from different solvents. There is a large difference between the size distribution of these samples. This indicates strong inhibition of crystal growth at some crystal faces and inducement to more growth at other faces for the needlelike (from hexane) crystals compared to the polyhedral or grainlike crystals (from ethanol or methanol).

The DSC results (Table 1) indicate that there is no significant difference (Tucky's test, $P < .05$)

Table 1

Melting Point Onset, Melting Peak Temperatures, and Enthalpy of Fusion ΔH_f for Ibuprofen Crystallized from Different Solvents

Crystallized from	Melting Point Onset (°C)	Melting Peak (°C)	ΔH_f (J/g)
Methanol	75.7	77.4	135.6
Ethanol	75.8	77.8	125.9
Isopropanol	75.9	77.8	120.8
Hexane	75.7	77.1	113.7

between the mean values of the melting point onsets and melting points of the ibuprofen samples crystallized from different solvents, indicating that no polymorphic modification occurred during the crystallization in these particles.

The X-ray powder diffraction spectra of samples are presented in Fig. 4. X-ray powder diffraction has been a useful method for determining the presence of polymorphs or crystal habit modifications in drug crystals. In general, for two forms of crystals, when the patterns (i.e., peak positions) are identical, they have the same internal structures,

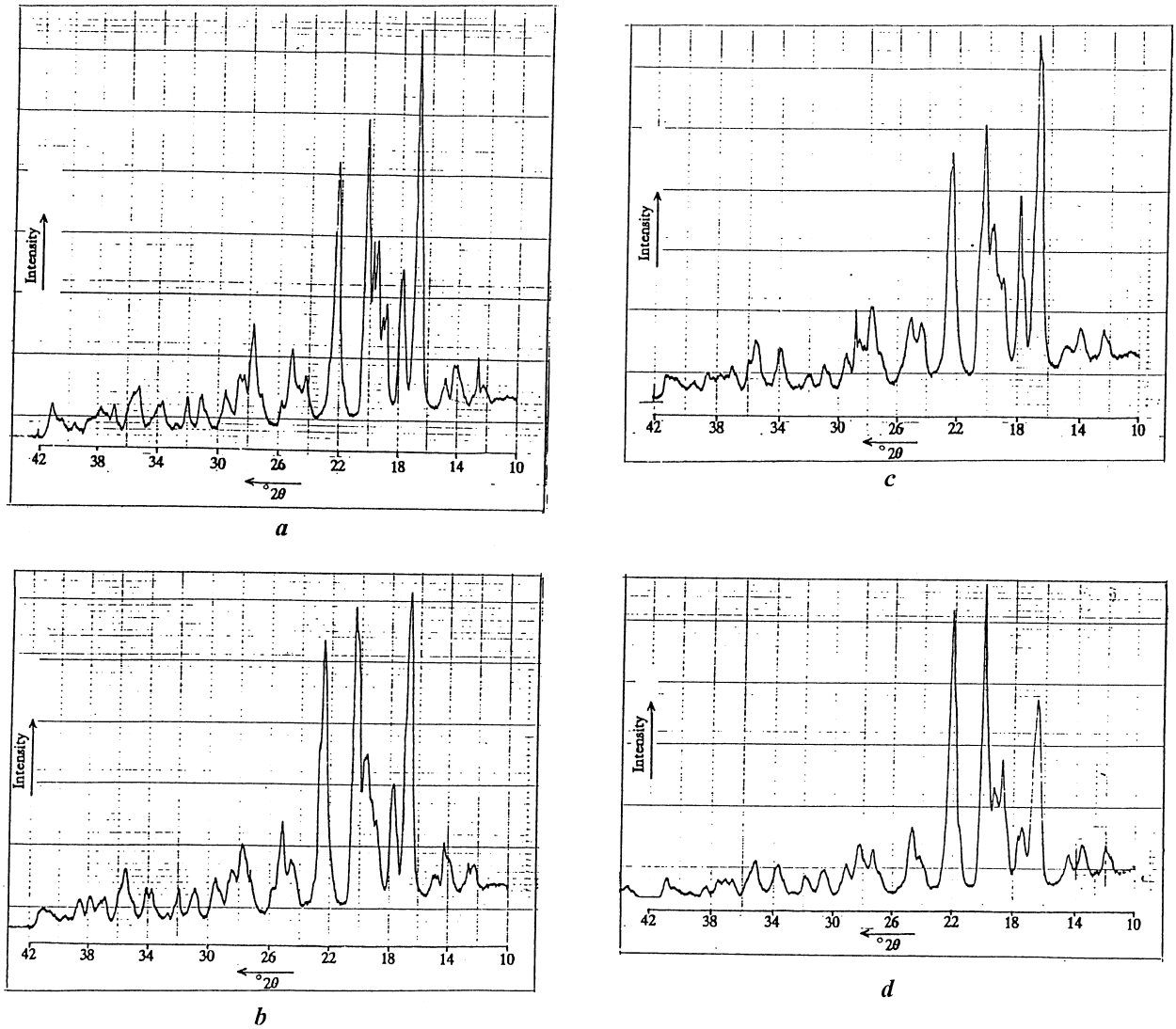

Figure 4. The X-ray powder diffraction spectra of ibuprofen crystallized from (a) methanol, (b) ethanol, (c) hexane, and (d) isopropanol.

Table 2

Bulk Densities and Flow Rates for Ibuprofen Crystallized from Different Solvents

Crystallized from	Bulk Density ± SD (g/ml)	Flow Rate ± SD (g/S)
Methanol	0.45 ± 0.03	4.4 ± 0.5
Ethanol	0.45 ± 0.01	5.2 ± 0.7
Isopropanol	0.42 ± 0.03	3.6 ± 0.6
Hexane	0.29 ± 0.05	0 ± 0

whereas if the patterns are different, then the crystals have different internal structures and are polymorphs (10). Here, all the samples exhibited spectra with similar peak positions (2θ values) (Fig. 4). Therefore, the presence of different polymorphs of ibuprofen in these samples was ruled out. However, the relative intensities of their XPD peaks were modified. This was attributed to the markedly different crystal habits of the samples. Therefore, the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peaks (5,7), or this may be due to differences in the crystal sizes (11).

Table 2 shows the values of bulk densities of ibuprofen samples crystallized from different solvents. The samples crystallized from ethanol and methanol had the highest bulk densities, followed by the samples obtained from isopropanol and those obtained from hexane. These differences may be related to their markedly different crystal habits, leading to different contact points and frictional and cohesive forces between the crystals. These factors affect the sliding of the particles against each other, leading to different packing geometry and thus different bulk densities. Table 2 also shows that crystals obtained from ethanol and methanol exhibited the best flow rate, while those from hexane had the least flow. These results are in agreement with the morphology and bulk density data that polyhedral crystals with higher bulk densities exhibited a better flow rate.

The effect of compression force on the crushing strength of tablets made from ibuprofen crystals is illustrated in Fig. 5. Two-way analysis of variance showed that there were significant differences between the crushing strength of tablets made from

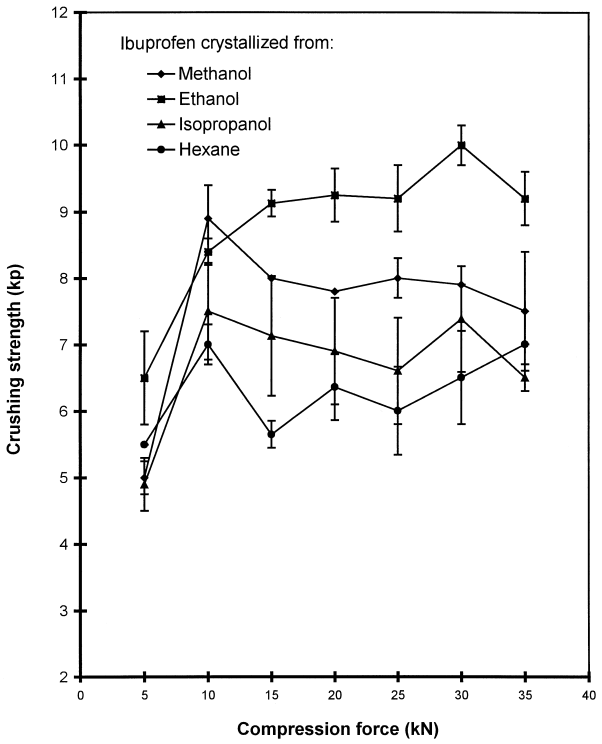

Figure 5. The effect of compression force on the crushing strengths of tablets made from ibuprofen crystallized from different solvents.

different samples of ibuprofen ($P < .05$). The samples obtained from ethanol exhibited the best compression properties, and at each compression force, the tablets had higher crushing strength than tablets made from other samples.

Figure 5 also indicates that, with increasing compression force beyond 10 kN, the crushing strength for all the samples decreased except for the samples obtained from ethanol. This may indicate that ibuprofen crystallized from ethanol underwent more plastic and less elastic deformation during compression than other samples.

It has been reported that poor compressibility of drug crystals can be attributed to the presence of crystal faces that give poor adhesion to other crystals and the absence of the faces that are required for optimal adhesion (12). Here, for the needlelike and grainlike ibuprofen crystals (Fig. 2), the relative abundance of the different faces within the crystals was modified. This can affect the interparticulate bonding between these crystals, resulting

in different compression properties. In a similar study, Garekani et al. (5) reported that thin, plate-like crystals of paracetamol underwent more elastic deformation during compaction than polyhedral crystals.

CONCLUSIONS

Crystallization of ibuprofen from ethanol, methanol, isopropanol, and hexane caused marked modifications to its crystal habit. The samples obtained from ethanol and methanol were polyhedral or grainlike, and those obtained from isopropanol and hexane were elongated and needlelike, respectively. It was shown that these samples were structurally similar, and polymorphic modifications were ruled out.

Crystal habit had a great influence on the mechanical properties of ibuprofen. Samples obtained from ethanol and methanol exhibited the best flow rate. The samples obtained from ethanol also exhibited better compression properties with higher crushing strength than other samples. The samples obtained from hexane showed the worst flow and compression properties.

ACKNOWLEDGMENT

The financial support for this study was obtained from the Vice Chancellor of Research of Mashhad University of Medical Sciences, Iran.

REFERENCES

1. Mullin, J.W. In *Crystallisation*, 3rd Ed.; Butterworths: Oxford, UK, 1993.
2. Huttenrauch, R. Modification of Starting Materials to Improve Tableting Properties. Pharm. Ind. **1983**, *4*, 435–440.
3. York, P. Solid-State Properties of Powders in the Formulation and Processing of Solid Dosage Forms. Int. J. Pharm. **1983**, *14*, 1–28.
4. Marshall, P.V.; York, P. The Compaction Properties of Nitrofurantoin Samples Crystallised from Different Solvents. Int. J. Pharm. **1991**, *67*, 59–65.
5. Garekani, H.A.; Ford, J.L.; Rubinstein, M.H.; Rajabi-Siahboomi, A.R. Formation and Compression Properties of Prismatic Polyhedral and Thin Plate-like Crystals of Paracetamol. Int. J. Pharm. **1999**, *187*, 77–89.
6. Gonda, I.; Abd-El Khalik, A.F.; Britten, A.Z. Solid Forms of Hexamethylmelamine. J. Pharm. Pharmacol. **1985**, *37*, 117P.
7. Marshall, P.V.; York, P. Crystallisation Solvent Induced Solid-State and Particulate Modifications of Nitrofurantoin. Int. J. Pharm. **1989**, *55*, 257–263.
8. Garti, N.; Tibika, F. Habit Modifications of Nitrofurantoin Crystallised from Formic Acid Mixtures. Drug Dev. Ind. Pharm. **1980**, *6*, 379–398.
9. Davey, R.J.; Mullin, J.W.; Whiting, M.J.L. Habit Modification of Succinic Acid Crystals Grown from Different Solvents. J. Cryst. Growth **1982**, *58*, 304–312.
10. Byrn, S.R. In *Solid-State Chemistry of Drugs*; Academic Press: New York, 1982; 29–59.
11. El-Said, Y. Effect of Co-solvents on Water Content and Physical Properties of Acetaminophen Crystallised from Aqueous Solutions. STP Pharma Sci. **1995**, *5*, 232–237.
12. Milosovitch, G. Direct Compression of Tablets. Drug Cosm. Ind. **1963**, *5*, 557–669.
13. Marshall, K. Compression and Consolidation of Powder Solids. In *Theory and Practice of Industrial Pharmacy*, 3rd Ed.; Lachman, L., Liberman, H.A., Kanig, J.L., Eds.; Lea and Febiger: Philadelphia, 1986; 66–89.
14. York, P. Particle Slippage and Rearrangement During Compression of Pharmaceutical Powders. J. Pharm. Pharmacol. **1978**, *30*, 6–10.