MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 7, pp. 739–744, 2003

RESEARCH PAPER

Preparation and Characterization of Glassy Celecoxib

A. R. Paradkar,[1,*] B. Chauhan,[1] S. Yamamura,[2] and A. P. Pawar[1]

[1]Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune, Maharashtra State, India
[2]School of Pharmaceutical Sciences, Toho University, Funabashi, Chiba, Japan

ABSTRACT

Celecoxib, a poorly water-soluble drug, was converted into a glassy state by melt quenching. The properties of glassy celecoxib were studied using infrared (IR) spectroscopy, differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), intrinsic dissolution rate (IDR), and thin-layer-chromatography (TLC). Glass transition occurred at 51.8°C. Infrared spectrum of glass has revealed significant changes due to H-bonding. Celecoxib glass shows around 15 times faster dissolution as compared with the crystalline state. Heckel plot analysis has shown better compressibility in glassy state. Unpulverized glass remained stable for 3 months, whereas after pulverization about 70% crystallinity was gained in 100 hours. Further attempts may be carried out to stabilize the glass.

Key Words: Celecoxib; Glassy state; Crystallization; Degree of crystallinity; Compressibility; X-ray powder diffraction.

INTRODUCTION

Improvement in the solubility of drugs can be achieved by many techniques. Various techniques have been reported for the improvement of drug solubility e.g., micronization, salt formation, and solid dispersion.[1,2] The amorphous state can be achieved by solid dispersion or direct conversion into the glassy state. Glass is an amorphous material formed when the thermal energy of an ensemble of molecules, ions, etc., is removed at a rate that precludes the organization of those particles into a crystal lattice. The glassy or vitreous state of solids offers advantages such as higher solubility, dissolution rate, and sometimes better compression characteristics as compared with its crystalline form.[3] But as it is thermodynamically unstable, due to devitrification during processing and storage, commercial applications of

*Correspondence: A. R. Paradkar, Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune-411038, Maharashtra State, India; Fax: 91-20-543 9383; E-mail: arparadkar@rediffmail.com.

DOI: 10.1081/DDC-120021773
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

the glassy state are limited.[4–8] Thus, the rate of devitrification is an important parameter in the study of stability of glasses. The glassy state is obtained by various techniques such as melt quenching, spray drying, freeze drying, non-solvent precipitation, etc.[3,9,10]

Celecoxib, 4-[5-(4-methyl phenyl)-3-tri fluro methyl-1H-pyrazol-1-yl] benzene sulfonamide, a poorly water-soluble, anti-inflammatory drug, has been transformed to the glassy state by melt quenching. The glassy state has been characterized by infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and x-ray powder diffraction (XRPD) techniques.[11,12] Comparative evaluation of the glass and crystalline forms was carried out for intrinsic dissolution rate and compression properties by Heckel plot analysis. Crystallization of the pulverized glassy state was carried out by x-ray diffractometry.[11]

MATERIALS

Celecoxib was kindly provided by Lupin Laboratories, Pune, India. Sodium hydroxide pellets were purchased from Merck, Mumbai, India.

METHODS

Preparation of Glassy Celecoxib

Celecoxib powder was melted in an aluminum pan by heating on a paraffin oil bath at 170°C, and the melt was solidified by cooling on an ice bath. For dissolution studies, a matrix of glassy celecoxib was prepared by allowing the melt to cool down to room temperature in a mold made up of aluminum with an internal diameter of 1.3 cm. The solidified melt formed was placed in a dessicator over silica until use.

Characterization of Glass

Thin-Layer Chromatography (TLC)

The chemical stability of solidified melt was studied using TLC. Celecoxib samples were dissolved in acetonitrile and spotted on reversed-silica gel plate, which was developed with a solvent system [aqueous potassium dihydrogen phosphate (pH 4.8; 0.01 M)-acetonitrile (45:55)] and detected by iodine vapor.

Differential Scanning Calorimetry (DSC)

A Mettler Toledo DSC 821 (Mettler-Toledo, Switzerland) equipped with intracooler, a refrigerated cooling system, was used. Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through the DSC cell at a flow rate of 50 mL/min and 100 mL/min through the cooling unit. The sample (5–10 mg) was hermetically sealed in an aluminum pan and the heating rate was 20°C/min.

X-Ray Powder Diffraction (XRPD)

The x-ray powder diffraction patterns of powdered samples were recorded using a Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α—radiation (1.542 Å) and analyzed between 2–50° (2θ). The voltage and current used were 30 kV and 30 mA respectively. The range was 5×10^3 cycles/s and the chart speed was kept at 100 mm/2θ.

Infrared Spectroscopy

Fourier transform infrared (FT-IR) spectra were obtained on a Jasco V5300 (Jasco, Japan) FT-IR system using the KBr disk method and were recorded over the wave number range of 3600 to 600 cm^{-1}.

Dissolution Studies

The intrinsic dissolution rate (IDR) was determined using U.S. Pharmacopeia (USP) 24 type II dissolution apparatus (Electrolab TDT-06P, Mumbai, India). Celecoxib powder was compressed using a KBr hydraulic press at 3 ton in a stainless steel die with an internal diameter of 1.3 cm. Celecoxib glass for IDR study was obtained by cooling the melt directly in the die. The die containing glassy matrix and compacted powder was placed at the bottom of the dissolution vessel containing 900 mL 0.1 N NaOH maintained at 37 ± 0.5°C and stirred with a paddle at 100 rpm. Samples were collected, filtered through Whatman filter paper-41, and the concentration of celecoxib was determined spectrophotometrically at 251.2 nm using Jasco V500 spectrophotometer.

Heckel Plot Studies

The crystalline and glassy powders (400 ± 5 mg) were compacted at 0.5, 1.0, 2.0, 3.0, 4.0, and 5 tons using a 1.3 cm flat-faced punch-and-die set for 60 sec. The compacts were stored in a desiccator over silica gel for 24 hours to enable elastic recovery to occur. Compacts of zero porosity were obtained by compressing the powder at 7 tons.[13] The results were treated using the Heckel equation to obtain mean yield pressure (MYP).

$$\ln\{1/(1-D)\} = kP + A \quad (1)$$

where k and A are constants and D is the density of the powder compact at pressure P. The mean yield pressure is the reciprocal of K.

Crystallization of Glass

A mass of glassy celecoxib was pulverized in a mortar, and the 60–100 mesh fraction was collected using standard sieves and stored at room temperature in a desiccator over silica gel for various storage times. The degree of crystallization of celecoxib was evaluated from the change of scattering pattern by Herman's method,[14,15] assuming the existence of proportionality between the observed integral diffraction intensity and the crystalline fraction, and between the amorphous intensity and amorphous fraction. The integral intensities were obtained by cutting and then weighing the diffraction pattern measured in the range of 2–50° (2θ). Since the plot of the integral diffraction intensities from crystalline region against whole scattering intensity (the total intensity from both crystalline and amorphous regions) was constant, the corrections for the Lorentz factor and polarization factor were not required. The linear relation also indicates that scattering intensity from crystalline fraction and amorphous fraction can be corrected by the regression line without internal standard material.

RESULTS AND DISCUSSION

The solidified melt of celecoxib was a transparent and brittle glassy mass. The TLC of crystalline and glass obtained by melt quenching has shown a single spot with $R_f = 0.6$, indicating that decomposition did not occur during the process of glass formation.

Thermal behavior of celecoxib was characterized using DSC studies (Fig. 1). The DSC curve of crystalline celecoxib (Fig. 1A) as shown in a single endotherm at 163°C ($\Delta H = -91.25 \pm 5.9$ J/g) is ascribed to drug melting. Glassy celecoxib (Fig. 1B) exhibits a small jump in heat capacity at 51.8°C, identified as a glass transition (T_g), an exothermic peak with crystallization at 105°C ($\Delta H = 61.89 \pm 4.5$ J/g) and an endothermic peak with melting of crystallized celecoxib at 163.9°C ($\Delta H = -86.97 \pm 3.5$ J/g). To confirm T_g and crystallization temperature, additional DSC curves were obtained with different thermal cycles. The DSC curve of a glassy sample shows crystallization exotherm at 105°C when heated up to 130°C (Fig. 1C). The same sample when cooled to 25°C and reheated to 130°C did not show T_g and exotherm (Fig. 1D). This confirmed that crystallization of glassy celecoxib occurred at 105°C. It was also confirmed by heating the glassy sample up to 80°C (Fig. 1E), cooling to 25°C and reheating up to 80°C, showing T_g at 51.8°C (Fig. 1F). It suggests that the glassy state was maintained when heated up to 80°C, which is below the crystallization temperature (105°C).

A halo pattern was seen in XRPD of glassy celecoxib (Fig. 2B). It showed broad and diffuse

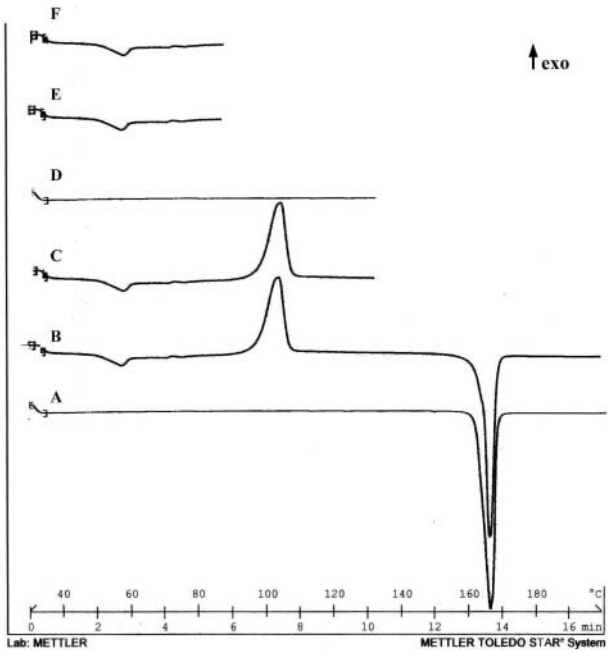

Figure 1. Thermal behavior of crystalline and amorphous celecoxib. (A) DSC curve of crystalline celecoxib; (B) DSC curve of glassy celecoxib; (C) amorphous to crystalline transformation of glassy celecoxib at 105°C; (D) DSC curve of glassy celecoxib obtained after cooling the sample heated to 130°C; (E) and (F) DSC curves of glassy celecoxib between 25°C to 80°C.

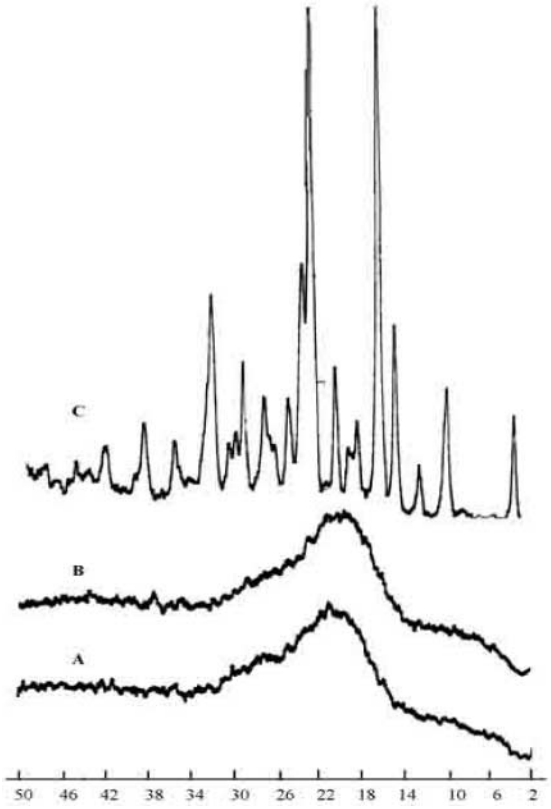

Figure 2. X-ray powder diffraction pattern of crystalline and glassy celecoxib. (A) 3 month storage at room temperature without pulverizing; (B) glass; and (C) crystalline.

maxima due to the relatively random arrangement of the constituent molecules, which produced poorly coherent scatters. These patterns were quite distinct from those produced by the crystalline celecoxib, which gave sharp and defined diffraction peaks.

In IR spectra, absorption peaks characteristic of celecoxib are -NH stretching and sulphonamide at 3342 and 3105 cm^{-1}. The sulphonyl SO_2 group shows strong absorption bands at 1330 cm^{-1} for asymmetric stretching, at 1160 cm^{-1} for the symmetric, and at 1275 and 1230 cm^{-1} assigned to $-CF_3$. Infrared spectra of glassy celecoxib (Fig. 3) show significant differences in intensities and slight changes in the position of these peaks. Peaks at 3105 cm^{-1} and 1330 cm^{-1} exhibited decreased intensity due to formation of glass. Decrease in the intensity of peak of sulphonamide SO_2 may be due to hydrogen bonding, which is considered responsible for glass formation by preventing crystallization.[16]

Dissolution studies were carried out in 0.1 N NaOH so as to maintain sink conditions.[17] Dissolution profiles of matrices of crystalline and glassy

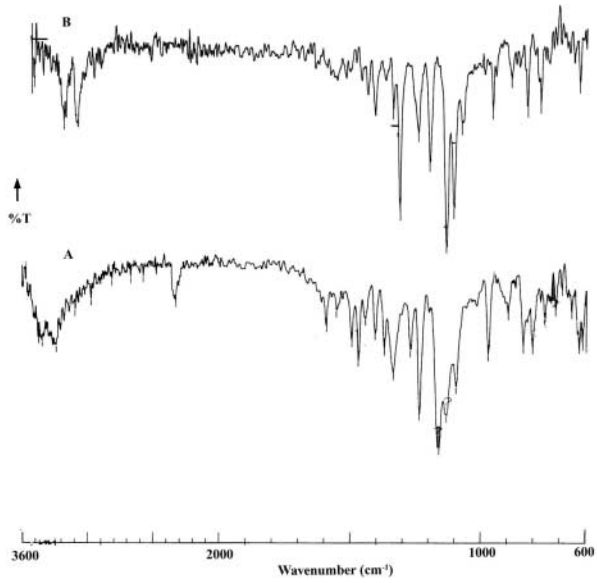

Figure 3. FT-IR spectra of crystalline and glassy celecoxib. (A) crystalline; (B) glassy.

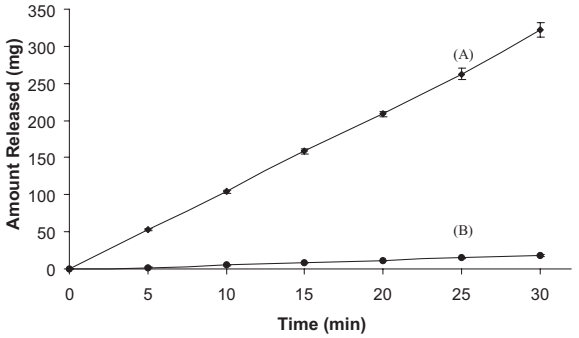

Figure 4. Dissolution curves of crystalline and glassy celecoxib. (A) crystalline; (B) glassy.

celecoxib in 0.1 N NaOH are shown in Fig. 4. A marked increase in the intrinsic dissolution rate of glassy celecoxib (7.26 mg/cm^2 min) over crystalline celecoxib (0.478 mg/cm^2 min) indicates conversion to the glassy state. Thus, the glassy state shows about 15 times IDR compared with the crystalline state. It was also observed that 10 minutes from the onset of dissolution, the surface of glassy celecoxib started to become opaque and gradually turned white. Fukuoka et al.,[11] reported devitrification of glass during dissolution, where the rate of devitrification was dependent on composition of dissolution medium. But in the present study devitrification of glassy celecoxib matrix during dissolution did not significantly affect the rate of dissolution.

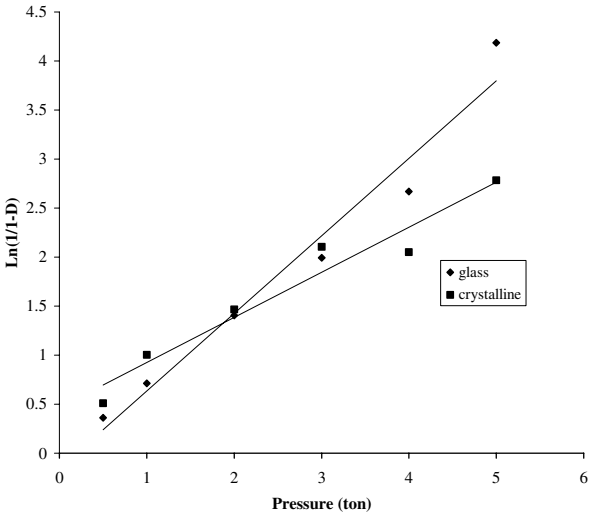

Figure 5. Heckel plot of crystalline and glassy celecoxib.

The Heckel plots of crystalline and glassy celecoxib are shown in Fig. 5. The mean yield pressure (MYP) for crystalline and glassy celecoxib were 2.13 and 1.26 tons respectively, which indicates better compressibility of glassy form. High MYP of celecoxib shows its poor compressibility. Tensile strength of the compacts (4.8 kg/cm^2) did not show any significant differences, and neither was affected by pressure. Lerk[18] reported significant differences in the compression behavior of crystalline and amorphous lactose, and differences in the tensile strength of their compacts was attributed to differences in the moisture content. The compression mechanism of celecoxib cannot be completely elucidated in the presence study.

Figure 6 shows the variation of x-ray diffraction patterns of pulverized glassy celecoxib during storage. The plot of integral intensities due to scattering from crystalline ($\int Ic(2\theta)\,d\theta$) and amorphous regions ($\int Ia(2\theta)\,d\theta$) is shown in Fig. 7. As a linear relationship was observed, the corrections for the Lorentz factor and polarization factor were not required. The slope was calculated to be -0.8329 by the least square method, and the degree of crystallinity (X_{cr}) was calculated using the following equation:

$$X_{cr} = \frac{\int Ic(2\theta)\,d\theta}{\int Ic(2\theta)\,d\theta + (1/k)\int Ia(2\theta)\,d\theta} \qquad (2)$$

Changes in the degree of crystallinity of glassy celecoxib during storage is shown in Fig. 8. The unpulverized celecoxib glass was found to be stable and was amorphous for at least 3 months without pulverizing (Fig. 2A). Pulverized glass, however, was unstable, and crystallization started within 24 hours. It took about 100 hours to reach maximum crystallization, and the degree of crystallinity was found to be about 70%.

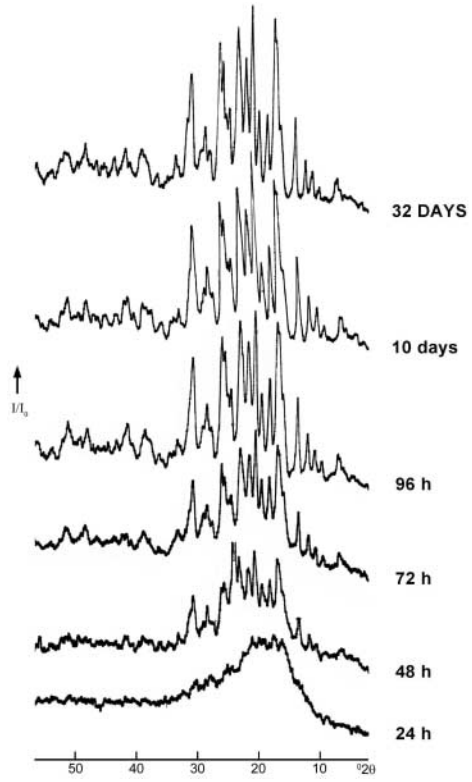

Figure 6. The variation of x-ray powder diffraction pattern of pulverized glassy celecoxib. (A) 24 h; (B) 48 h; (C) 72 h; (D) 96 h; (E) 10 d; and (F) 32 d.

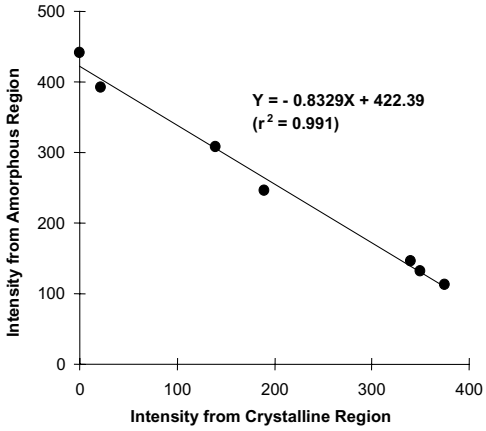

Figure 7. The regression line for the scattering intensities from crystalline and amorphous region of celecoxib samples with different crystallinities obtained.

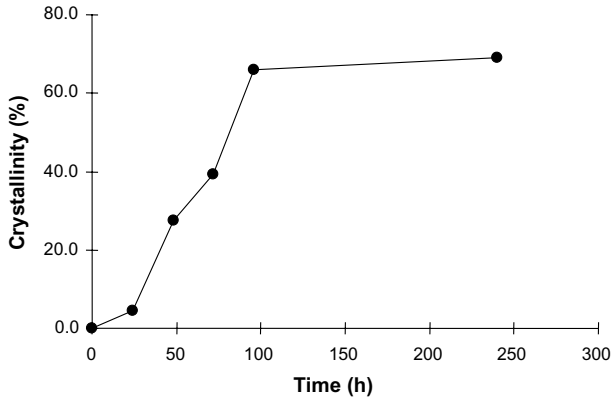

Figure 8. Shows change in degree of crystallinity on standing in room temperature.

CONCLUSIONS

In the present study glassy celecoxib was obtained by melt quenching. The glass has T_g 51.8°C, which becomes crystallized at 105°C. The glassy state exhibited higher IDR and compressibility as compared with crystalline form. Unpulverized celecoxib glass was found to be stable for 3 months. Further attempts are required to stabilize the glass.

ACKNOWLEDGMENTS

The authors are thankful to Lupin Laboratories, India for providing gift sample of celecoxib. Bhaskar Chauhan is thankful to All India Council for Technical Education (AICTE), New Delhi, India for providing JRF.

REFERENCES

1. Broman, E.; Khoo, C.; Taylor, L.S. A comparison of alternative polymer excipients and processing methods for making solid dispersion of a poorly water soluble drug. Int. J. Pharm. **2001**, *222*, 139–151.
2. Leuner, C.; Dressman, J. Improving drug solubility for oral delivery using solid dispersion. Eur. J. Pharm. Biopharm. **2000**, *50*, 47–60.
3. Lian, Y. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Ad. Drug Del. Rev. **2001**, *48*, 27–42.
4. Fukuoka, E.; Makita, M.; Yamamura, S. Glassy state of pharmaceuticals II: thermal properties and stability of glassy pharmaceuticals and their binary glass systems. Chem. Pharm. Bull. **1989**, *37*, 1047–1057.
5. Sric, S.; Kerc, J.; Urleb, U.; Zupancic, I.; Lahajnar, G.; Kofler, B.; Smid-Korbar, J. Investigation of felodipine polymorphism and its glassy state. Int. J. Pharm. **1992**, *87*, 1–10.
6. Yamaguchi, T.; Nishimura, M.; Okamata, R.; Takeuchi, T.; Yamamoto, K. Chem. Phar. Bull. **1993**, *41*, 1812–1816.
7. Hancock, B.C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceuticals. J. Pharm. Sci. **1997**, *86*, 1–12.
8. Craig, D.Q.M.; Royall, P.G.; Kett, V.L.; Hopton, M.L. The relevance of the amorphous state to pharmaceutical dosage forms: glassy drugs and freeze dried systems. Int. J. Pharm. **1999**, *2*, 179–207.
9. Yamaguchi, T.; Nishimura, M.; Okamata, R.; Takeuchi, T.; Yamamoto, K. Glass formation of 4″-*O*-(4-methoxy phenyl) acetylosin and physicochemical stability of amorphous solid. Int. J. Pharm. **1992**, *85*, 87–96.
10. Yonemochi, E.; Kitahara, S.; Maeda, S.; Yamamura, S.; Oguchi, T.; Yamamoto, K. Physicochemical properties of amorphous clarithromycin obtained by spray drying & grinding. Eur. J. Pharm. Sci. **1999**, *7*, 331–338.
11. Fukuoka, E.; Makita, M.; Yamamura, S. Some physicochemical properties of glassy indomethacin. Chem. Pharm. Bull. **1986**, *34*, 4314–4321.
12. Hassan, M.A.; Najib, N.M.; Suleiman, M.S. Investigation of glebenclamide glass. Int. J. Pharm. **1991**, *67*, 131–137.
13. Strickland, W.A.; Busse, L.W.; Higuchi, T. J. Am. Pharm. Assoc. **1956**, *45*, 482.
14. Hermans, P.H.; Weidinger, A. Quantitative X-ray investigations on the crystallinty of cellulose fibres. J. App. Phy. **1948**, *19*, 491–506.
15. Bontea, D.; Caruntu, G.; Aelenei, N.J. The characterization of some silylcellulose derivatives by X-RD macromol. Sci. Pure Appl. Chem. **2000**, *A37*, 395–405.
16. Fox, D.; Labes, M.M.; Wiessberger, A. *Physics and Chemistry of the Organic Solid State*; Interscience: New York, 1963; 572 pp.
17. Paradkar, A.R.; Pawar, A.P.; Chordiya, J.K.; Patil, V.B.; Ketkar, A.R. Spherical crystallization of celecoxib. Drug. Dev. Ind. Pharm. **2002**, *28*, 1213–1220.
18. Lerk, C.F. Consolidation and compaction of lactose. Drug Dev. Ind. Pharm. **1993**, *19*, 2359.