Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 321 (2006) 27–34
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Crystal modification of dipyridamole using different solvents and crystallization conditions

R. Adhiyaman [a,1], Sanat Kumar Basu [b,*]

[a] *Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India*
[b] *Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India*

Received 21 March 2005; received in revised form 10 April 2006; accepted 17 April 2006
Available online 13 May 2006

Abstract

Dipyridamole crystals having different types of habits, improved dissolution rate were prepared by recrystallization from selected solvents, such as acetonitrile, benzene and methanol (Method I); crystals have also been made by solvent change using methanolic solution of dipyridamole in the presence of 2% solutions of Tween-80, Povidone K_{30} and polyethylene glycol (PEG) 4000 (Method II). Scanning electron microscopy, X-ray powder diffractometry, IR spectrometry and differential scanning calorimetry were used to investigate the physicochemical characteristics of the crystals. The comparative dissolution behavior of the newly developed crystals and that of the untreated dipyridamole were also studied. It was found that the newly developed crystals were different from each other with respect to physical properties but are chemically identical. The crystals, obtained (Method I) from benzene and acetonitrile, produced needle shaped crystals and that obtained from methanol produced rectangular shaped crystals. But the crystals obtained (Method II) with the methanolic solution of the drug in the presence of Tween-80, Povidone K_{30} and PEG-4000 produced smooth needle shaped crystals. X-ray diffraction spectra and differential scanning calorimetry study of the newly developed crystals, clearly indicate that dipyridamole exist in different crystal modification. The dissolution rate of newly developed crystals was found to be greater than the pure drug dipyridamole. Stability studies at 40 °C (75% RH) for 1 month for the modified crystals as well as the pure drug did show some changes in the XRD and DSC but not in IR studies.

Keywords: Dipyridamole; Recrystallization; Physicochemical characterization

1. Introduction

Different physiological and formulation factors are responsible for the bioavailability of drug from the dosage form. One of the most important physical factors, which affect the bioavailability and therapeutic efficacy of drug, is the existence of active ingredients in various crystal forms having different internal structure and physical properties (Kapoor et al., 1998). The different crystal form of a drug have different physicochemical characteristics, namely crystal shape, crystal size, melting point, density, flow properties solubility pattern, dissolution characteristics and XRD pattern, though they are chemically identical. A physical form having improved dissolution rate and solubility is useful for improving the bioavailability of a drug (Burt and Mitchell, 1980; Watanable et al., 1982). The crystal habit is an important variable in pharmaceutical manufacturing, where some factors, such as the polarity of crystallization solvent and the presence of impurities in the solvent, affect crystallization (Chow et al., 1985; Femi-Oyewo and Spring, 1994; Garekani et al., 2000). Among them, solvent strongly affects the habit of crystalline materials; however, the role-played by solvent interactions in enhancing or inhibiting crystal growth is still not completely understood (Lahra and Leiserowitz, 2001). The drug dipyridamole used herein is practically insoluble in water. Its main use in therapy as antiplatelet aggregating and peripheral vasodilating effect is well known. But the water insolubility and the poor bioavailability are the limitations of its effective use clinically. Keeping this in view, crystal modification of dipyridamole has been undertaken to improve dissolution and bioavailability. Dipyridamole is a derivative of 1,3,5,7-tetra azanaphthalene and used mainly for cardiovascular diseases for the above-mentioned purposes. It has been recrystallized

* Corresponding author.
E-mail addresses: eskebee@yahoo.com (R. Adhiyaman), basusanat_kumar@hotmail.com (S.K. Basu).
[1] Present address: J.S.S. College of Pharmacy, The Rocklands, Ootacamund-643001, Tamil Nadu, India.

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.

from selected solvents and solvent system. The newly developed dipyridamole crystals were characterized by some physicochemical approaches.

2. Materials and methods

2.1. Materials

Dipyridamole was obtained as generous gift from German Remedies (Mumbai, India). The solvents used for the present work were acetone, benzene, methanol, obtained from Ranbaxy Chemical Laboratories (S.A.S. Nagar, India) and Tween-80, Povidone K_{30} and polyethylene glycol (PEG) 4000 were obtained from SDS Chemical Limited (Boisar, India).

2.2. Preparation of dipyridamole crystals

Two different methods used in this study to observe the effect of solvents on the development of crystal habits in the changed environment are given below.

2.2.1. Method I

One gram of dipyridamole was dissolved separately in 50 ml of selected solvents in a conical flask. The solution was heated at the boiling point of the respective solvents and filtered, concentrated and the solution was left at room temperature (28–30 °C) until the solvent was completely evaporated. The crystals were further dried under vacuum at room temperature and stored in appropriate airtight container for further use.

2.2.2. Method II

One gram of dipyridamole was dissolved in 40 ml of methanol in a conical flask and the solution was heated and filtered. The resultant solution was concentrated at 60 °C and then cooled down at room temperature (28–30 °C). The clear solution, thus obtained, was rapidly added to equal volume of cold water (5 °C) containing 2% solution of Tween-80, PVP K_{30} and PEG-4000, separately under agitation by means of a glass rod and then left for 1 h at 10–15 °C. The crystals were then recovered by filtration under vacuum using a sintered glass funnel. They were then kept in airtight container for further use.

2.3. Stability studies

One month's accelerated stability test was carried out for each sample after preparation, when the crystals were kept in humidity chambers (75% RH) and at a temperature 40 °C and the physicochemical changes of the crystals as observed are compared with that of the drug dipyridamole under identical conditions. The results are summarized in Figs. 9 (XRD) and 10 (DSC), respectively.

2.4. Scanning electron microscopy

Electron micrograph of crystals was obtained using a scanning electron microscope (JEOL JSM—5200) operating stub (with double side adhesive tape) and coated under vacuum with gold in an argon atmosphere prior to observation.

2.5. X-ray powder diffraction

The cavity of the metal sample holder of X-ray diffractometer was filled with ground sample powder and then smoothed out with a spatula. X-ray diffraction pattern of dipyridamole crystals were obtained using the X-ray diffractometer (Rich Seifert Model 3000P) at 30 kV, 30 mA over a range of 10–100 2θ, using Cu Kα radiation wavelength 1.5405 Å.

2.6. Infrared spectroscopy

The spectra were recorded on an IR spectrophotometer (PERKIN-ELMER USA MODEL—248), after respective samples were mixed with dried KBr powder and compressed to a 12 mm disc by a hydraulic press at 10 tonnes compression for 30 s.

2.7. Thermal analysis

Differential scanning calorimetry (DSC) of the samples, 10 mg, was carried out using a thermal analysis system (METTLER TA 4000 System). Calibration with standard was undertaken prior to subjecting the samples, which were heated at 10 °C/min in an aluminum pan under a nitrogen atmosphere and a similar empty pan was used as the reference. The instrument automatically calculated onsets of melting points and enthalpy of fusion.

2.8. Dissolution studies

Dipyridamole and its crystals, 25 mg in each case were accurately weighed and dissolution profile of the drug was determined in a USP Type II Dissolution test apparatus at 37 °C, with basket (100 mesh) with a stirring speed of 50 rpm. The dissolution medium was 600 ml of phosphate buffer pH 4.0, I.P. (Indian Pharmacopoeia). Samples were withdrawn from the dissolution vessels at selected time intervals and analyzed for dipyridamole content at 285 nm on a UV spectrophotometer (BECKMAN-UM-64). The results are shown as the graphical plots in Figs. 7 and 8, respectively.

3. Results and discussion

3.1. Morphology of crystals

Fig. 1 shows the scanning electron micrographs (SEM) of untreated and recrystallized dipyridamole from different solvents under solvent evaporation method (Method I). It is clear from the figure that the untreated dipyridamole is having small irregular needle shaped crystals (Fig. 1d), whereas the crystals obtained from acetonitrile is needle shaped (Fig. 1c) and that from benzene is rod shaped (Fig. 1b). Recrystallization of dipyri-

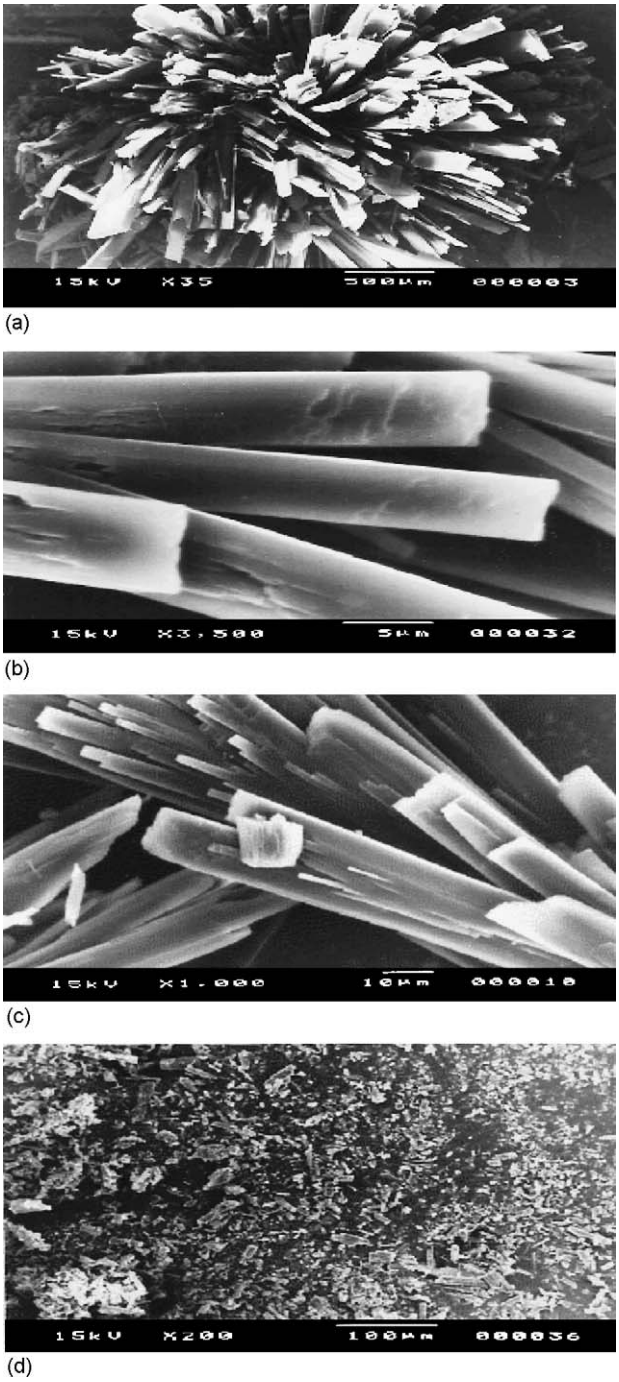

Fig. 1. Scanning electron micrographs of dipyridamole recrystallized from (a) methanol, (b) benzene, (c) acetonitrile and (d) untreated dipyridamole.

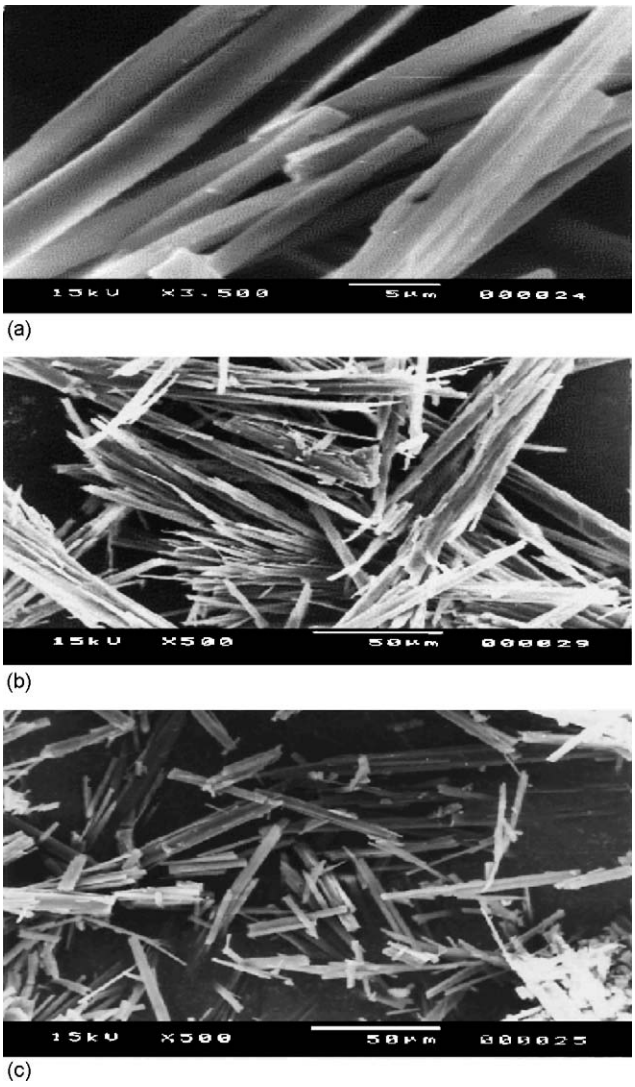

Fig. 2. Scanning electron micrographs of dipyridamole recrystallized from methanol with 2% solutions of (a) Tween-80 (SCT); (b) PEG-4000 (SCPEG); (c) $PVPK_{30}$ (SCPVP).

rectangular needle shaped crystals (Fig. 1a), while using solvent change method (Method II), the shape of crystals changes to fine needles (Fig. 2a–c). The results also showed that the size of crystals produced from Methods I and II are somewhat different from the size of untreated dipyridamole and follows the order, i.e. Method I > Method II (compare the magnification of the SEM in Figs. 1 and 2). Therefore, it can be concluded that cooling rate decreases the crystal size due to incomplete growth

3.2. X-ray diffraction

To obtain information on the physicochemical characteristics of the prepared crystals, X-ray powder diffraction measurements were conducted.

XRD spectra for all crystals are presented in Figs. 3 and 4. In the powder diffractogram sharp peak at diffraction angle (2θ) 30.04, 20.74, 20.81, 12.33, 17.45, 10.25, and 20.93 were obtained in case of drug dipyridamole and the modified crystals obtained from methanol, benzene, acetonitrile, Tween-80, PEG-400, PVP K_{30}, respectively. The presences of these sharp peaks are clearly evident in the comparative diffractogram presented in Figs. 3 and 4 and the data recorded therein. From the data recorded, it is clearly evident that there is significant difference in the entire diffraction pattern or *d*-spacing values between treated and untreated dipyridamole samples. The intensity of the peak in methanol is the highest than that of all other modified

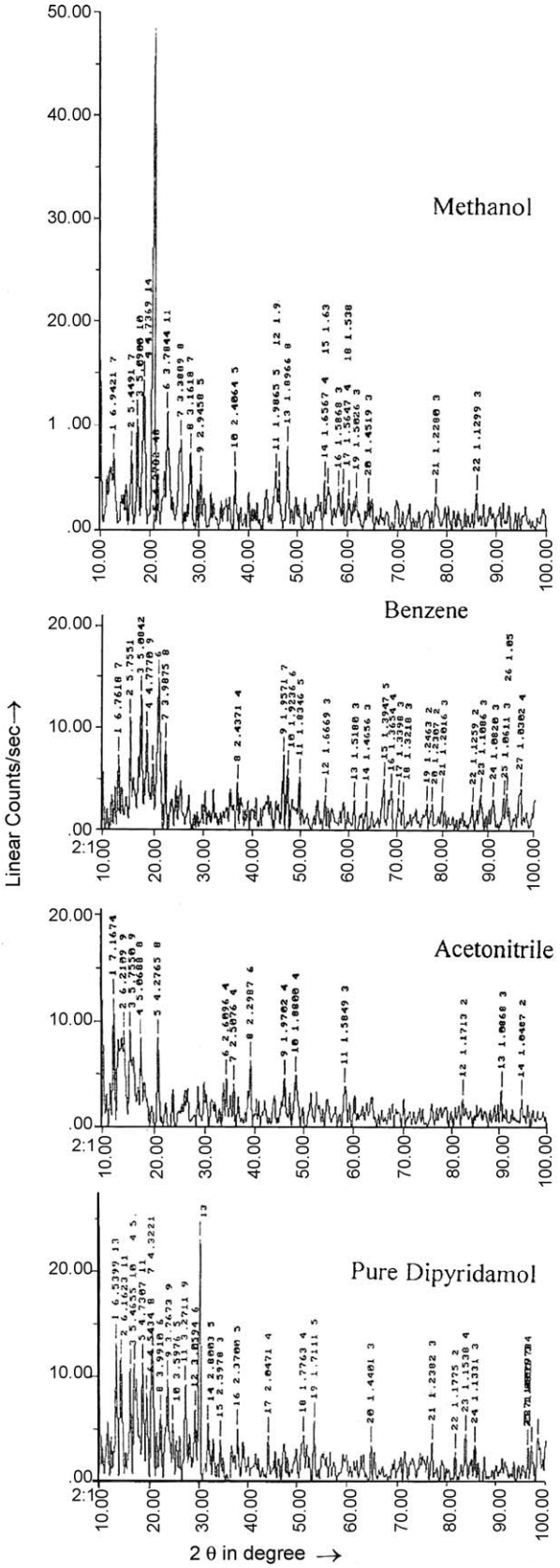

Fig. 3. X-ray powder diffraction pattern of pure dipyridamole and dipyridamole recrystallized from methanol; benzene; acetonitrile.

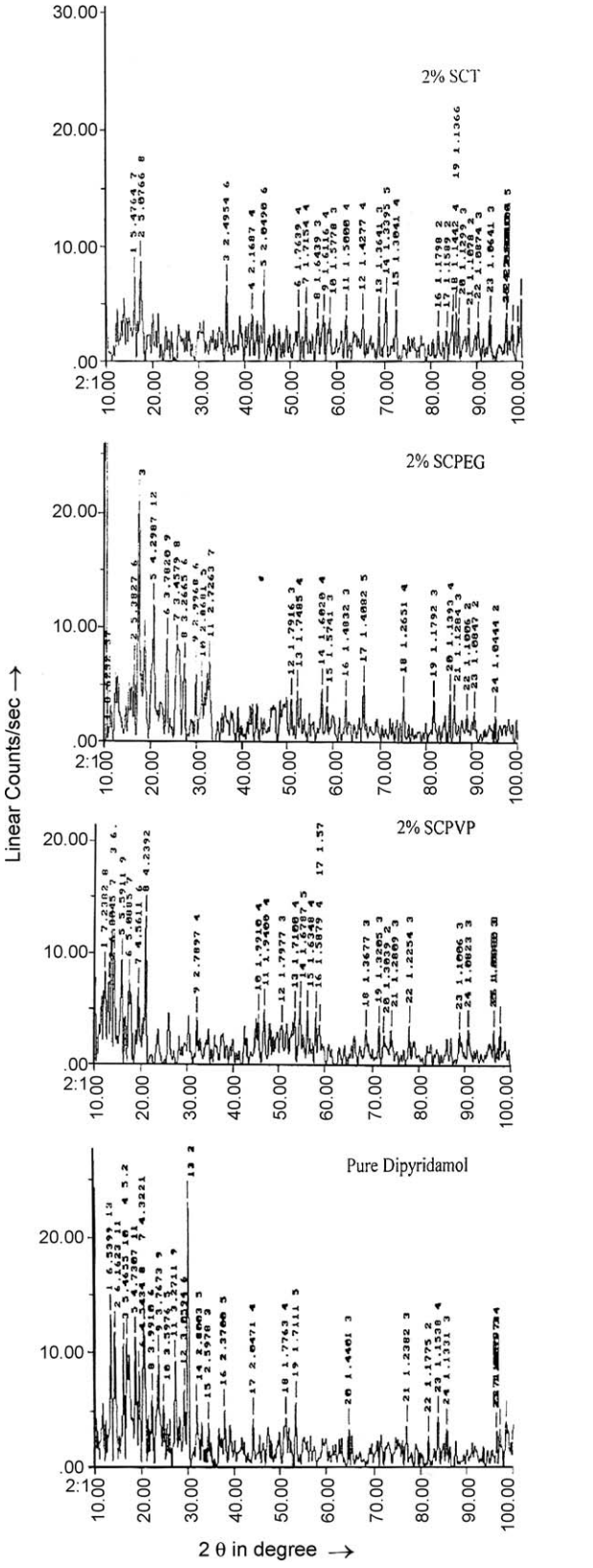

Fig. 4. X-ray powder diffraction pattern of pure dipyridamole and dipyridamole recrystallized from methanol with 2% solutions of Tween-80 (SCT); PEG-4000 (SCPEG); PVP K_{30} (SCPVP).

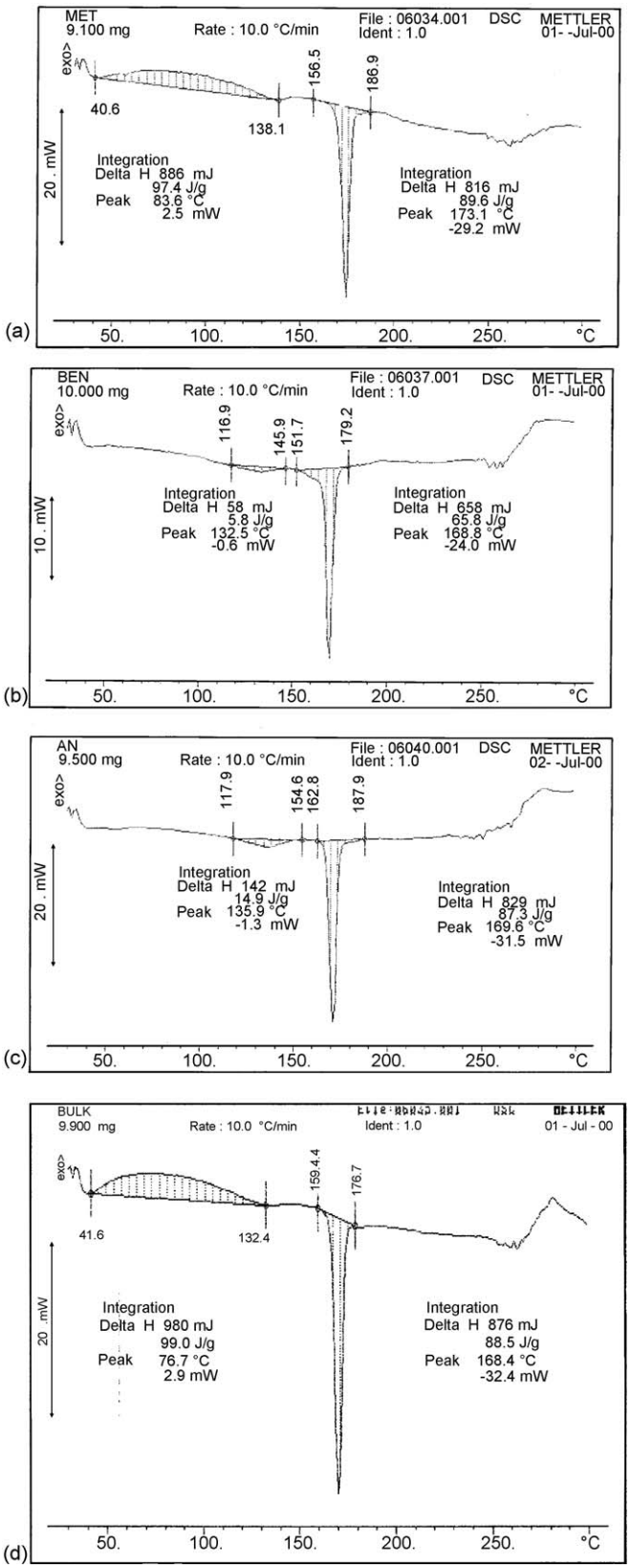

Fig. 5. Differential scanning calorimetric thermographs of dipyridamole recrystalized from (a) methanol; (b) benzene; (c) acetonitrile; (d) untreated dipyridamole.

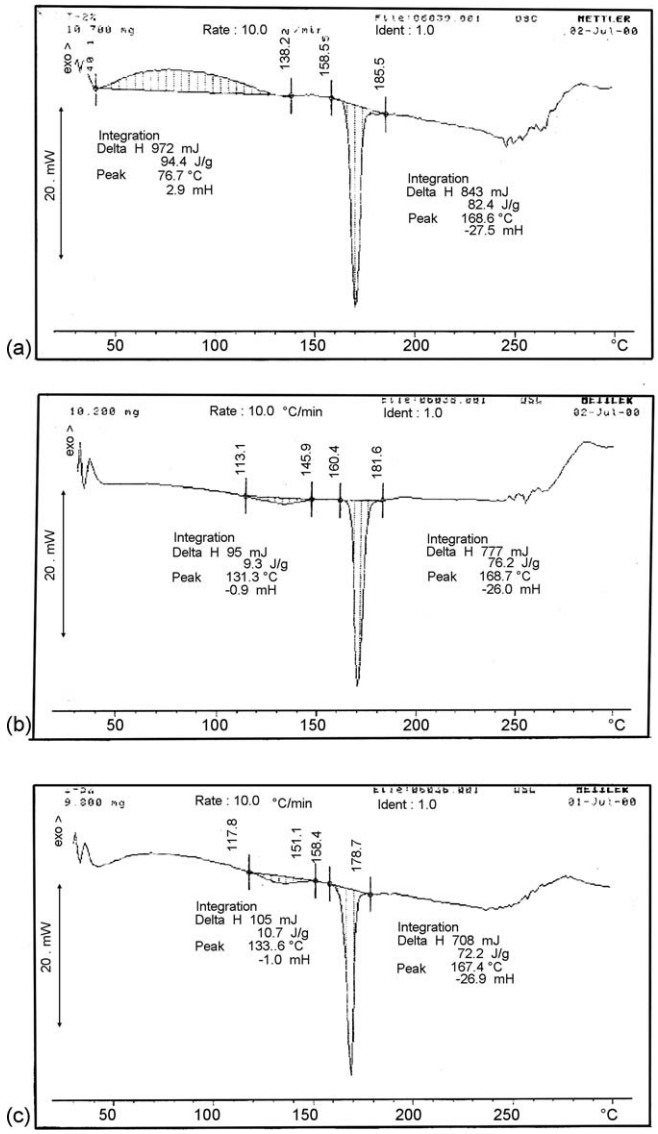

Fig. 6. Differential Scanning Calorimetric thermographs of dipyridamole recrystalized from methanol with 2% solution of (a) Tween-80(SCT); (b) PEG-4000 (SCPEG); (c) PVP K_{30} (SCPVP).

perfection in this condition of crystallization (Nokhodchi et al., 2003).

3.3. Infrared spectroscopy

The spectra of all modified crystals were identical and the main absorption bands of dipyridamole appeared in all of the spectra. This indicates that there were no difference between the internal structure and conformations of these samples, because these were not associated with changes at molecular level.

3.4. Thermal analysis

The DSC data for drug dipyridamole (untreated) and the modified crystals are shown in Figs. 5 and 6. It should be noted that the DSC thermo grams (Figs. 5 and 6) of all modified crys-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.