REVIEW ARTICLE

Accepted 5 November 2003
Revised 21 August 2003
Received 20 February 2003
Indian J. Pharm. Sci., 2004, 66(2): 142-147

Effect of Solvent and Polymer Additives on Crystallization

S. MALLICK*
Division of Formulation Development and Drug Delivery Systems,
Department of Pharmaceutics, Seemanta Institute of Pharmaceutical Sciences,
Jharpokharia, Mayurbhanj-757086.

A particular crystalline form of a drug is important in the preformulation study of bulk lots for the development of dosage form. Suspension often destabilizes due to particle aggregation and particle growth during storage. Inhibition of crystal growth is possible by addition of polymer that resists the approach of the drug molecules from the solution to the crystal surface. Crystal habit of a particular material influences flowability and compression behaviour during formulation of solid dosage forms. It also has a great importance in suspension stability and dissolution rate that directly affect absorption and bioavailability. Changing crystallizing conditions, such as solvent change and polymer presence, may easily alter crystal habit. Characterization and evaluation of crystals are necessary for the assessment of the reproducibility of the dosage forms. Characterizations utilizing a variety of analytical techniques reveal that the forms are actually solvates or have different crystal habits or polymorphs or agglomerates.

Crystalline solids have definite geometric shapes and orderly arrangements of units. Ionic and atomic crystals in general are very hard and brittle and have high melting points. The molecular crystals of organic compounds have low melting points as they are held together by weak van der Waals forces and hydrogen bonding. Cubic crystals as well as amorphous substances are usually isotropic, that is, they exhibit similar properties in all directions. Crystal growth is a process wherein solute molecules reach the growing faces of a crystal by diffusion through the supersaturated liquid phase. Growth of crystals from solution involves two steps, formation of new particles i.e. nucleation, and growth of the nuclei into crystals.

Comprehensive characterization of all preformulation bulk lots is necessary for better solubilization and stabilization and this is dependant upon a particular crystalline form. The development of dosage forms for advanced drug delivery requires a good understanding and control of polymorphism, which depends on optimization of physical properties to achieve intended functions[1]. Since the amorphous forms are usually of higher thermodynamic energy than any other crystalline form of a given molecule[2,3], instability can occur during bulk processing or within the dosage forms and this is a major problem for developing an amorphous form. The crystallization of glycine as different polymorphs and salt forms during freeze drying[4] and spray drying[5] significantly changes particle morphology and size. These changes may influence the suitability of these powders for pharmaceutical formulations. Grinding and milling of organic crystals may produce significant properties of amorphous or strained crystalline materials[6]. Hence, differences in dissolution and absorption rates between polymorphs and amorphous form of a given compound may also be observed. Recent studies suggest that the enantiomers of pseudoephedrine are observed to react in a solid state to form the racemic compound[7]. Alteration in crystallization conditions often results in the deviation of crystal habits from the ideal[8]. The factors responsible for controlling crystal habit are, rapid deposition on a face during growth, shielding effect on certain faces, and presence of

*For correspondence
E-mail: smallickin@yahoo.co.in

additives or impurities in the mother liquor.

Crystal growth in suspension and its inhibition:

Temperature fluctuations, polymorphic transformation and Ostwald ripening destabilize the suspensions owing to particle aggregation and particle growth during storage[9]. When solubility of drug is strongly dependent on temperature, crystals of drug may dissolve and form supersaturated solutions at raised temperature, which favours crystal growth. The difference in the solubility of polymorphs also provide a driving force for crystal growth in suspension and the process is accelerated if the drug used contains a mixture of polymorphs. Dissolved impurities may affect the rate of crystallization and even change the crystal habit, provided that these impurities are surface active and become adsorbed on the nuclei or growing crystals[10-12]. Polysorbate 80 or octoxynol 9 (0.005%) significantly inhibit the growth of methyl prednisolone crystals in aqueous media. Gelatin, polyvinylpyrrolidone (PVP) at concentration <0.10% retard the crystal growth of sulphathiazole in the water. Inhibition of crystal growth by PVP in acetaminophen suspensions has been reported earlier[13]. The study states that some of the segments of the polymer PVP attach to the free spaces on the drug crystal lattice and a hydration shell surround the polymer. The adsorbed segments form a barrier that resists the approach of the drug molecules from the solution to the crystal surface and inhibit crystal growth. The adsorption of the polymer on the crystal surface becomes more irreversible as the molecular weight of PVP increases and more effective for inhibiting crystal growth. Lucks *et al.*[14] suggested that the physical stability of the suspension might be enhanced due to the repulsion of like charged particles induced by a cationic surfactant.

Alteration of crystal habit:

The crystal habit may be altered due to interference with the uniform approach of crystallizing molecules to the different faces of a crystal, resulting in anhedral (irregular) or euhedral (regular) crystals[15,16]. Polymorphism is known to influence dissolution rates that directly affect absorption and bioavailability of drugs[17,18]. When estrogen ethynylestradiol is crystallized from solvents acetonitrile, methanol and chloroform saturated with water, four different crystalline solvates are formed[19]. Crystallization of sulfamerazine has been studied from selected solvents to understand the preferential formation of polymorphs[20]. Consolidative behavior of a particular drug material can be influenced by crystal habit under appreciable applied force[21,22]. Substance possessing rhombohedral lattice arrangements were noticed to be tableted with difficulty than those with a cubic lattice[23]. Solids undergo some elastic deformation when subjected to some external compressional forces. Armstrong and his colleague[24] reported that lamination of tablet structure resulted from considerable elastic recovery on decompression. Ibuprofen exhibits poor compression ability due to excessive elastic recovery, making its tableting by direct compression problematic[25].

Crystal habit can also be of great importance in suspension redispersibility, sedimentation, physical stability and appearance. Agglomerate of crystals of sulfisoxazole on caking in a suspension system may exhibit little tendency to redisperse because of the tenacity of the clumps[26]. These clumps may exhibit retarded dissolution and thus retarded bioavailability rates. Tiwari and his colleague[27,28] worked on the choice of crystal habit and improved suspension stability and bioavailability.

Literature reveals that flowability and compressibility of dry powders, during formulation of solid dosage forms may be improved by modifying crystal properties[29-31]. Several studies have recently been reported to improve tableting characteristics of paracetamol by modifying its crystal properties by employing different solvents[32-35] and low level additives[36-39]. Gordon and Amin reported that equidimensional crystal habit improves flow and compaction of ibuprofen granules as compared to needle-shaped crystals[25]. It has been found that water miscibility of the solvent and the addition of polymers such as agar, gelatin, polyvinylpyrrolidone and hydroxypropylmethylcellulose, alter the crystal habit and improve the tableting ability[33,36,39].

Kachrimanis *et al.*[40] reported recently the physicomechanical properties of ibuprofen-Eudragit S100 crystal agglomerates by solvent change technique. Later Kachrimanis[41] prepared crystals by same technique in presence of polymers that increased crystal yield and improved compression behavior during tableting. It has also been reported that crystal agglomerate microcapsules produced by solvent change technique in presence of polymer(s) such as ethylcellulose, Eudragit RS-100, Eudragit RL-100 have shown sustained release of drugs and could effectively be tableted[42-44]. The crystal agglomerates of drugs provided enhancement of bioavailability even though the drugs have substantial first pass metabolism[45,46].

The fabulous inhibiting effect of ethanol-soluble PVP on crystal yield was reported earlier for crystallization of paracetamol[39] and sulfathiazole[47]. The polymers, which are

insoluble in ethanol such as agar, PEG and gelatin resulted in crystal yield increase of paracetamol and affected greatly by the polymer concentration[41]. The addition of polymers contributed to the reduction of elastic recovery or increase in plasticity and a greater tendency for brittleness[41,48]. Kulkarni *et al.*[49] in their review article discussed four spherical crystallization techniques, spherical agglomeration, quasi-emulsion solvent diffusion, ammonia diffusion system, and neutralization method. Spherical crystals exhibited, improved flow ability and compressibility, enhanced dissolution and hence the bioavailability of drugs and controlled drug release.

Characterization:

It is important to realize that a multidisciplinary approach must be taken for complete physicochemical characterization of a pharmaceutical solid. Characterization of crystal morphology has been suggested in the assessment of the reproducibility of dosage forms[50].

X-ray powder diffractometry is precisely used for identification and quantification of percent crystallinity, polymorphism, solvatomorphism and phase identification of a compound having different crystal lattices. The plot of measured values of amorphous intensity (I_a) against crystalline intensity (I_c) will result a straight line with a slope *m*, as stated by $Ia=b-mI_c$...*(i)*. Then the degree of crystalline intensity of an unknown sample can be calculated as[51-54] $C=I_c 100/(I_c+mI_a)$...*(ii)*

Recent reports suggest that water vapor sorption measurement was a very sensitive indicator of crystal lattice disorder[55-56]. Standard Reference Materials are provided by the National Institute of Standards and Technology for calibrating powder X-ray diffractometers and also to measure instrument sensitivity[57]. Low-temperature X-ray diffraction has been used to monitor the crystallization of glycine from frozen solutions and during freeze drying[58]. Quantification of the content of crystalline drug in ethylcellulose microspheres containing tolnaftate was studied by X-ray powder diffraction method[59].

Polymorphism, solvation/desolvation, degradation, drug-carrier interaction and purity of crystal can be evaluated also by thermal methods such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), modulated DSC, isothermal calorimetry, solution calorimetry, dynamic mechanical thermal analysis and thermogravimetry (TG) during the course of drug development[60-73]. In this context, techniques such as density measurements[74] and dielectric spectroscopy[75,76] have also been used so far during global evaluation of the disorder of powders (Buckton and Darcy[77]) for a general review. The enthalpy of fusion of tolnaftate, studied by DSC was also used as a measure of crystalline content of drug in the ethylcellulose microspheres[59]. DTA and DSC can be used to obtain useful and characteristic thermal and melting point data for crystal polymorphs or solvate species. This information is particularly important for the compounds that can crystallize in more than one structural modification in addition to XRD methodology. Chloroquine phosphate form I consists of a simple endotherm with melting point at 216^0 while the thermogram of form II is complicated one and melts at 196^0 [78]. This indicates that form I is thermodynamically more stable form at the elevated temperature. DTA is a powerful aid to explain the polymorphism and solvates associated with several sulfonamide[79]. The temperature used in the spray drying of phenylbutazone has been shown to determine the polymorphic form of the compound[80]. DSC can effectively be used to screen the solvates with a variety of solvents. Six solvates and two anhydrous forms of piretanide[81] were obtained after recrystallization from 27 different solvents as revealed by DSC. These distinct crystal forms were ascertained by XRD. Khankari *et al.*[82] described the water content in hydrate species can be determined using DSC technique. Indrayanto and his colleagues[83] studied that famotidine was compatible with talc, magnesium stearate and avicel PH 101 and that interaction took place with primojel, kollidon, emcompress, crospovidone and lactose, based on DSC work. A simultaneous thermogravimetry and DSC study observed for certain crystal modifications of mefloquinine hydrochloride permitted the assignment of these crystal forms as solvates[84]. TG is a measure of thermally induced weight loss (desolvation) as a function of temperature[85] and it can determine not only the water but also other solvents. Thermally stimulated current technique (TSC) is a particularly powerful method to detect, to characterize and to analyze dynamics of crystalline/ amorphous phases. Dynamics of molecular mobility prior to melting in crystalline phases and molecular movements involved in the glass transition specific to amorphous phases are possible for characterization[86]. The use of solid state nuclear magnetic resonance (NMR) for the investigation of polymorphism or pseudopolymorphism is easily understood[87-90]. The two different (pseudo) polymorphic forms exhibit a different chemical shift interaction for each carbon, and ultimately, a different isotropic chemical shift for the same carbon atom. Recently, one report came up on combination of solid-state NMR spectroscopy and X-ray

crystallography in the studies of structure and dynamics in molecular crystal of penicillines[91] Three resonances exist for each carbon for two of the polymorphic forms of aspartame, indicating three crystallographically inequivalent sites. Two dimensional exchange spectroscopy using high speed MAS and very high power ^{1}H decoupling on uniformly ^{13}C labeled aspartame is a very powerful tool for assigning each resonance in the solid-state NMR spectrum of aspartame[92]. Ikeda *et al.* worked on ^{1}H and ^{13}C-NMR spectroscopies of captopril inclusion complex in aqueous solution (solution state NMR) by kinetic methods and by molecular dynamic calculations[93].

Both optical and electron microscopies have found wide spread use for the surface morphology of crystals. The crystal habit has been used for the purposes of identification when the crystallization solvent used to generate the carefully controlled test crystals. When the crystals are imperfectly formed and the relationship between the faces cannot be estimated, it is still possible to provide more empirical judgment for the overall shape, discreteness and agglomeration of the particles[5,94,95]. Morphology and elastic constants of crystals of pharmaceutical compounds can be predicted by utilizing computer-modeling techniques[95,96]. Mechanical stability of the polymorphs can be determined from elastic constants.

The complete characterization of a pharmaceutical solid is not possible without vibrational analysis. Various crystal modifications can be differentiated by means of IR analysis[97-100]. In some cases[97] the variations in IR absorption led to the conclusions of intermolecular hydrogen bonding and for others to identify the polymorphs. The IR spectroscopy is also very important in the characterization of pseudopolymorphic systems, especially hydrates. The sharpness of the band is evidence of a bound species (crystalline water) even at the lowest levels of moisture content[101]. FT-Raman spectroscopy has been used to differentiate polymorphic forms of cimetidine[102] and carbamazepine[103]. The FT-Raman spectra of a range of drugs (theophylline, indomethacine, diclofenac and promethacine) in several polymers have been obtained[104,105]. The quantitative measurements of crystallinity can be made from the peak intensity ratio and the study demonstrates the related information of lattice structure[106,107].

CONCLUSIONS

Crystal growth in aqueous suspensions during storage is significantly inhibited by polymer such as gelatine, PVP that resists the approach of molecules from solution to the crystal surface. Crystallization by solvent change technique, in presence of polymers may permit an increase in crystal yield, alteration of crystal shape and improvement of compression behavior during tableting. Significant improvement in suspension redispersibility, sedimentation, drug dissolution and bioavailability may be possible by modifying crystal habit. Complete characterization of altered crystal habit is possible by utilizing variety of analytical techniques. A mathematical model could be developed to predict the solubility, flowability, compressibility and bioavailability of a drug by quantifying its degree of crystallinity.

REFERENCES

1. Suryanarayanan, R. and Byrn, S.R., **Adv. Drug Delivery Rev.**, 2001, 48, 27.
2. Hancock, B.C. and Zografi, G., **J. Pharm. Sci.**, 1997, 86, 1.
3. Craig, D.Q.M., Royall, P.G., Kett, V.L. and Hopton, M.L., **Int. J. Pharm.**, 1999, 179, 179.
4. Akers, M.J., Milton, N., Byrn, S.R. and Nail, S.L., **Pharm. Res.**, 1995, 12, 1457.
5. Yu, L. and Kingman, N.G., **J. Pharm. Sci.**, 2002, 91, 2367.
6. Florence, A.T. and Attwood, D., Eds., In; Physicochemical Principles of Pharmacy, 2nd. Edn., Chapman and Hall, New York, 1988, 1.
7. Duddu, S.P., Khin-Khin, A., Grant, D.J.W. and Suryanarayanan, R., **Pharm. Res.**, 1992, 9, 149.
8. Gibb, T.R.P., In; Optical Methods of Chemical Analysis, McGraw-Hill, New York, 1942, 239.
9. Martin, A., Bustamante, L. and Chun, A.H.C., In; Physical Pharmacy, 4th Edn., B.I. Waverly Pvt. Ltd., New Delhi, 1993, 435.
10. Ross, S. and Morrison I.D., In; Colloidal Systems and Interfaces, Wiley, New York, 1988, 300.
11. Schoff, H., In; Gennaro, A.R., Eds., Remington: The Science and Practice of Pharmacy, 19th Edn., Mack Publishing Co., Easton, Pennsylvania,1995, 255.
12. Hilemenz, P.C., In; Principles of Colloidal and Surface Chemistry, 2nd Edn., Dekker, New York, 1986, 534.
13. Ziller, K.H. and Rupprecht, H., **Drug Develop. Ind. Pharm.**, 1988, 14, 2341.
14. Luck, J.S., Muller, B.W. and Muller, R.H., **Int. J. Pharm.**, 1990, 58, 229.
15. Haleblian, J.K., **J. Pharm. Sci.**, 1975, 64, 1269.
16. Takubo, H., Kume, S. and Koizumi, M., **J. Cryst. Growth.**, 1984, 67, 217.
17. Moustafa, M.A., Khalil, S.A., Ebian, A.R. and Motawi, M.M., **J. Pharm. Pharmacol.**, 1972, 24, 921.
18. Khalafallah, M., Khalil, S. A. and Moustafa, M. A., **J. Pharm. Sci.**, 1974, 63, 861.
19. Martin, A., Bustamante, L. and Chun, A.H.C., In; Physical Pharmacy, 4th Edn., B.I. Waverly Pvt. Ltd., New Delhi, 1993, 35.
20. Zhang, G.G.Z., Gu, C., Zell, M.T., Burkhardt, R.T. and Munson,

E.J., **J. Pharm. Sci.**, 2002, 91, 1089.
21. Marshall, K., In; Lachman, L., Lieberman, H.L., and Kanig, J.L., Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing House, Mumbai, 1987, 73.
22. Sun, C. and Grant, D.J.W., **Pharm. Res.**, 2001, 18, 274.
23. Jaffe, J. and Foss, N.E., **J. Amer. Pharm. Assn., Sci. Edn.**, 1959, 48, 26.
24. Armstrong, N.A. and Haines Nutt, R.F., **J. Pharm. Pharmacol.**, (Suppl.), 1970, 22, 85.
25. Gordon, R.E. and Amin, S.I., **European Patent Appl.**, EP, 1984, 120, 587.
26. Patel, N.K., Kennon, L., Levinson, R.S., In; Lachman, L., Lieberman, H.L. and Kanig, J.L., Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing House, Mumbai, 1987, 486.
27. Tiwary, A.K. and Panpalia, G.M., **Indian J. Pharm. Sci.**, 2000, 62, 267.
28. Tiwary, A.K. and Panpalia, G.M., **Pharm. Res.**, 1999, 16, 261.
29. Shotton, E. and Obiorah, B.A., **J. Pharm. Pharmacol.**, 1973, 25S, 37.
30. Summers, M.P., Enever R.P. and Carless J.E., **J. Pharm. Pharmacol.**, 1976, 28, 89.
31. York, P., **Drug Develop. Ind. Pharm.**, 1992, 18, 677.
32. Nichols, G. and Framton, C.S., **J. Pharm. Sci.**, 1998, 87, 684.
33. Nath, B.S. and Khalil, S.S., **Indian J. Pharm. Sci.**, 1984, 46, 106.
34. Fachaux, J.M., Guyot-Hermann, A.M., Guyot, J.C., Conflant, P., Drachu, M., Huvenne, J.P. and Bouche, R., **Int. J. Pharm.**, 1993, 99, 99.
35. El-Said, Y., **S.T.P. Pharma.**, 1995, 5, 232.
36. Garekani, H.A., Ford, J.L., Rubinstein, M.H. and Rajabi-Siahboomi, A.R., **Pharm. Res.**, 1996, 13, 9 (Suppl.) Abstract PT 6211, S-209.
37. Chow, A.H.L., Chow, P.K.K. and Wang, Z.G.D., **Int. J. Pharm.**, 1985, 24, 239.
38. Nath, B.S. and Nalwade, P., **Indian Drugs**, 1987, 25, 146.
39. Femi-Oyewo, M.N. and Spring, M.S., **Int. J. Pharm.**, 1994, 112, 17.
40. Kachrimanis, K., Ktistis, G. and Malamataris, S., **Int. J. Pharm.**, 1998, 173, 61.
41. Kachrimanis, K. and Malamataris, S., **J. Pharm. Pharmacol.**, 1999, 51, 1219.
42. Mallick, S., Gupta, B.K. and Ghoshal, S.K., **Acta Polon. Pharm-Drug Res.**, 1999, 56, 297.
43. Mallick, S., Gupta, B.K. and Ghoshal, S.K., **Acta Polon. Pharm-Drug Res.**, 1999, 56, 289.
44. Mallick, S., Gupta, B.K. and Ghoshal, S.K., **J. Sci. Ind. Res.**, 1999, 58, 1010.
45. Mallick, S, Gupta, B.K. and Ghoshal, S.K., **Acta Polon. Pharm-Drug Res.**, 2000, 57,175.
46. Mallick, S, Gupta, B.K. and Ghoshal, S.K., **Indian J. Pharm. Sci.**, 2000, 62, 303.
47. Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., **J. Pharm. Sci.**, 1970, 59, 633.
48. Malamataris, S. and Rees, J.E., **Int. J. Pharm.**, 1993, 92, 123.
49. Kulkarni, P.K. and Nagavi, B.G., **Indian J. Pharm. Educ.**, 2002, 36, 66.
50. Byrn, S., Pfeiffer, R., Ganey, M., Hoiberg, C. and Poochikian, G., **Pharm. Res.**, 1995, 12, 945.
51. Nakai, Y., Fukuoka, E., Nakajima, S. and Morita, M., **Chem. Pharm. Bull.**, 1982, 30, 1811.
52. Morita, M.S., **Chem. Pharm. Bull.**, 1982, 30, 3288.
53. Hermans, P.H. and Weidinger, A., **J. Appl. Physics.**, 1948, 19, 491.
54. Alexander, L.E., In; X-ray Diffraction Methods in Polymer Science, Wiley, New York, 1969, 137.
55. Saleki-Gerhardt, A., Ahlneck, C. and Zografi, G., **Int. J. Pharm.**, 1994, 101, 237.
56. Buckton, G. and Darcy, P., **Int. J. Pharm.**, 1995, 123, 265.
57. Brochure entitled " Powder Diffraction", Standard Reference Materials, National Institute of Standards and Technology, Gaithersburg, Md., 1993.
58. Pyne, A. and Suryanarayanan, R., **Pharm. Res.**, 2001, 18, 1448.
59. Dash, A.K., Khin-Khin, A. and Suryanarayanan, R., **J. Pharm. Sci.**, 2002, 91, 983.
60. Ghiron, D., **J. Pharm. Biomed. Anal.**, 1986, 4, 755.
61. Ghiron-Fores, D., Goldbrown, C. and Piechon, P., **J. Pharm. Biomed. Anal.**, 1991, 7, 1421.
62. Townsend, I., **J. Therm. Anal.**, 1991, 37, 2031.
63. Barnes, A.F., Hardy, M.J. and Lever, T.J., **J. Therm. Anal.**, 1991, 37, 2031.
64. Phillips, E.M., **Int. J. Pharm.**, 1997, 149, 267.
65. Shamblin, S.L., Tang, X., Chang, L., Hangcock, B.C. and Pikal, M.J., **J. Phys. Chem. B.**, 1999, 103, 4113.
66. Guinot, S. and Leveiller, F., **Int. J. Pharm.**, 1999, 199, 63.
67. Saklatvala, R., Royall, P.G. and Craig, D.Q.M., **Int. J. Pharm.**, 1999, 192, 55.
68. Buckton, G., Darcy, P. and Mackellar, A.J., **Int. J. Pharm.**, 1995, 117, 253.
69. Sebhatu, T., Angberg, M. and Ahlneck, C., **Int. J. Pharm.**, 1994, 104, 135.
70. Pikal, M.J., Lukes, A.L., Lang, J.E. and Gaines, K., **Correlations With Stability**, 1978, 67, 767.
71. Amidone, G.E., Grant, D.J.W., Marshall, K. and Itai, S., **Pharm. Forum**, 1999, 25, 9266.
72. Craig, D.Q.M. and Johnson, F.A., **Thermochem. Acta**, 1995, 248, 97.
73. Kerc, J. and Srcic, S., **Thermochem. Acta**, 1995, 248, 81.
74. Suryanarayanan, R. and Mitchell, A.G., **Int. J. Pharm.**, 1985, 24, 1.
75. Craig, D.Q.M., **STP Pharm Sci.**, 1995, 5, 421.
76. Craig, D.Q.M. and Johnson, F.A., **Drug Develop. Ind. Pharm.**, 1994, 18, 1207.
77. Buckton, G. and Darcy, P., **Int. J. Pharm.**, 1999, 179, 141.
78. Aerde, P.V., Remon, J.P., DeRudder, D., Severen, R. and Van Braeckman, P., **J. Pharm. Pharmacol.**, 1984, 36, 190.
79. Yang, S.S. and Guillory, K., **J. Pharm. Sci.**, 1972, 61, 26.
80. Matsuda, Y., Kawaguchi S., Kobayshi H. and Nishijo, J., **J. Pharm. Sci.**, 1984, 73, 173.
81. Chikaraishi, Y., Sano, A., Tsujiyama, T., Otsuka, M. and Matsuda, Y., **Chem. Pharm. Bull.**, 1994, 42, 1123.
82. Khankari, R.K., Law, D. and Grant, D.J.W., **Int. J. Pharm.**, 1992,

82, 117.
83. Indrayanto, G., Mugihardjo, A. and Handayani, R., **Drug Develop. Ind. Pharm.,** 1994, 24, 911.
84. Kitamura, S., Chang L.C. and Guillory, J.K., **Int. J. Pharm.,** 1994, 101, 127.
85. Keattch, C.J. and Dollimore, D., In; Introduction to Thermogravimetry, 2nd Edn., Heyden, London, 1975, 1.
86. Boutonnet-Fagegaltier, N., Menegotto, J., Lamure, A., Duplaa, H., Caron, A., La Cabanne, C. and Bauer, M., **J. Pharm. Sci.,** 2002, 91, 1548.
87. Burger, A. and Ramberger, R., **Mikrochim. Acta [Wien],** 1979, II, 259.
88. Burger, A. and Ramberger, R., **Mikrochim. Acta [Wien],** 1979, II, 273.
89. Martin, A., Swarbrick, J. and Cammarate, A., In; Physical Pharmacy, 3rd Edn., Lea & Febiger, Academic Press, New Delhi, 1983, 575.
90. Byrn, S.R., In; Solid State Chemistry of Drug, Academic Press, New Delhi, 1982, 79.
91. Wendeler, M., Fattach, J., Twyman, J., Edwards, A.J. and Dobson, C.M., **J. Amer. Chem. Soc.,** 1997, 119, 9793.
92. Zell, M.T., Padder, B.E., Grant, D.J.W., Schoeder, S.A., Wachholder, K.L., Prakash, I. and Munson, E.J., **Tetrahedron,** 2000, 56, 6603.
93. Ikeda, Y., Motoune, S., Matsuoka, T., Arima, H., Hirayama, F. and Uekama, K., **J. Pharm. Sci.,** 2002, 91, 2390.
94. Amidon, G.E., **Pharm. Forum,** 1992, 18, 4089.
95. Coombes, D.S., Catlow, R.A., Gale, J.D., Hardy, M.J. and Saunders, M.R., **J. Pharm. Sci.,** 2002, 91, 1652.
96. Newman, A.W. and Brittain H.G., In; Brittain H.G., Eds., Physical characterization of pharmaceutical solids, Marcel Dekker, Inc, New York, 1995, 127.
97. Martiez-Oharriz, M.C., Martin, C., Goni, M.M., Rodriguez-Espinosa, C., Tros de Ilarduya-Apaolaza, M.C. and Sanchez, M., **J. Pharm. Sci.,** 1994, 83, 174.
98. Neville, G.A., Beckstead, H. D. and Shurvell, H.F., **J. Pharm. Sci.,** 1992, 81, 1141.
99. Chao, R.S. and Vail, K.C., **Pharm. Res.,** 1987, 4, 429.
100. Lin, S.Y., **J. Pharm. Sci.,** 1992, 81, 872.
101. Morris, K.R., Newman, A.W., Bugay, D.E., Ranadive, S.A., Singh, A.K., Szyper, M., Varia, S.A., Brittain, H.G. and Serajuddin, T.M., **Int. J. Pharm.,** 1994, 108, 195.
102. Tudor, A.M., Davies, M.C., Melia, C.D., Lee, D.C., Mitchell, R.C., Hendra, P.J. and Church, S., **J. Spetrochim. Acta,** 1991, 47A, 1389.
103. McMahon, L.E., Williams, A.C., York, P., Edwards, H.G.M. and Timmins, P., In; Yu, N.T. and Li, X.Y. Eds., Proceedings of the XIV th International Conference on Raman Spectroscopy, John Wiley & Sons, Chichester, 1994, 908.
104. Davies, M.C., Binns, J.S., Melia, C.D. and Bourgeosis, D., **Spectrochim. Acta,** 1990, 46A, 277.
105. Davies, M.C., Binns, J.S., Melia, C.D., Hendra, P.J., Bourgeosis, D., Church, S.P. and Stephenson, P.J., **Int. J. Pharm.,** 1990, 66, 223.
106. Sawh, D.G., Craig, D.Q.M., Newton, J.M., Williams, A.C. and Simpkin, G.T., **J. Pharm. Pharmacol.,** 1993, 45 (suppl. 2), 1149.
107. Sawh, D.G., Craig, D.Q.M., Newton, J.M., Williams, A.C. and Johnson, M.C.R., **Pharm. Res.,** 1993, 10 (suppl.), 150.