Combining refinement programs and advanced modeling tools allows a faster route to determining the structures of both inorganic and molecular crystals. An effective way to know the atomic structure is by means of diffraction techniques using neutrons from nuclear reactors and particle accelerators or X-rays from X-ray tubes and synchrotrons. The single-crystal diffraction technique, using relatively large crystals of the material, gives a set of separate data from which the structure can be obtained. However, the *powder* diffraction technique is used in conditions where it is not possible to grow large crystals. The drawback of this conventional *powder* method is that the data grossly overlap, thereby preventing proper determination of the structure. The "Rietveld method" creates an effective separation of these overlapping data, thereby allowing an accurate determination of the structure. An even more widely used application of the method is the determination of the components of chemical mixtures.

6.4.1 Crystalline Index of Refraction

As different polymorphs have different internal structures, they belong to different crystal systems; therefore, polymorphs can be distinguished by using polarized light and a microscope. The crystals can be either isotropic or anisotropic. In isotropic crystals, the velocity of light is the same in all directions, whereas anisotropic crystals have two or three different light velocities or refractive indices. In terms of crystal systems, only the cubic system is isotropic and the other six are anisotropic.

6.5 Solvates

In addition to polymorphs, solvates (inclusion of the solvent of crystallization) are also often formed during the crystallization process. These forms are also called pseudopolymorphs. The solvent molecules fill the spaces in the crystal lattice and generally reduce the solubility and dissolution rates. This phenomenon is thermodynamically driven. If the solvate contains an organic solvent, this would not be admitted by the regulatory authorities. According to the International Conference on Harmonization (ICH) guidelines, the class I solvents, such as benzene, carbon tetrachloride, and 1,2-dichloromethane, must be avoided, as these are carcinogenic. The class II solvents should be limited and include nongenotoxic animal carcinogens, such as cyclohexane and acetonitrile. The class III solvents, including acetic acid, alcohol, and acetone, which have low toxicity potential, are allowed as long as the daily permissible dose does not exceed 50 mg. Generally, an allowed solvate would likely be removed during the manufacturing process, but in some instances, the presence of the solvate is desired, as in the case of the beclomethasone dipropionate product of Glaxo that includes trichlorofluoromethane solvate. This solvate prevents crystal growth in sprays containing trichlorofluoromethane as a propellant. A U.S. Patent issued to Glaxo 5270305 demonstrates the use of trichlorofluoromethane.