Drug Development and Industrial Pharmacy, 35:555–567, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802459452

informa
healthcare

Initial Salt Screening Procedures for Manufacturing Ibuprofen

Tu Lee and Yeh Wen Wang

Department of Chemical and Materials Engineering, National Central University, Jhong-Li City, Taiwan, Republic of China

The aim of this paper is to design initial salt screening procedures for manufacturing ibuprofen. Salt forms of a pharmaceutical acid racemic (*R*,*S*)-(±)-ibuprofen and their "developable" synthetic routes were ferreted out simultaneously through the screening of seven bases of sodium hydroxide, potassium hydroxide, L-arginine, L-histidine, L-lysine, diethanolamine, and tris(hydroxymethyl)aminomethane (THAM), and the match with the use of nine organic solvents of methanol, dimethyl sulfoxide, ethanol, *N*, *N*-dimethylformamide, acetonitrile, isopropyl alcohol, 1,4-dioxane, acetone, and tetrahydrofuran mainly in the presence of water in 20 mL scintillation vials. Racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate, a well-known ibuprofen salt and the newly discovered racemic (*R*,*S*)-(±)-THAM ibuprofen, appeared as white-squared powders with a molecular weight of 327.42 g/mol, a melting point of 160.17°C, and the apparent solubility product, K'_{sp}, of 6.0×10^{-4} M^2 at 25°C were successfully synthesized by the initial salt screening methods. The new amine salt of ibuprofen was monoclinic and had a space group of $P2_1/c$ and lattice parameters of a = 17.578(8)°, b = 10.428(4)°, c = 9.991(4) Å, α = 90.00°, β = 97.17(1)°, γ = 90.00°, and V = 1,817.05(244) $Å^3$. The aspect ratio of the amine salt crystals of ibuprofen of ≈ 1.0 implied that the crystals had a better flowability than the sodium salt counterparts. This amine salt of ibuprofen was more stable in moist or dried atmospheres and was more hydrophobic than the sodium salt of ibuprofen. Moreover, the slow dissolution of this amine salt of ibuprofen might have made it less bitter and more suitable as a sustained release drug than the sodium salt of ibuprofen. The future work is to search for the different polymorphs of this amine salt of ibuprofen and to extend the initial salt screening working logics to the formation of co-crystals.

Keywords ibuprofen; tris(hydroxymethyl)aminomethane; Trizma base; sodium ibuprofen dihydrate; initial salt screening

INTRODUCTION

Potential drug candidates for early drug development are usually free bases, free acids, or neutral molecules, rather than their salts (Bastin, Bowker, & Slater, 2000). As the generally higher molecular weights of modern drug substances have made the drug candidates become more lipophilic than ever (Bastin et al., 2000), one common way to modulate aqueous solubility and dissolution rate along with other biological and physiochemical properties of a drug candidate (Berge, Bighley, & Monkhouse, 1977) without changing its chemical structure is by the formation of salts with the conjugate acids or bases (Steffen Paulekuhn, Dressman, & Saal, 2007). An estimated 50% of drug molecules used in medicinal therapy are administered as salts (Kumar, Amin, & Bansal, 2007).

The high-throughput salt screening methods (Carlson et al., 2005; Kumar et al., 2007; Morissette et al., 2004), the grinding method (Trask, Haynes, Samual Motherwell, & Jones, 2006), and the solvent-drop grinding method (Trask et al., 2006) meant to remove the bottleneck of the formation and selection of salts in late discovery and early development (Alsenz & Kansy, 2007) only reveal the maximum available numbers and the physicochemical properties of salt forms. Little information is obtained for the possible manufacturing route of the salt formation. In practice, it usually takes another 12–18 months to identify a viable synthetic route after the right salt form of the most promising drug candidate is chosen (Bastin et al., 2000). As a consequence, the bottleneck of the formation and selection of salts has shifted from discovery to preclinical and clinical drug development.

Although there is a large number of publications covering methods for high-throughput salt screening (Carlson et al., 2005; Kumar et al., 2007; Morissette et al., 2004), principles for salt formation (Serajuddin, 2007), case-by-case methods for salt formation (Agharkar, Lindenbaum, & Higuchi, 1976; Bruzzese, Ferrari, & SPA-Socita Prodotti Antibiotici, 1981; Chidambaram et al., 2007; Gwak, Choi, & Choi, 2005), approved salt forms (Berge et al., 1977; Steffen Paulekuhn et al., 2007), criteria for salt selection (Engel, Farid, Faul, Richardson, & Winneroski, 2000; Gould, 1986; Kawakami, Ida, & Yamaguchi, 2005; Morris et al., 1994), and the effects of pH, supersaturation, and temperature of crystallization on the physicochemical properties of salts (Jones, Davey, & Cox, 2005; Li et al., 2005), there is almost no publication dealing with a method for salt screening readily to be scaled-up as a manufacturing route (Balbach & Korn, 2004; Black, Collier, Davey, & Roberts, 2007). Therefore, the aim of this paper is to

Address correspondence to Tu Lee, Department of Chemical and Materials Engineering, National Central University, 300 Jhong-Da Road, Jhong-Li City, 320 Taiwan, Republic of China. E-mail: tulee@cc.ncu.edu.tw

develop initial salt screening procedures for manufacturing applicable at the stage of late drug discovery and early drug development.

Conventional high-throughput salt screening methods (Carlson et al., 2005; Kumar et al., 2007; Morissette et al., 2004) involve dissolving approximately 50 mg of the active pharmaceutical ingredient (API) in volatile but "non-green" solvents (Constable, Jimenez-Gonzalez, & Henderson, 2007), such as dichloromethane (Carlson et al., 2005) or dimethyl sulfoxide (DMSO) (Alsenz & Kansy, 2007), and dispensing a fixed volume of this API solution into each microplate well. After removal of the solvent by *evaporation*, an equal amount of API solids remained in each microplate well assuming that no solvates are formed. If the API is a free acid, concentrated solutions of various bases in either methanol or water (the salt reactants) are dispensed sequentially in an equimolar or other appropriate stoichiometric ratio. *The formation of salts* takes place in this step where the microplate is sealed and shaken at room temperature for 4 h. The covers are then removed and the solvents are *evaporated*. Twelve different re-crystallization solvents are added. The microplate cells are sealed and heated to 60°C for 4 h. The slurry in each well is filtered subsequently. A small portion of the filtrate is used for the solubility measurement (Alsenz & Kansy, 2007) at 60°C, and the rest of the filtrate is utilized for re-crystallization by *cooling* the microplate from 60 to 10°C. This is a *polymorph-screening step*. The residual solids are subjected to thermal, microscopic, and spectroscopic analyses for the characterization of salts and their polymorphs. The remaining slurry is filtered again at 10°C for the solubility measurement (Alsenz & Kansy, 2007) at 10°C.

To avoid the mode of evaporation and the use of organic solvents in the formation of salts, initial salt screening procedures intentionally involve crystallization pathways such as temperature cooling (Lee, Kuo, & Chen, 2006), the addition of an anti-solvent (Lee, Chen, & Wang, 2008), and the extensive use of water. Water is preferred because salts, particularly of weak acids or bases, that form readily in water can be missed completely in non-aqueous solvents because of the small or negative difference between the acid and base dissociation constants ($\Delta pK_a < 2$) caused by the shift of pK_a values in organic solvents (Black et al., 2007). Salt formation is verified (Agharkar et al., 1976) by transmission Fourier transform infrared spectroscopy (FTIR). Crystal structures of salts are characterized (Engel et al., 2000) by single crystal X-ray diffraction (SXD), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Crystal habits of salts (Lee et al., 2008) are examined by optical microscopy (OM). Moisture sorption studies (Morris et al., 1994), pH-solubility profile (Serajuddin, 2007), and dissolution rate of salts (Agharkar et al., 1976) are also determined and compared.

In this study, the model pharmaceutical acid, racemic (*R,S*)-(±)-ibuprofen ((*R,S*)-(±)-2-(4-isobutylphenyl)propionic acid, $C_{13}H_{18}O_2$), was selected because of its worldwide commercial values in analgesic, anti-inflammatory, and anti-pyretic therapy (Armitage, Lampard, & Smith, 2001), its abundant information in the literature (Bunyan, Shankland, & Sheen, 1991; Cano, Gabas, & Canselier, 2001; Freer, Bunyan, Shankland, & Sheen, 1993; Garzón & Martínez, 2004; Hansen, Perlovich, & Bauer-Brandl, 2003; Martino et al., 2002; Nada, Al-Saidan, & Mueller, 2005; Perlovich, Kurkov, Hansen, & Bauer-Brandl, 2004; Rasenack & Müller, 2002; Romero, Savastano, & Rhodes, 1993; Romero & Rhodes, 1991; Shankland, David, Csoka, & McBride, 1998; Winn & Doherty, 1998), its possible esterification with excipients containing hydroxyl groups (Armitage et al., 2001), and the reported formation of its sodium (Armitage et al., 2001), lysine (Bruzzese et al., 1981), and arginine salts (Bruzzese et al., 1981; Sádaba et al., 2006). Seven salt-forming agents, such as sodium hydroxide, potassium hydroxide, L-arginine, L-histidine, L-lysine, diethanolamine, and tris(hydroxymethyl)aminomethane (THAM or TRIS or Trizma base), were chosen to react with the pharmaceutical acid—racemic (*R,S*)-(±)-ibuprofen.

MATERIALS AND METHODS

Materials

White racemic (*R,S*)-(±)-ibuprofen ((*R,S*)-(±)-2-(4-isobutylphenyl)propionic acid, $C_{13}H_{18}O_2$, 99%, melting point of 75–78°C, molecular weight of 206.28 g/mol, Lot GK01) rod-shaped powders were used as received from TCI (Tokyo, Japan). Sodium hydroxide (Lot SS-2631W) and potassium hydroxide (Lot 52280) were used as received from Showa Chemical Co., Ltd. (Tokyo, Japan) and Riedel-de Haën (C.O.O., Germany), respectively. L-Arginine (Lot 245OH) obtained from MP Biomedicals, LLC (OH, USA) was used as Solon, received. L-Histidine (Lot 423834) purchased from Fluka (Steinheim, Germany) was used as received. L-Lysine (Lot 522268-224) obtained from Sigma-Aldrich (Steinheim, Germany) was used as received. Diethanolamine (Lot V50661) was used as purchased from J. T. Baker (NJ, USA). Tris(hydroxymethyl)aminomethane (THAM or TRIS or Trizma base) (Lot 41350) was used as received from Riedel-de Haën (C.O.O., Germany). Magnesium chloride (Lot 07312bH-347) was used as received from Aldrich (Steinheim, Germany). Magnesium nitrate hexahydrate (Lot 1338968) was used as purchased from Fluka (Buchs, Germany). Sodium chloride (Lot sp-2642v) was used as obtained from Showa (Tokyo, Japan). Colorless concentrated hydrochloric acid (37% by weight, Lot AC0741) was used as purchased from Scharlau Chemie S.A. (Barcelona, Spain). White pellets of sodium hydroxide (Lot SS-2631W) were used as received from Showa Chemical Co., Ltd. Acetone (Lot 411050), *N,N*-dimethylformamide (DMF) (Lot 020505), DMSO (Lot 202060), isopropyl alcohol (IPA) (Lot 503027), methanol (Lot 411070), tetrahydrofuran (THF) (Lot 411013) were all obtained from Tedia company (Fairfield, USA). 1,4-Dioxane

(Lot sp-3432R) was obtained from Showa Chemical Co., Ltd. Ethanol was purchased from Echo Chemical Co. Ltd. (Taipei, Taiwan). Acetonitrile (Lot 0043X29B30) was obtained from Mallinckredt Baker, Inc. (Paris, KY, USA). Reversible osmosis (RO) water was clarified by water purification system (model: Milli-RO Plus) bought from Millipore (Billerica, MA, USA). 1-Octanol for the partition coefficient measurements (Lot E39586) was purchased from J. T. Baker (Phillipsburg, NJ, USA).

Methods

A Suntex microprocessor pH meter SP-2200 (Suntex Instruments Co. Ltd., Taipei, Taiwan) was used to measure and monitor the pH values of aqueous solutions of the different salts of racemic (*R,S*)-(±)-ibuprofen. The pH meter was calibrated by buffer solutions of pH 4.01 and 7.00.

Transmission Fourier Transform Infrared Spectroscopy

Transmission FTIR was utilized to measure purity, detect bond formation, and verify chemical identity. Transmission FTIR spectra were recorded on a Perkin Elmer Spectrum One spectrometer (Perkin Elmer Instruments LLC, Shelton, CT, USA). The KBr sample disk was scanned with a scan number of 8 from 450 to 4,000 cm^{-1} having a resolution of 2 cm^{-1}.

Differential Scanning Calorimetry

DSC analysis was used to identify the solid–liquid (melting) or solid–solid transformation temperature. Thermal analytical data of 3–5 mg of samples in perforated aluminum sample pans (Perkin Elmer Instruments LLC) (25 μL) were collected on a Perkin Elmer DSC-7 calorimeter (Perkin Elmer Instruments LLC) with a temperature scanning rate of 10ºC/min from 50 to 250ºC under a constant nitrogen 99.990% purge. The instrument was calibrated with indium 99.999% (Perkin Elmer Instruments LLC).

Thermogravimetric Analysis

TGA analysis was carried out by TGA 7 (Perkin Elmer, Norwalk, CT, USA) to monitor sample weight loss as a function of temperature. The heating rate was 10°C/min ranging from 50 to 250°C. The open platinum pan and stirrup were washed with ethanol and burned by spirit lamp to remove all impurities. All samples were heated under nitrogen atmosphere to avoid oxidization. About 3 mg of sample were placed on the open platinum pan suspended in a TGA's heating furnace.

Powder X-Ray Diffraction

PXRD patterns were obtained from samples using a wide-angle powder X-ray diffractometer Bruker AXS D8 Advance (Karlsruhe, Germany). X-ray radiation CuK α1 (λ = 1.5405 Å) was set at 30 kV and 20 mA was passed through a nickel filter with divergence slit (0.5°), scattering slit (0.5°), and receiving slit (1 mm). Samples were subjected to X-ray powder diffraction analysis with a sampling width of 0.01° in the continuous mode with a scanning rate of 1°/min over an angular range 2θ of 2°–35°.

Single Crystal X-Ray Diffraction

SXD data of newly found racemic (*R,S*)-(±)-ibuprofen salts were recorded on the Siemens SMART CCD-based Bruker X8 APEX X-ray diffractometer (Karlsruhe, Germany) equipped with Mo Kα source (λ = 0.7137 Å) operated at 3 kW. Data collection was performed by Bruker Apex2 software package and the structure was solved and refined using Bruker SHELXTL version 5.10 software package. The size of the crystal sample was 0.1–1.0 mm. The crystal packing plot of SXD was drawn using Diamond 3.1 computer software (Crystal Impact GbR, Brandenberg, Germany).

Optical Microscopy

Crystal habits were examined and measured by an Olympus SZII Zoom Stereo Microscope (Olympus, Tokyo, Japan) equipped with a Sony SSC-DC 50A digital color video camera (Sony Corporation, Tokyo, Japan).

Experiments

Moisture Sorption Studies

Three capped plastic bottles were used to provide a closed but controlled atmosphere. About 50–100 mg of racemic (*R,S*)-(±)-ibuprofen salts were introduced into each container which was placed in a capped plastic bottle filled with saturated aqueous solutions of either $MgCl_2$ or $Mg(NO_3)_2$ or NaCl. The three plastic bottles were kept in an oven at 25°C to maintain 33, 52, and 75% relative humidity (Morris et al., 1994) inside each bottle, respectively, for two consecutive days. The weights of the containers filled with racemic (*R,S*)-(±)-ibuprofen salts were recorded every day.

pH-Solubility Studies

Aqueous stock solutions with pHs of 2, 3, 4, 5, and 6 were prepared by varying the amount of concentrated HCl solution added to RO water, and aqueous stock solutions with pHs of 9, 10, 11, 12, and 13 were prepared by adjusting the amount of NaOH pellets added to RO water. Approximately 10 mg of racemic (*R,S*)-(±)-ibuprofen salts were weighted in a 20 mL scintillation vial. Drops of stock solution at a different pH were titrated carefully with a micropipette into the vial with intermittent shaking until all racemic (*R,S*)-(±)-ibuprofen salts were just dissolved. The aqueous solubility of racemic (*R,S*)-(±)-ibuprofen salts at 25°C and at a given pH was calculated as the weight of the racemic (*R,S*)-(±)-ibuprofen salts divided by the total volume of the stock solution of a specific pH value added to a vial.

The Partition Coefficient

Log *P* was determined by dividing the solubility in 1-octanol at 25°C by the solubility in water at 25°C and taking the log of that number (Carlson et al., 2005). The solubility was determined by the usual gravimetric method (Lee et al., 2006).

Dissolution Tests

A dissolution test station (SR6, Hanson Research Corporation, Chatsworth, CA, USA) Type II (paddle method) at a rotation speed of 50 rpm was used for in vitro testing. Dissolution tests of ground racemic (*R,S*)-(±)-ibuprofen salt powders were carried out on a 200-mg base. RO water with a pH of 6.0 was used as the dissolution medium. The volume and temperature of the dissolution medium were 900 mL and 37.5 ± 0.2°C, respectively (Sorasuchart, Wardrop, & Ayres, 1999). The real-time concentration of the dissolved racemic (*R,S*)-(±)-ibuprofen salts was monitored by the electrical conductivity meter (CONSORT K611, Conductivity Instruments, Turnhout, Belgium) which was calibrated with 0.01 M of KCl each time before use with an extrapolated conductivity of 1,413 μS at 25°C. The dissolution measurements were repeated three times over the full course to obtain mean values and *SD*s for each time point.

Salt Formation

About 0.1–0.5 g of racemic (*R,S*)-(±)-ibuprofen and an amount of base which was a little more than an equimolar amount were added to the 20-mL scintillation vial to ensure that racemic (*R,S*)-(±)-ibuprofen was reacted completely. For every 30 min, water was introduced into the vial dropwise with intermittent shaking. The vial was constantly maintained at 50°C in a water bath. The following two conditions would occur upon the addition of water:

1. If the suspension had turned clear, the clear solution would be cooled from 50–25°C overnight and the solids generated would be filtered, oven dried at 40°C overnight for thermal, microscopic, and spectroscopic analyses, moisture sorption studies, pH-solubility studies, and dissolution tests. If the solution stayed clear by temperature cooling from 50 to 25°C, an anti-solvent (i.e., with respect to the salts) miscible with water such as methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, acetone, and THF derived from the Form Space (Lee et al., 2006) of racemic (*R,S*)-(±)-ibuprofen, would be added dropwise with intermittent shaking. The addition of an anti-solvent would be stopped at the point where the solution either becomes oiling out or remaines clear after the total liquid volume had gone beyond 80% of the volume of the vial or has turned cloudy. The cloudy solution would be given enough time to precipitate out under agitation at 25°C. Solids harvested at this step would be filtered, oven dried at 40°C overnight and analyzed by thermal analytical methods, microscopy, and spectroscopy. Moisture sorption studies, pH-solubility studies, and log *P* and dissolution tests would also be performed.
2. If the suspension had not turned clear, when there was no sign for the suspension to turn clear and the addition of water was stopped, so that the total amount of water in the vial was kept at a minimum. A good solvent (i.e., with respect to racemic (*R,S*)-(±)-ibuprofen) miscible with water, such as methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, acetone, and THF derived from the Form Space (Lee et al., 2006) of racemic (*R,S*)-(±)-ibuprofen, would be added dropwise with intermittent shaking at 50°C hopefully to dissolve the suspended solids of racemic (*R,S*)-(±)-ibuprofen. Three possible conditions might happen after the addition of a good solvent: oiling out, clear solution, and suspension. No further action was required to be taken for suspension. Temperature cooling from 50 to 25°C and keeping the temperature at 25°C overnight with or without seeding might eventually precipitate out solids from the conditions of oiling out or clear solution. Solids produced from either way would be filtered, oven dried at 40°C overnight and subjected to thermal, microscopic, and spectroscopic analyses, moisture sorption studies, pH-solubility studies, and log *P* and dissolution tests. If the conditions remained the same after the addition of a good solvent with the total liquid volume beyond 80% of the volume of the vial, no further actions would need to be taken.

RESULTS AND DISCUSSION

The seven salt forming agents chosen to react with the pharmaceutical acid racemic (*R,S*)-(±)-ibuprofen (pK_a = 5.2) (Garzón & Martínez, 2004) to form salts were either strong bases such as sodium hydroxide and potassium hydroxide or organic bases such as L-arginine (pK_a = 9) (Lide, 2005), L-histidine (pK_a = 9.09) (Lide, 2005), L-lysine (pK_a = 9.16) (Lide, 2005), diethanolamine (pK_a = 8.7) (Terashima, Kageyama, Katsuyama, & Fuji Photo Film Co., Ltd., 1990), and THAM (pK_a = 8.1) (Klenell, Snoeijs, & Pedersén, 2004) with aqueous pK_a values at 25°C of at least two units (Black et al., 2007) higher than the one of racemic (*R,S*)-(±)-ibuprofen.

The specific working route and its corresponding final state in Figure 1 associated with each salt-forming agent and the nine good solvents for racemic (*R,S*)-(±)-ibuprofen were mapped out as follows:

1. The introduction of sodium hydroxide gave the route of A → B → E → N without the need of using any organic solvents. A suspension was obtained and *solids* were successfully isolated for chemical and physical analyses.
2. The employment of potassium hydroxide gave the route of A → B → D → L for all of the nine anti-solvents (i.e., with respect to the salts) of methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, acetone, and THF. However, only a *clear solution* was obtained at the end regardless of which organic solvent was utilized.

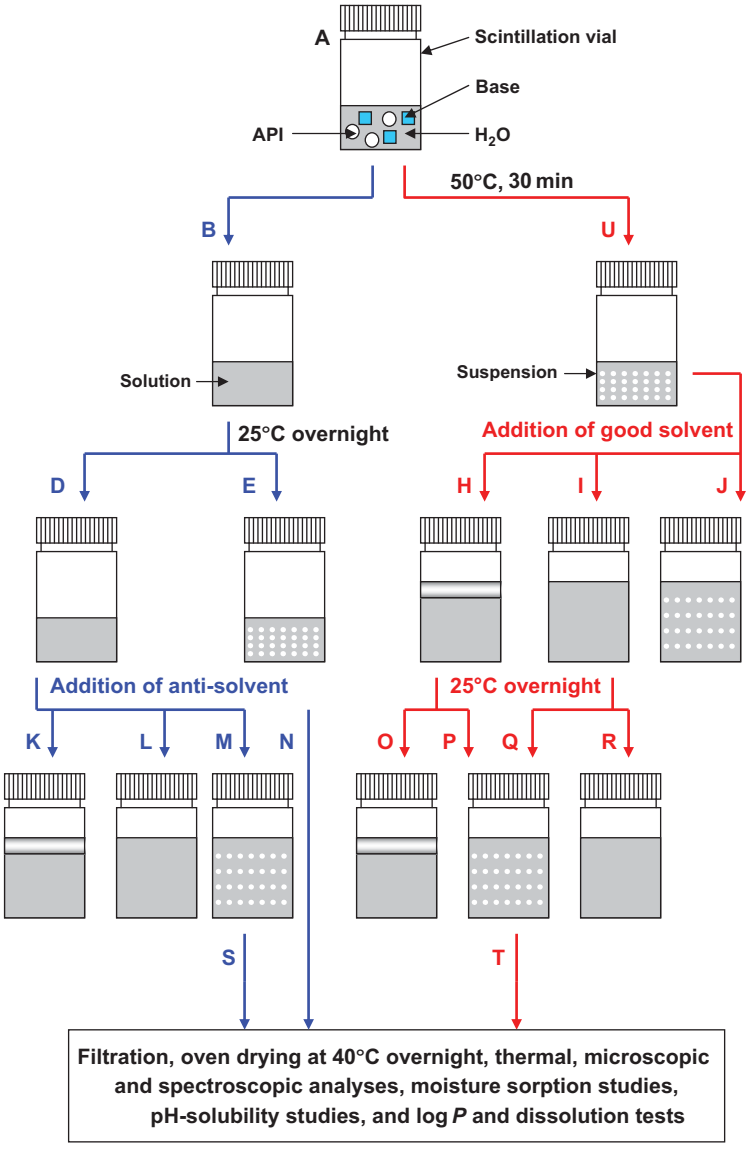

FIGURE 1. The workflow logics of the initial salt screening procedures for racemic (*R*,*S*)-(±)-ibuprofen.

3. The usage of L-arginine gave either the route of A → B → D → L for the four anti-solvents of methanol, ethanol, DMF, and IPA or the route of A → B → D → K for the other five remaining anti-solvents of DMSO, acetonitrile, 1,4-dioxane, acetone, and THF. Either a *clear solution* or a *phase separation* associated with oiling out was obtained.
4. The utilization of L-histidine resulted in either the route of A → U → H → P for the five anti-solvents of methanol, DMSO, ethanol, DMF, and IPA or the route of A → U → H → O for the other four remaining anti-solvents of acetonitrile, 1,4-dioxane, acetone, and THF. Either a *suspension* of fine racemic (*R*,*S*)-(±)-ibuprofen solids or a *phase separation* associated with oiling out was obtained. Seeding did not seem to solve the problem at all.
5. The introduction of L-lysine gave the route of A → B → D → L for the anti-solvents of methanol, ethanol, and IPA and the route of A → B → D → K for the rest of the anti-solvents of acetonitrile, DMSO, 1,4-dioxane, acetone, and THF. Either a *phase separation* associated with oiling out or a cloudy *suspension* was observed. The addition of DMF followed the route of A → B → D → M to give a suspension and *solids* were filtered and oven dried at 40°C overnight for chemical and physical analyses.
6. The employment of diethanolamine gave the route of A → B → D → L for all the nine anti-solvents of methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, acetone, and THF. Only *clear solution* was achieved at the end. Finally,

7. the usage of THAM gave the route of A → U → I → Q → T for the all nine good solvents (i.e., with respect to racemic (*R,S*)-(±)-ibuprofen) of methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, acetone, and THF. A suspension was obtained and *solids* were filtered and oven dried at 40°C overnight for chemical and physical analyses.

The occurrence of a clear solution inferred that the resulting ibuprofen salt had an extremely good solubility in even a small amount of water at 25°C as in the cases of using potassium hydroxide and diethanolamine as salt-forming agents. Therefore, this kind of ibuprofen salt stayed dissolved even in the solvent mixture with a very low volume ratio of water to an organic anti-solvent and could only be precipitated out by evaporation which was an undesirable process in manufacturing.

Phase separation associated with oiling out or cloudiness appeared upon the introduction of basic amino acids, such as L-arginine, L-histidine, and L-lysine. This was usually related to the incongruity among the polarities (Kim, Wei, & Kiang, 2003) of racemic (*R,S*)-(±)-ibuprofen, basic amino acid, and the solvent system (Barton, 1991). The oiling out problem could be overcome in principle by altering the solvent volume ratio of the solvent system and by keeping the overall polarity, *P'*, in the mid-region of around 5 in the Snyder's polarity scale from 0 to 10 (Kim et al., 2003). Although this might be worth pursuing because of the reported existence of the arginine salt and the lysine salt of ibuprofen, further development of a new crystallization protocol was purposely avoided here at this initial stage of salt screening because of the failure for us in repeating the results published in the existing patented protocols (Bruzzese et al., 1981). However, when 0.101 g of ibuprofen and 0.0725 g of L-lysine were dissolved in 0.1 mL of water at 50ºC, white solids of poor crystallinity as verified by PXRD were generated in the solution at 25ºC upon the addition of DMF.

Solids were generated only from the sodium hydroxide–racemic (*R,S*)-(±)-ibuprofen system and the THAM–racemic (*R,S*)-(±)-ibuprofen system by our initial salt screening procedures. For the sodium hydroxide–racemic (*R,S*)-(±)-ibuprofen system, about 0.50 g of racemic (*R,S*)-(±)-ibuprofen and 0.10 g of sodium hydroxide were dissolved together in 0.8 mL of RO water at 50°C. Solids were then crystallized out by cooling the solution to 25°C overnight without any organic solvents (Armitage et al., 2001), collected by filtration and oven dried at 40°C overnight. For the THAM–racemic (*R,S*)-(±)-ibuprofen system, about 0.10 g of racemic (*R,S*)-(±)-ibuprofen and 0.061 g of THAM were dissolved in 3 mL of RO water at 50°C, to which an anti-solvent at 50°C such as 1 mL of methanol or 1.6 mL of DMSO or 0.45 mL of ethanol or 0.65 mL of DMF or 0.5 mL of acetonitrile or 0.4 mL of IPA or 0.7 mL of 1,4-dioxane or 0.6 mL of acetone or 0.2 mL of THF was slowly added. Solids were produced by cooling the solution to 25°C and kept at that temperature overnight.

Racemic (*R,S*)-(±)-Sodium Ibuprofen Dihydrate

Solids generated from the sodium hydroxide–racemic (*R,S*)-(±)-ibuprofen system were characterized by FTIR, DSC, TGA, and OM. The FTIR spectrum of the solids (Figure 2B) showed a disappearance of the broad band peak for hydrogen bonding that was observed from 3,485 to 2,300 cm^{-1} (Oberoi, Alexander, & Riga, 2005) for ibuprofen dimers in the solid state (Shankland, Wilson, Florence, & Cox, 1997) (Figure 2A). This verified that neutralization had taken place. Sodium cations occupied the spaces between the ibuprofen molecules and prevented the formation of hydrogen bonding. A shift in the frequency near 1,740 cm^{-1} for the C=O stretch (Oberoi et al., 2005) of a carboxylic acid group –COOH (Figure 2A) to a strong asymmetric $–COO^-$ stretching vibration at 1,650–1,540 cm^{-1} for the carboxyl salts (Colthup, Daly, & Wiberley, 1990b) (Figure 2B) was also observed which could be accounted for by the change in the chemical environment. In addition, the DSC thermogram of two endothermic peaks at 99.2 and 199.6°C, the TGA scan with a weight loss of 13.3% (theoretical value 13.6%) between 44 and 105°C, and the OM image of a hexagonal crystal habit agreed with the ones obtained for racemic (*R,S*)-(±)-sodium ibuprofen dihydrate in the prior article (Lee, Chen, & Zhang, 2007). This suggested that the synthesized solids were indeed *racemic (R,S)-(±)-sodium ibuprofen dihydrate* (Zhang & Grant, 2005) which has a molecular weight of 264.29 g/mol, which is triclinic and has a space group of $P\bar{1}$ and lattice parameters of a = 5.7396(4)°, b = 6.0284(4)°, c = 23.8301(17) Å, α = 83.457(1)°, β = 89.241(1)°, γ = 63.154(1)°, and V = 730.20(9) $Å^3$ with a lamellar structure of a layer of H_2O molecules and sodium cations, a layer of protonated (*S*)-(+)-ibuprofen (protonated *S* layer), a layer of protonated (*R*)-(−)-ibuprofen (protonated *R* layer) and a layer of

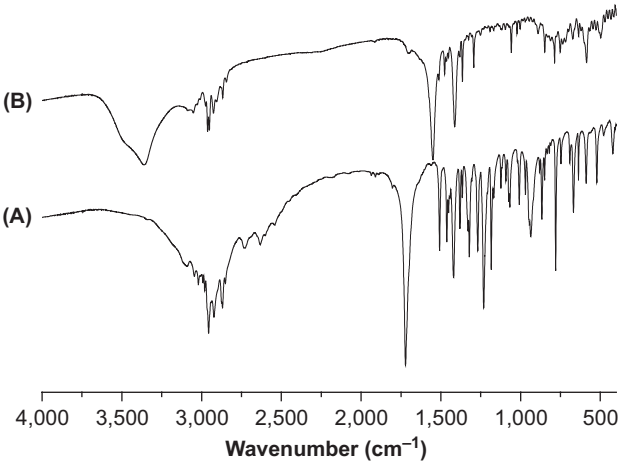

FIGURE 2. FTIR spectra of (A) commercially purchased racemic (*R,S*)-(±)-ibuprofen, and (B) synthesized racemic (*R,S*)-(±)-sodium ibuprofen dihydrate.

H_2O molecules and sodium cations as reported earlier (Lee et al., 2007).

The amounts of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate solids were directly scaled-up based on the synthetic route identified from the initial salt screening method. About 5.6113 g of racemic (*R,S*)-(±)-ibuprofen and 1.0944 g of NaOH were dissolved in 8 mL of RO water at 50°C. Solids were formed by cooling the saturated, the resulting aqueous solution from 50 to 25°C and filtered. The product weight was 4.9468 g and the yield was 80 mol.%. Dihydrate salts for the pH-solubility studies and dissolution test were obtained by oven drying the solids at 40°C overnight. Anhydrate salts for moisture sorption studies were obtained by oven drying the solids at 50°C for 3 days.

Racemic (*R,S*)-(±)-Tris(hydroxymethyl)aminomethane Ibuprofen

All the solids grown from nine different THAM–racemic (*R,S*)-(±)-ibuprofen systems corresponding to nine different anti-solvents in the presence of water gave the same FTIR spectrum, DSC thermogram, and PXRD pattern. A typical FTIR spectrum, DSC thermogram, and PXRD pattern of the solids grown in water–acetone system are shown in Figures 3–5. Similar to the changes in the FTIR spectra for the formation of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate from racemic (*R,S*)-(±)-ibuprofen, the FTIR spectrum of the solids grown from the THAM–racemic (*R,S*)-(±)-ibuprofen system (Figure 3C) demonstrated a disappearance of the broadband peak for hydrogen bonding from 3,485 to 2,300 cm^{-1} (Figure 3A) and a shift in the frequency near 1,740 cm^{-1} for the C=O stretch (Oberoi et al., 2005) of a carboxylic acid group –COOH

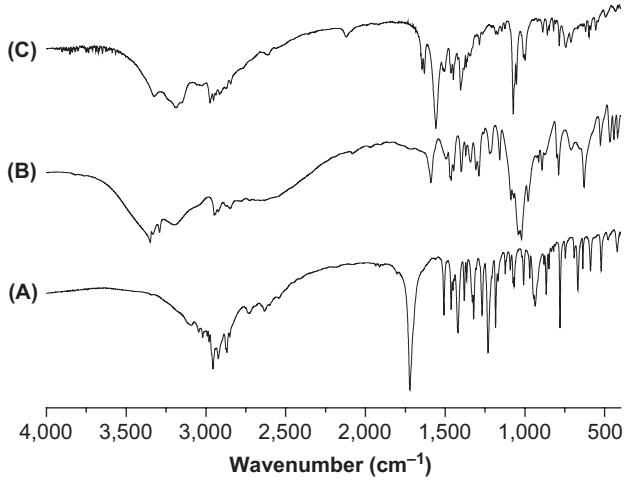

FIGURE 3. FTIR spectra of (A) commercially purchased racemic (*R,S*)-(±)-ibuprofen, (B) commercially received tris(hydroxymethyl)aminomethane, and (C) synthesized racemic (*R,S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen in water–acetone system.

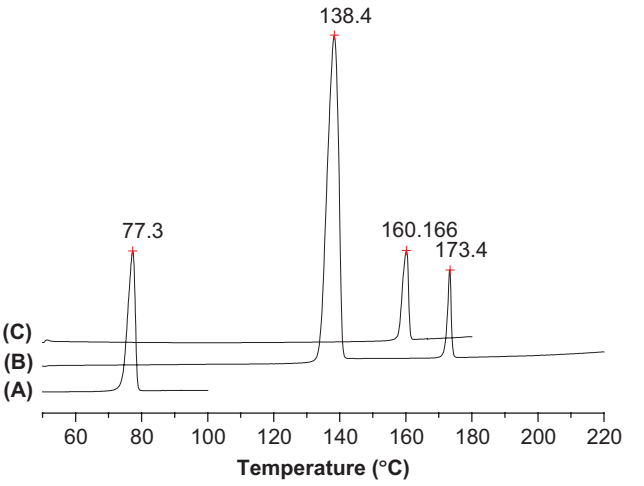

FIGURE 4. DSC thermograms of (A) commercially purchased racemic (*R,S*)-(±)-ibuprofen, (B) commercially received tris(hydroxymethyl) aminomethane, and (C) synthesized racemic (*R,S*)-(±)-tris(hydroxymethyl) aminomethane ibuprofen in water–acetone system.

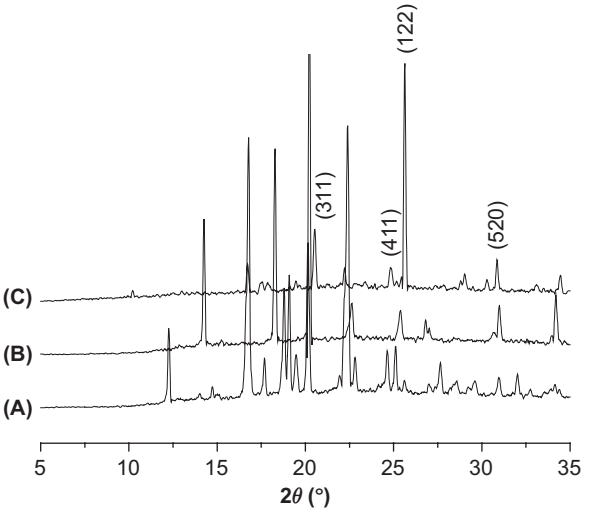

FIGURE 5. PXRD patterns of (A) commercially purchased racemic (*R,S*)-(±)-ibuprofen, (B) commercially received tris(hydroxymethyl)aminomethane, and (C) synthesized racemic (*R,S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen in water–acetone system.

(Figure 3A) to a strong asymmetric $–COO^-$ stretching vibration at 1,650–1,540 cm^{-1} for the carboxyl salts (Colthup et al., 1990b) (Figure 3C). Furthermore, the FTIR spectrum of the solids also illustrated the appearance of an isolated band between 2,800 and 2,000 cm^{-1} for the amine salts (Colthup, Daly, & Wiberley, 1990a) (Figure 3C), whereas the NH stretching vibration (Colthup et al., 1990a) for THAM giving rise to a weak band at 3,500–3,300 cm^{-1}(Figure 3B) remained unchanged after neutralization (Figure 3C). According to the

DSC scans in Figure 4, the melting endotherm at 160.17°C of the solids (Figure 4C) was distinctive and very different from the melting endotherm at 77.3°C of racemic (*R,S*)-(±)-ibuprofen (Lee et al., 2006) (Figure 4A) and the two endothermic peaks at 138 and 173°C of THAM (Eilerman & Rudman, 1980) whose first peak was the solid–solid transition from orthorhombic ordered Form II to orientationally disordered (plastic) crystalline (ODIC) Form I and the second peak was corresponding to the melting of Form I (Figure 4B). Similarly, the PXRD pattern of the solids (Figure 5C) was unique and different from the ones of racemic (*R,S*)-(±)-ibuprofen (Khan & Jiabi, 1998) (Figure 5A) and THAM (Figure 5B). All these thermal and spectroscopic evidences had pointed to the fact that acid–base reaction did take place and the solids were the newly synthesized racemic (*R,S*)-(±)-THAM ibuprofen with a molecular weight of 327.42 g/mol. Unlike racemic (*R,S*)-(±)-sodium ibuprofen dihydrate, TGA indicated that this compound was an anhydrate because of no weight loss before its melting point of 160.17°C.

Once racemic (*R,S*)-(±)-THAM ibuprofen was synthesized, it was re-crystallized again for the SXD study. A saturated solution of racemic (*R,S*)-(±)-THAM ibuprofen in methanol at 60°C was prepared (solubility at 60°C in methanol = 134.87 mg/mL) and then cooled to the room temperature along with the water bath by simply turning off the power supply of it. This extremely slow cooling rate of the water bath because of the large heat capacity of the water body had made the gradually grown crystals of racemic (*R,S*)-(±)-THAM ibuprofen ideal for SXD analysis. The SXD crystal packing plot in the (0 1 0) plane (i.e., the *ac*-plane) viewing down along the [0 1 0] direction (i.e., *b*-axis) is shown in Figure 6. The acidic proton from each carboxylic group, –COOH, of racemic (*R,S*)-(±)-ibuprofen was transferred to each amine group, $–NH_2$, of THAM. The resultant carboxylate ions, $–COO^-$, and the ammonium ions, $–NH_3^+$, had clustered in a proximity on the (1 0 0) plane and (2 0 0) plane (i.e., the two *bc*-planes on both ends of the unit cell) along the [0 0 1] direction and the [0 1 1] direction (i.e., the two *c*-axes on both ends of the unit cell). Unlike the crystalline structure of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate (Lee et al., 2007), the protonated *S*-ibuprofen and *R*-ibuprofen of racemic (*R,S*)-(±)-THAM ibuprofen were packed in an alternation with the absence of water molecules. Racemic (*R,S*)-(±)-THAM ibuprofen is monoclinic and has a space group of $P2_1/c$ and lattice parameters of a = 17.578(8)°, b = 10.428(4)°, c = 9.991(4) Å, α = 90.00°, β = 97.17(1)°, γ = 90.00°, and V = 1817.05(244) $Å^3$. The characteristic crystal planes of (3 1 1), (4 1 1), (1 2 2), and (5 2 0) corresponding to 2θ = 21.5°, 25°, 26°, and 31°, respectively, calculated using Diamond 3.1 computer software matched very well with the PXRD pattern in Figure 5C.

Optical micrographs in Figures 7A–H showed that almost all crystal habits of racemic (*R,S*)-(±)-THAM ibuprofen produced from the eight anti-solvents of methanol, DMSO, ethanol, DMF, acetonitrile, IPA, 1,4-dioxane, and acetone in the presence of water were squared with an aspect ratio of length-to-breath of ≈1.0. But when THF was used as an anti-solvent, the crystals were hexagonal in shape with an aspect ratio of 1.3 (Figure 7I).

The amount of racemic (*R,S*)-(±)-THAM ibuprofen solids was directly scaled-up 40 folds based on the synthetic route identified from the initial salt screening method. About 4.0033 g of racemic (*R,S*)-(±)-ibuprofen and 2.4066 g of THAM were dissolved in 120 mL of RO water at 50°C. Solids were formed

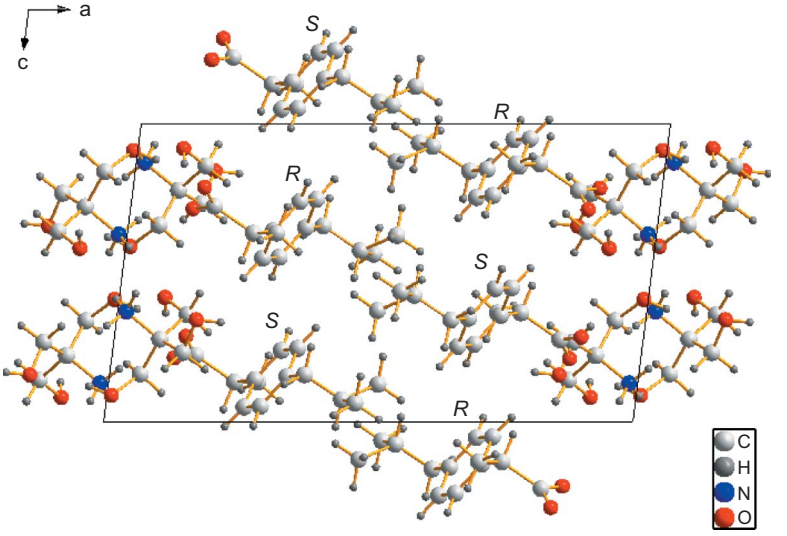

FIGURE 6. SXD crystal packing plot of racemic (*R,S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen in the (0 1 0) plane viewing down along the [0 1 0] direction.

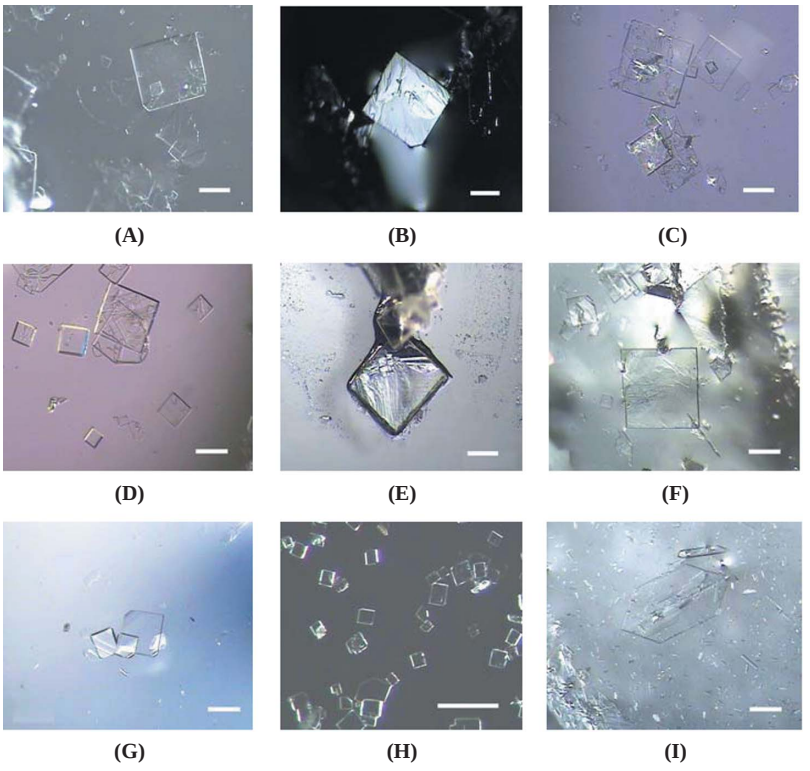

FIGURE 7. Optical micrographs of crystal habit of racemic (*R*,*S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen solids grown in nine different organic solvents in the presence of water by cooling: (A) methanol, (B) dimethyl sulfoxide, (C) ethanol, (D) *N*,*N*-dimethylformamide, (E) acetonitrile, (F) isopropyl alcohol, (G) 1,4-dioxane, (H) acetone, and (I) tetrahydrofuran (scale bar is 200 μm).

by the slow addition of 24 mL of acetone at 50°C followed by temperature cooling to 25°C overnight and filtered. The product weight was 3.7033 g and the yield was 58 mol.%. Salts for the moisture sorption studies, pH-solubility studies, and log *P* and dissolution tests, were obtained by oven drying the solids at 40°C overnight.

Moisture Sorption Studies

The weights of racemic (*R*,*S*)-(±)-sodium ibuprofen anhydrate increased from 0.38 to 0.44 g, from 0.44 to 0.51 g, and from 0.42 to 0.49 g (increased by 16 wt%) after two-day exposure to 33, 52, and 75% RH, respectively. The anhydrate salt had become a dihydrate. As for racemic (*R*,*S*)-(±)-THAM ibuprofen, no weight gain was observed after the same treatments. The incapability of being hydrated or dehydrated has made racemic (*R*,*S*)-(±)-THAM ibuprofen more stable than the sodium salt in moist or dried atmospheres.

pH-Solubility Profiles

Figure 8A and B gave the pH-solubility profiles of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate and racemic (*R*,*S*)-(±)-THAM ibuprofen, respectively, when they were used as starting materials for the determination of solubility, where pH was adjusted by using aqueous solutions of HCl or NaOH, as necessary. When an acidic compound or its salt was dissolved in water, the following equilibrium existed (Serajuddin, 2007):

$$A^- + H_2O \Leftrightarrow HA + OH^- \tag{1}$$

and

$$K_a = \frac{\left[H_3O^+\right]\left[A^-\right]}{[HA]}, \tag{2}$$

where A^- and HA represented deprotonated (salt) and free acid forms of the compound, respectively. When the aqueous medium at a given pH was saturated with the free acid, the total solubility, S_T, at that pH could be expressed as follows (Serajuddin, 2007):

$$\begin{aligned} S_T, \text{acid}(\text{pH} < \text{pH}_{max}) &= [HA]_s + [A^-] \\ &= [HA]_s \left(1 + \frac{K_a}{\left[H_3O^+\right]}\right) \\ &= [HA]_s (1 + 10^{\text{pH}-\text{p}K_a}), \end{aligned} \tag{3}$$

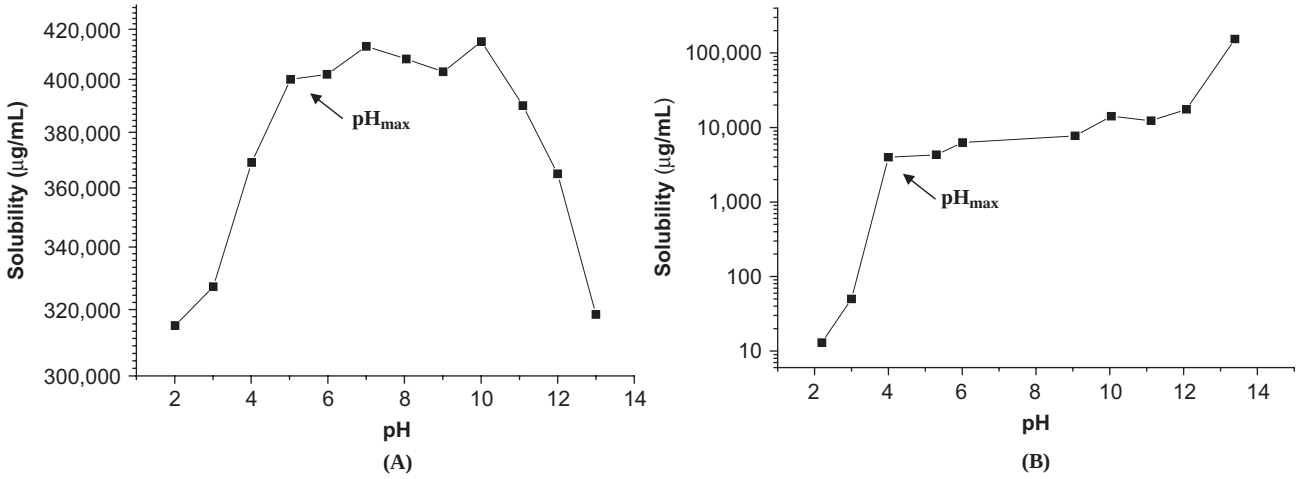

FIGURE 8. pH-solubility profiles at 25°C of (A) racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate and (B) racemic (*R*,*S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen determined by using HCl or NaOH.

where the subscript "s" denotes the saturation species. The free acid would be the equilibrium species at a pH below pH_{max} and it would convert to a salt only if it was equilibrated with a solution at a pH above pH_{max} by adding a sufficient quantity of an alkali or organic counter ion. When the salt was the saturation species, the total equilibrium solubility at a particular pH might be expressed by (Serajuddin, 2007)

$$\begin{aligned} S_T, \text{salt}(\text{pH} > \text{pH}_{max}) &= [\text{A}^-]_s + [\text{HA}] \\ &= [\text{A}^-]_s \left(1 + \frac{[\text{H}_3\text{O}^+]}{K_a}\right) \\ &= [\text{A}^-]_s (1 + 10^{\text{p}K_a - \text{pH}}). \end{aligned} \quad (4)$$

For racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate in Figure 8A, Eq. (3) depicted the portion of the curve below pH_{max} = 5 and Eq. (4) the relatively flat region from pH_{max} = 5 to pH = 10. If the solid phase being in equilibrium with a solution was analyzed, it would be racemic (*R*,*S*)-(±)-ibuprofen at pH < 5 and racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate at pH > 5. Only at pH_{max} = 5 could both racemic (*R*,*S*)-(±)-ibuprofen and racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate coexist as solids. In all cases, racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate had higher solubilities than the ones of racemic (*R*,*S*)-(±)-ibuprofen (Eq. (3)). Therefore, the higher buffer capacity provided by racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate (Eq. (4)) had dampened the change of the total equilibrium solubilities from pH_{max} = 5 to pH = 10. However, the addition of an excess amount of NaOH during the pH adjustment above 10 decreased the overall solubilities of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate. This was not only because of common-ion effect (Serajuddin, 2007) in sodium cations but also because of salting out effect that decreased self-association of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate molecules (Lee et al., 2008; Serajuddin, 2007). From the relatively flat solubility profile between pH 5 and 10, the apparent solubility product at 25°C (Li et al., 2005), K'_{sp}, could be calculated as $(\text{solubility})^2 = 2.4\ \text{M}^2$.

By the same token, for racemic (*R*,*S*)-(±)-THAM ibuprofen in Figure 8B, Eq. (3) depicted the portion of the curve below pH_{max} = 4, and Eq. (4) the plateau from pH_{max} = 4 to pH = 10. If the solid phase being in equilibrium with a solution was analyzed, it would be racemic (*R*,*S*)-(±)-ibuprofen at pH < 4 and racemic (*R*,*S*)-(±)-THAM ibuprofen at pH > 4. From the relatively flat solubility profile between pH 4 and 10, the apparent solubility product at 25°C (Li et al., 2005) K'_{sp}, might be calculated as $(\text{solubility})^2 = 6.0 \times 10^{-4}\ \text{M}^2$. The aqueous solubility at 25°C of racemic (*R*,*S*)-(±)-THAM ibuprofen near pH = 7 (Figure 8B) was 40–42 folds less than the one of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate (Figure 8A). However, the continuing addition of an excess amount of NaOH during the pH adjustment beyond the buffer range from 4 to 12 would increase the overall solubilities of racemic (*R*,*S*)-(±)-THAM ibuprofen solids because of the partial conversion of it into a better dissolving salt form of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate with a higher K'_{sp} value of of $2.4\ \text{M}^2$. Although the melting point of racemic (*R*,*S*)-(±)-THAM ibuprofen (m.p. = 160.1°C) was less than the one of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate (m.p. = 199.6°C), the solubility of racemic (*R*,*S*)-(±)-sodium ibuprofen dihydrate (i.e., aqueous solubility at 25°C = $(K'_{sp})^{1/2}$ = 5.76 M) was higher than the one of racemic (*R*,*S*)-(±)-THAM ibuprofen (i.e., aqueous solubility at 25°C = $(K'_{sp})^{1/2} = 2.4 \times 10^{-2}$ M). This implied that lattice energies played a less important role than hydration energies in salt solubility (Serajuddin, 2007) of racemic (*R*,*S*)-(±)-ibuprofen.

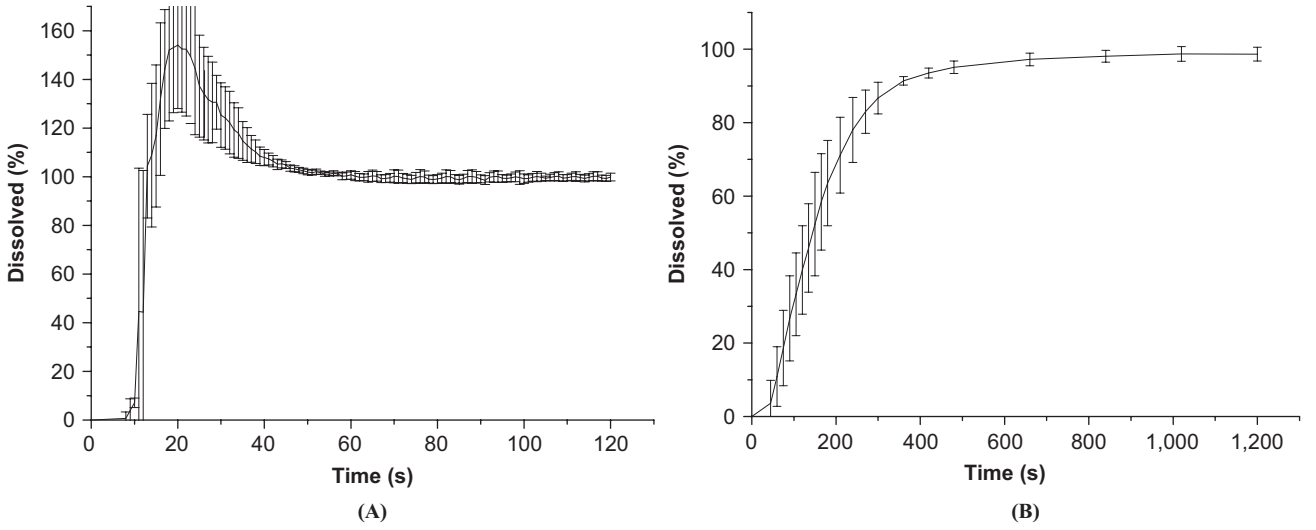

FIGURE 9. Dissolution profiles of (A) racemic (*R,S*)-(±) sodium ibuprofen dihydrate and (B) racemic (*R,S*)-(±)-tris(hydroxymethyl)aminomethane ibuprofen.

The Partition Coefficient

Log *P* values for racemic (*R,S*)-(±)-sodium ibuprofen dihydrate and racemic (*R,S*)-(±)-THAM ibuprofen were −1.82 and −0.99 at 25°C, respectively. Hence, the amine salt of ibuprofen with a higher partition coefficient was more hydrophobic (Carlson et al., 2005) than the sodium salt of ibuprofen and might be preferentially distributed to hydrophobic compartments such as lipid bilayers of cells.

Dissolution Tests

The dissolution profiles of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate and racemic (*R,S*)-(±)-THAM ibuprofen are shown in Figure 9A and B, respectively. The sudden surge of the amount of salt dissolved which past beyond 100% in Figure 9A was probably due to the interference on the conductivity meter caused by the many fine suspended particles or a polymorphic transformation (Rodríguez-Hornedo & Murphy, 2004) of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate. The 50% drug release times for solids of racemic (*R,S*)-(±)-sodium ibuprofen dihydrate and racemic (*R,S*)-(±)-THAM ibuprofen were determined to be 12 and 150 s, respectively, and with most of the salt being released within 60 and 1,200 s, respectively. The seemingly disadvantageous slow dissolution of the amine salt of ibuprofen might have advantageously (Berge et al., 1977) made it less bitter and more suitable as an sustained release drug than the sodium salt of ibuprofen.

CONCLUSIONS

Systematic initial salt screening procedures for manufacturing had been applied to the formation of ibuprofen salts involving crystallization pathways of temperature cooling, the addition of an anti-solvent, and the extensive use of water. Water was preferred because salts, particularly of weak acids or bases, that form readily in water could be missed completely in non-aqueous solvents because of the small or negative difference between the acid and base dissociation constants ($\Delta pK_a < 2$) caused by the shift of pK_a values in organic solvents. Highly crystalline solids of sodium salt and the THAM salt of racemic (*R,S*)-(±)-ibuprofen were successfully synthesized by this "green" initial salt screening method and can readily be scaled-up for comprehensive analyses of thermal behaviors, crystal lattice structures, pH-solubility studies, moisture sorption studies, and dissolution tests. But to further search for the other polymorphs of those two salts, they will be subjected to initial solvent screening with 23 organic solvents (Lee et al., 2006, 2007), and the workflow logics of the initial salt screening method will be extended to the salt formation of other acidic and basic drugs and the synthesis of co-crystals (Fleischman et al., 2003; Hehm, Rodríguez-Spong, & Rodríguez-Hornedo, 2006; Morissette et al., 2004; Remenar et al., 2003) in the future work.

ACKNOWLEDGMENTS

This work was supported by a research grant from the National Science Council of Taiwan, ROC (NSC 95-2113-M-008-012-MY2). Suggestions from Ms. Jui-Mei Huang in DSC and TGA, Ms. Shew-Jen Weng in XRD at National Central University Precision Instrument Center and High Valued Center and Ms. Pei-Lin Chen in SXD at Instrument Center at National Tsing Hua University, Hsin-chu, Taiwan, ROC are gratefully acknowledged.

REFERENCES

Agharkar, S., Lindenbaum, S., & Higuchi, T. (1976). Enhancement of solubility of drug salts by hydrophilic counterions: Properties of organic salts of an antimalarial drug. *J. Pharm. Sci., 65*(5), 747–749.

Alsenz, J., & Kansy, M. (2007). High throughput solubility measurement in drug discovery and development. *Adv. Drug Deliv. Rev., 59*(7), 546–567.

Armitage, B. J., Lampard, J. F., & Smith, A. (2001). Composition of S(-) sodium ibuprofen. *US Patent No. 6,242,000 B1*.

Balbach, S., & Korn, C. (2004). Pharmaceutical evaluation of early development candidates "the 100 mg-approach." *Int. J. Pharm., 275*(1–2), 1–12.

Barton, A. F. M. (1991). Solvent scales. In *CRC handbook of solubility parameters and other cohesion parameters*. (2nd ed., chap. 8, pp. 294–295). Boston, USA: CRC Press.

Bastin, R. J., Bowker, M. J., & Slater, B. J. (2000). Salt selection and optimisation procedures for pharmaceutical new chemical entities. *Org. Proc. Res. Dev., 4*(5), 427–435.

Berge, S. M., Bighley, L. D., & Monkhouse, D. C. (1977). Pharmaceutical salts. *J. Pharm. Sci., 66*(1), 1–19.

Black, S. N., Collier, E. A., Davey, R. J., & Roberts, R. J. (2007). Structure, solubility, screening, and synthesis of molecular salts. *J. Pharm. Sci., 96*(5), 1053–1068.

Bruzzese, T., Ferrari, R., & SPA-Socita Prodotti Antibiotici. (1981). Method of relieving pain and treating inflammatory conditions in warm-blooded animals. *US Patent No, 4279926*.

Bunyan, J. M. E., Shankland, N., & Sheen, D. B. (1991). Solvent effects on the morphology of ibuprofen. *AIChE Symp. Ser., 87*(284), 44–57.

Cano, H., Gabas, N., & Canselier, J. P. (2001). Experimental study on the ibuprofen crystal growth morphology in solution. *J. Cryst. Growth, 224*(3–4), 335–341.

Carlson, E. D., Cong, P., Chandler, W. H., Jr., Desrosiers, P. J., Christopher Freitag, J., & Varni, J. F., & Symyx Technologies. (2005). Apparatuses and methods for creating and testing pre-formulations and systems for same. *US Patent No. 6,939,515 B2*.

Chidambaram, R., Derbin, G. M., Endo, M., Gao, J., Lee, T., Motheram, R., Parker, W. L., Rosso, V. W., Varia, S. A., & Bristol-Myers Squibb. (2007). Oral Administration of N-(2-Chloro-6-Methylphenyl)-2-[[6-[4-(2-Hydroxyethyl)-1-Piper-Azinyl]-2-Methyl-4-Pyrimidinyl]Amino]-1,3-Thiazole-5-Carboxamide and Salts Thereof, *WO 035874, A1*.

Colthup, N. B., Daly, L. H., & Wiberley, S. E. (1990a). Amines, C=N, and N=O compounds. In *Introduction to infrared and Raman spectroscopy*. (3rd ed., chap. 11, pp. 340–343). San Diego, CA: Alexander Press.

Colthup, N. B., Daly, L. H., & Wiberley, S. E. (1990b). Carbonyl compounds. In *Introduction to infrared and Raman spectroscopy*. (3rd ed., chap. 9, pp. 317–319). San Diego, CA: Alexander Press.

Constable, D. J. C., Jimenez-Gonzalez, C., & Henderson, R. K. (2007). Perspective on solvent use in the pharmaceutical industry. *Org. Proc. Res. Dev., 11*(1), 133–137.

Eilerman, D., & Rudman, R. (1980). Polymorphism of crystalline poly(hydroxymethyl) compounds. III. The structures of crystalline and plastic tris(hydroxymethyl)aminomethane. *J. Chem. Phys., 72*(10), 5656–5666.

Engel, G. L., Farid, N. A., Faul, M. M., Richardson, L. A., & Winneroski, L. L. (2000). Salt form selection and characterization of LY333531 mesylate monohydrate. *Int. J. Pharm., 198*(2), 239–247.

Fleischman, S. G., Kuduva, S. S., McMahon, J. A., Moulton, B., Bailey Walsh, R. D., Rodríguez-Hornedo, N., & Zaworotko, M. J. (2003). Crystal engineering of the composition of pharmaceutical phases: Multiple-component crystalline solids involving carbamazepine. *Cryst. Growth Des. 3*(6), 909–919.

Freer, A. A., Bunyan, J. M., Shankland, N., & Sheen, D. B. (1993). Structure of (S)-(+)-ibuprofen. *Acta Cryst., C49*, 1378–1380.

Garzón, L. C., & Martínez, F. (2004). Temperature dependence of solubility for ibuprofen in some organic and aqueous solvents. *J. Sol. Chem., 33*(11), 1379–1395.

Gould, P. L. (1986). Salt selection for basic drugs. *Int. J. Pharm., 33*(1–3), 201–217.

Gwak, H.-S., Choi, J.-S., & Choi, H.-K. (2005). Enhanced bioavailability of piroxicam via salt formation with ethanolamines. *Int. J. Pharm., 297*(1-2), 156–161.

Hansen, L. Kr., Perlovich, G. L., & Bauer-Brandl, A. (2003). Redetermination and H-atom refinement of (S)-(+)-ibuprofen. *Acta Cryst., E59*(9), o1357–o1358.

Hehm, S. J., Rodríguez-Spong, B., & Rodríguez-Hornedo, N. (2006). Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. *Cryst. Growth Des., 6*(2), 592–600.

Jones, H. P., Davey, R. J., & Cox, B. G. (2005). Crystallization of a salt of a weak organic acid and base: Solubility relations, supersaturation control and polymorphic behavior. *J. Phys. Chem. B, 109*(11), 5273–5278.

Kawakami, K., Ida, Y., & Yamaguchi, T. (2005). Effect of salt type on hygroscopicity of a new cephalosporin S-3578. *Pharm. Res., 22*(8), 1365–1373.

Khan, G. M., & Jiabi, Z. (1998). Preparation, characterization, and evaluation of physicochemical properties of different crystalline forms of ibuprofen. *Drug Dev. Ind. Pharm., 24*(5), 463–471.

Kim, S., Wei, C., & Kiang, S. (2003). Crystallization process development of an active pharmaceutical ingredient and particle engineering via the use of ultrasonics and temperature cycling. *Org. Proc. Res. Dev., 7*(6), 997–1001.

Klenell, M., Snoeijs, P., & Pedersén, M. (2004). Active carbon uptake in *Laminaria digitata* and *L. saccharina* (Phaeophyta) is driven by a proton pump in the plasma membrane. *Hydrobiologia, 514*(1–3), 41–53.

Kumar, L., Amin, A., & Bansal, A. K. (2007). An overview of automated systems relevant in pharmaceutical salt screening. *Drug Discov. Today, 12*(23–24), 1046–1053.

Lee, T., Chen, Y. H., & Wang, Y. W. (2008). Effects of homochiral molecules of (S)-(+)-ibuprofen and (S)-(?−)-sodium ibuprofen dihydrate on the crystallization kinetics of racemic (*R,S*)-(±)-sodium ibuprofen dehydrate. *Cryst Growth Des., 8*(2), 415–426.

Lee, T., Chen, Y. H., & Zhang, C. W. (2007). Solubility, polymorphism, crystallinity, crystal habit, and drying scheme of (*R,S*)-(±)-sodium ibuprofen dihydrate. *Pharm. Tech., 31*(6), 72–87.

Lee, T., Kuo, C. S., & Chen, Y. H. (2006). Solubility, polymorphism, crystallinity, and crystal habit of acetaminophen and ibuprofen by initial solvent screening. *Pharm. Tech., 30*(10), 72–92.

Li, S., Wong, S., Sethia, S., Almoazen, H., Joshi, Y. M., & Serajuddin, A. T. M. (2005). Investigation of solubility and dissolution of a free base and two different salt forms as a function of pH. *Pharm. Res., 22*(4), 628–635.

Lide, D. R. (2005). Biochemistry. In *CRC handbook of chemistry and physics* (86th ed., sect. 7, p. 7–1). Boston, MA: CRC Press.

Martino, P. D., Beccerica, M., Joiris, E., Palmieri, G. F., Gayot, A., & Martelli, S. (2002). Influence of crystal habit on the compression and the densification mechanism of ibuprofen. *J. Cryst. Growth, 243*(2), 345–355.

Morissette, S. L., Almarsson, Ö., Paterson, M. L., Remenar, J. F., Read, M. J., Lemmo, A. V., Ellis, S., Cima, M. J., & Gardner, C. R. (2004). High-throughput crystallization: Polymorphs, salts, co-crystals and solvates of pharmaceutical solids. *Adv. Drug Deliv. Rev., 56*(3), 275–300.

Morris, K. R., Fakes, M. G., Thakur, A. B., Newman, A. W., Singh, A. K., Venit, J. J., & Spagnuolo, C. J., Serajuddin, A. T. M. (1994). An integrated approach to the selection of optimal salt form for a new drug candidate. *Int. J. Pharm., 105*(3), 209–217.

Nada, A. H., Al-Saidan, S. M., & Mueller, B. W. (2005). Improving the physical and chemical properties of ibuprofen. *Pharm. Tech., 29*(11), 90–101.

Oberoi, L. M., Alexander, K. S., & Riga, A. T. (2005). Study of interaction between ibuprofen and nicotinamide using differential scanning calorimetry, spectroscopy, and microscopy and formulation of a fast-acting and possibly better ibuprofen suspension for osteoarthritis patients. *J. Pharm. Sci., 94*(1), 93–101.

Perlovich, G. L., Kurkov, S. V., Hansen, L. K., & Bauer-Brandl, A. (2004). Thermodynamics of sublimation, crystal lattice energies, and crystal structures of racemates and enantiomers: (+)- And (±)-ibuprofen. *J. Pharm. Sci., 93*(3), 654–666.

Rasenack, N., & Müller, B. W. (2002). Properties of ibuprofen crystallized under various conditions: A comparative study. *Drug Dev. Ind. Pharm., 28*(9), 1077–1089.

Remenar, J. F., Morissette, S. L., Peterson, M. L., Moulton, B., Michael MacPhee, J., Guzmán, H. R., & Almarson, Ö. (2003). Crsytal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids. *J. Am. Chem. Soc., 125*(28), 8456–8458.

Rodríguez-Hornedo, N., & Murphy, D. (2004). Surfactant-facilitated crystallization of dihydrate carbamazepine during dissolution of anhydrous polymorph. *J. Pharm. Sci., 93*(2), 449–460.

Romero, A. J., & Rhodes, C. T. (1991). Approaches to stereospecific preformulation of ibuprofen. *Drug Dev. Ind. Pharm., 17*(5), 777–792.

Romero, A. J., Savastano, L., & Rhodes, C. T. (1993). Monitoring crystal modifications in systems containing ibuprofen. *Int. J. Pharm., 99*(2-3), 125–134.

Sádaba, B., Campanero, M. A., Muñoz-JuarezGil-Aldea, M. J., García-Quetglas, I., Esteras, E. A., & Azanza, J. R. (2006). A comparative study of the pharmacokinetics of ibuprofen arginate versus dexibuprofen in healthy volunteers. *Eur. J. Clin. Pharmacol., 62*(10), 849–854.

Serajuddin, A. T. M. (2007). Salt formation to improve drug solubility. *Adv. Drug Deliv. Rev., 59*(7), 603–616.

Shankland, K., David, W. I. F., Csoka, T., & McBride, L. (1998). Structure solution of ibuprofen from powder diffraction data by the application of a generic algorithm combined with prior conformational analysis. *Int. J. Pharm., 165*(1), 117–126.

Shankland, N., Wilson, C. C., Florence, A. J., & Cox, P. J. (1997). Refinement of ibuprofen at 100 k by single-crystal pulsed neutron diffraction. *Acta Cryst., C53*, 951–954.

Sorasuchart, W., Wardrop, J., & Ayres, J. W. (1999). Drug release from spray layered and coated drug-containing beads: Effects of pH and comparison of different dissolution methods. *Drug Dev. Ind. Pharm., 25*(10), 1093–1098.

Steffen Paulekuhn, G., Dressman, J. B., & Saal, C. (2007). Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database. *J. Med. Chem, 50*(26), 6665–6672.

Terashima, K., Kageyama, S., Katsuyama, H., & Fuji Photo Film Co., Ltd. (1990). Integral multilayer analytical element for use in the measurement of alkaline phosphatase activity. *US Patent No. 4,900,665*.

Trask, A. V., Haynes, D. A., Samual Motherwell, W. D., & Jones, W. (2006). Screening for crystalline salts via mechanochemistry. *Chem. Commun.,* 51–53.

Winn, D., & Doherty, M. F. (1998). A new technique for predicting the shape of solution-grown organic crystals. *AIChE J., 44*(11), 2501–2514.

Zhang, Y., & Grant, D. J. W. (2005). Similarity in structures of racemic and enantiomeric ibuprofen sodium dihydrates. *Acta Cryst., C61*, m435–m438.