Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 282 (2004) 73–85
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Solubility, dissolution rate and phase transition studies of ranitidine hydrochloride tautomeric forms

M. Mirmehrabi [a], S. Rohani [a,*], K.S.K. Murthy [b,1], B. Radatus [b]

[a] *Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ont., Canada N6A 5B9*
[b] *Brantford Chemicals Inc., 34 Spalding Drive, Brantford, Ont., Canada N3T 6B8*

Received 23 December 2003; received in revised form 27 May 2004; accepted 27 May 2004

Available online 23 July 2004

Abstract

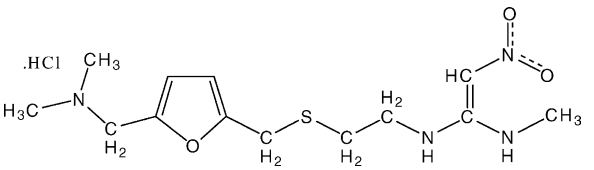
Understanding the polymorphic behavior of pharmaceutical solids during the crystallization process and further in post-processing units is crucial to meet medical and legal requirements. In this study, an analytical technique was developed for determining the composition of two solid forms of ranitidine hydrochloride using two peaks of Fourier transform infrared (FTIR) spectra without the need to grind the samples. Solubility studies of ranitidine hydrochloride showed that Form 2 has a higher solubility than Form 1. Solution-mediated transformation is very slow and occurs from Form 2 to Form 1 and not the reverse. No solid–solid transformation was observed due to grinding or compressing the pure samples of either forms and of a 50/50 wt.% mixture. Grinding was found to be a proper technique for increasing the bulk solid density of the ranitidine hydrochloride without the risk of solid–solid transformation. Dissolution rate found to be equally fast for both forms.

The solubility data were modeled using the group contribution parameters and UNIversal QUAsi-Chemical (UNIQUAC) theory. There was a good agreement between the experimental solubility data of ranitidine hydrochloride and the results of UNIQUAC equation.

Keywords: Ranitidine hydrochloride; Polymorphic transformation; Solubility measurement and prediction; UNIQUAC

1. Introduction

Ranitidine hydrochloride (RAN-HCl) exists in two solid forms with different morphology and physical properties. This drug is used to block acid production in the stomach, which is implicated in indigestion, acid reflux, heartburn, ulcers and Zollinger–Ellison syndrome (Canadian Pharmacists Association, 2000). One of the possible tautomers of this chemical is:



Ranitidine hydrochloride is the product of reaction between hydrogen chloride (HCl) and ranitidine base (RAN-B). Excess HCl leads the process toward the production of RAN-2HCl, which is considered an impurity. Ranitidine base, an amine with sulfurous odor,

* Corresponding author. Tel.: +1-519-661-4116; fax: +1-519-661-3498.
E-mail addresses: rohani@eng.uwo.ca (S. Rohani), kmurthy@brantfordchemicals.com (K.S.K. Murthy).
[1] Co-corresponding author. Tel.: +1-519-756-8942.

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.05.031

has a low solubility in water and is unstable if exposed to light. In contrast, ranitidine hydrochloride is very soluble in water, more stable and almost odorless. Tautomerism occurs in the nitroethenediamine moiety of the molecule and it is the reason of polymorphism in the solid state of RAN-HCl. Mirmehrabi et al. (2004a) showed that Form 2 exhibits molecular disorder in the crystal and contains two tautomers one of which is a nitronic acid and the other one an enamine. It was also expected (Mirmehrabi et al., 2004a) that Form 1 should be more ordered based on the NMR studies. It was found that polar solvents or solvent mixtures with water favor production of Form 2, but anhydrous less polar solvents or their mixtures results in the production of Form 1 during the reactive crystallization.

The original process for the production of Form 1 proposed by Price et al. (1978) results in a fluffy and spongy product with poor filtration and drying characteristics. This product is also strongly hygroscopic. In contrast, Form 2 shows well-formed crystals with proper filtration and drying characteristics (Crookes, 1987). Fig. 1 illustrates the products of these two procedures (Mirmehrabi et al., 2004b).

Many efforts have aimed to improve the quality of Form 1 in terms of filterability, drying and solid bulk density (Khanna et al., 1997; Schickaneder and Nikolopoulos, 1997; Murthy et al., 1995; Ngooi et al., 1998). Mirmehrabi et al. (2004b) reported an optimal process for producing high quality solids of Form 1. Their optimal process was built on the previous work of Brantford Chemical Inc., researchers (Murthy et al., 1995).

Agatonovic-Kustrin et al. (2000) reported an artificial neural network (ANN) method for quantifying the ranitidine hydrochloride forms in the solid mixture using X-ray powder diffraction and diffuse reflectance Fourier transformation infrared (DRIFT). Sertsou et al. (1999) analyzed the binary mixture of ranitidine hydrochloride solid forms employing only one peak of DRIFT spectra occurring at 1352 cm^{-1}. Using linear regression, they obtained a relationship between Kubelka–Munk value and weight percent of the Form 1 in the well-ground mixtures of both forms with $R^2 = 0.9733$. Forster et al. (1998) claimed that Form 1 converted to Form 2 during the grinding process. Agatonovic-Kustrin et al. (2000) observed that the pressure in the tableting process did not induce solid–solid transformation.

Activity coefficient models and equations of state are two classes of thermodynamic models that are used for phase equilibrium calculations. However, predicting the solubility of non-ideal systems using equations of state is generally not reliable. For strongly non-ideal systems, the UNIQUAC equation, which is an activity coefficient model, provides a good representation of equilibrium. There are many published (Grant and Higuchi, 1990; Chiavone and Rasmussen, 2000; Pinhoa and Macedob, 2002) contributions concerning the modeling of solid solubility using UNIQUAC but not for polymorphic or tautomeric systems.

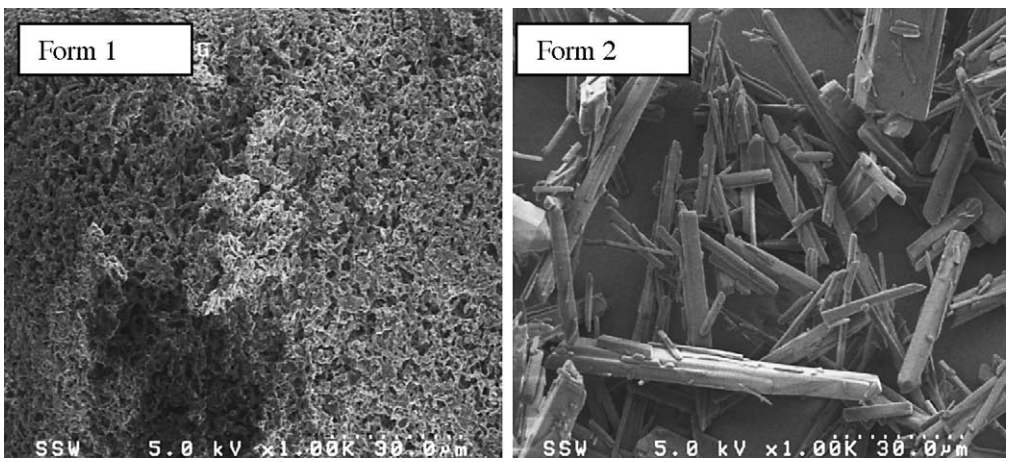


Fig. 1. SEM image of ranitidine hydrochloride Forms 1 and 2.

Mirmehrabi and Rohani (2004, in press) used UNIQUAC for modeling the solubility of stearic acid polymorphs in various solvents.

This paper presents the results of solid characterization, solubility studies, pH effect on the RAN-HCl in solution, effect of grinding and compressing on solid–solid transformation and finally modeling the solubility data using the UNIQUAC equation.

2. Material and methods

2.1. Materials

Ranitidine hydrochloride solid forms were produced using the procedures of related patents (Crookes, 1987; Murthy et al., 1995) . The identity of each form was confirmed by comparing to the FTIR spectra of standard samples for both forms provided by Brantford Chemicals Inc. (Brantford, Ont.). Ranitidine free-base and anhydrous hydrogen chloride-isopropanol (18.6 wt.% acid in HCl/IPA) solution were produced in Brantford Chemicals Inc., facilities (Brantford, Ont.). HPLC grade methanol, isopropanol and *n*-propanol were purchased from Sigma–Aldrich (Milwaukee, WC).

2.2. UV–vis spectrophotometer and pH

A Cary Bio 100 spectrophotometer (Varian, Mississauga, Ont.) was used for spectrophotometeric analysis. To find the effect of pH, 5 mg RAN-B was dissolved in 200 mL isopropanol at 25 °C then the pH was adjusted by HCl/IPA solution. After reaching to steady state condition based on the desired pH, a 5 mL sample was taken for analysis without further dilution. An epoxy coated pH meter (510 series, Oakton, IL) with temperature compensator was used for reading the pH.

2.3. Solid-state ATR-FTIR

A Vector 22 solid-state attenuated total reflection Fourier transform infrared spectrometer, ATR-FTIR (Bruker, Milton, Ont.), was employed for quantification of each form. The samples were analyzed in absorption mode through a zinc selenide crystal. Thirty-two scans with the resolution of 2 cm^{-1} in the range of 1020–1100 cm^{-1} were performed. The background was collected in the same range for air. Approximately 10 mg of sample was poured on the zinc selenide crystal for each analysis. Each binary mixture was analyzed three times and then the average was taken for analysis.

2.4. Solubility measurement, dissolution rate and solution mediated transformation

The solubility was measured using a precise gravimetric method presented by Mirmehrabi and Rohani (2004, in press). In this method a measured amount of solid and solvent is kept in a closed vial while shaking in a constant temperature bath (RTE 220, Neslab, Mississauga, Ont.) to find the temperature at which all the solids disappeared. A focused light (Leica CLS 150, Richmond Hill, Ont.) was used for visual monitoring of the end point. The temperature increase was 0.1 °C in every half an hour to make sure that the solution has reached saturation at the corresponding temperature. The accuracy of the balance and thermometer were ±0.01 mg and ±0.1 °C, respectively.

A 250 mL jacketed flask (Bellco Glass, Vineland, NJ) with a top-mounted two-bladed flat electromagnetically-driven stirrer was employed for dissolution rate experiment. The flask was connected to a Neslab RTE digital plus 740 bath circulator (Neslab, Mississauga, Ont.) for keeping the temperature at 25 °C. Samples of each solid form were ground and sieved to have the same crystal size distribution and a maximum size of 20 μm. This was done to compensate for the effect of size distribution on dissolution rate as the smaller particles dissolve faster than bigger ones. The spectrophotometric peak at 228 nm was considered for the quantitative analysis of the solution using pre-developed calibration curve. Solid (0.4 g) (about five times more than the solubility at 25 °C) was added to 200 mL isopropanol while mixing at 60 rpm. Every 1 min a 10 mL sample was pipette out and filtered using a 250 mL vacuum flask. The filtrate were collected in a 10 mL test tube. Membrane disk filter (VWR, Mississauga, Ont.) with 0.45 μm pore size was used. Further precise dilution with isopropanol was performed to bring the concentration of RAN-HCl in the range of spectrophotometer calibration.

A 50 mL jacketed flask (Bellco Glass, Vineland, NJ) was used for solution-mediated transformation stud-

ies, in which a Neslab RTE digital plus 740 bath circulator (Neslab, Mississauga, Ont.) provided heating and cooling. The flask was connected to a nitrogen line and also to a condenser. Mixing was performed using a magnetic stirrer. For each experiment 50 mL solvent and 2 g total solid were used. The initial solids were pure forms or 50/50 wt.% mixtures of them. The slurry was filtered at the end of the experiment and oven-dried followed by solid-state ATR-FTIR analysis.

2.5. Grinding and pressing device

Mortar and pestle were used for manual grinding. A manual Buehler mounting press with stainless steel die (Buehler, Evanston, IL) was employed for pressing the powders to make tablets with 31.7 mm diameter. Pressures of 135 bar and 285 bar were applied for compressing the tablets. The powder was held for 5 min under pressure.

2.6. Sonic sieves

A GilSonic autosiever (Gilson Co. Inc., Worthington, OH) was used for screening the ground particles. The particles smaller than 20 μm were used for the dissolution rate experiment.

2.7. Differential scanning calorimetry

Thermal analysis was conducted by differential scanning colorimeter (DSC, Mettler Toledo, Chicago, IL). The samples of 6–15 mg were prepared in a covered 40 μl aluminum crucible with a hole in the lid to allow venting. The heating rate of 0.5 °C/min for melting temperature and heat capacity measurement was used. To find the heat of fusion, a heating rate of 100 °C/min was employed to compensate the thermal degradation at melting point (Mirmehrabi et al., 2004a). So, the solid melted before degradation occurred. The sensors and the crucibles were under the flow of nitrogen during the experiment. The calibration of the instrument was performed using indium.

2.8. Software

MATLAB™ software was employed for calculating the adjustable parameters of UNIQUAC using *fmincon* command. OPUS™ software (Bruker, Milton, Ont.) was used for solid state ATR-FTIR data collection. Labview™ 6*i* (National Instrument, Austin, TX) was also used for recording the pH in the computer using a field point data acquisition system. Cary Win UV™ (Varian, Mississauga, Ont.) was used for collecting the spectrophotometric data. Mettler Toledo thermal analysis STARe™ software was used for acquisition and analysis of DSC data.

3. Results

3.1. Effect of HCl on ranitidine hydrochloride

Fig. 2 illustrates the changes in spectrophotometry spectra at different pHs. The spectra have two peaks at 326 nm and 228 nm, which are related to the nitroethenediamine moiety and the furanyl group, respectively. As pH decreases, the magnitude of nitroethenediamine peak decreases until it disappears at pH-0.92. This phenomenon is due to carbon protonation of the nitroethenediamine group rather than nitrogen protonation (Cholerton et al., 1984). At this pH all the ranitidine molecules convert to RAN-2HCl. Meanwhile the furanyl peak shows a little shift toward 220 nm while its magnitude increases.

Plotting the peak values at 326 nm against pH provides other important information (Fig. 3). At pH values less than 3.5, the formation of RAN-2HCl becomes a strong function of pH. So, based on this graph, the best range of operating pH for production of ranitidine hydrochloride is between 4.5 and 6.0. The same study can also be conducted for other solvents to find the proper operating values of pH.

3.2. Solid state ATR-FTIR standard curve

Fig. 4 illustrates FTIR spectra of both forms in the range of 1020–1100 cm^{-1}. Various binary mixtures of both forms were prepared to develop the FTIR standard curve. The same procedure as Sertsou et al. (1999) was performed for peak 1045 cm^{-1}, which is a specific peak of Form 2. The result was a linear correlation with $R^2 = 0.9070$ for absorbance versus wavenumber. In this study, it was observed that the in-

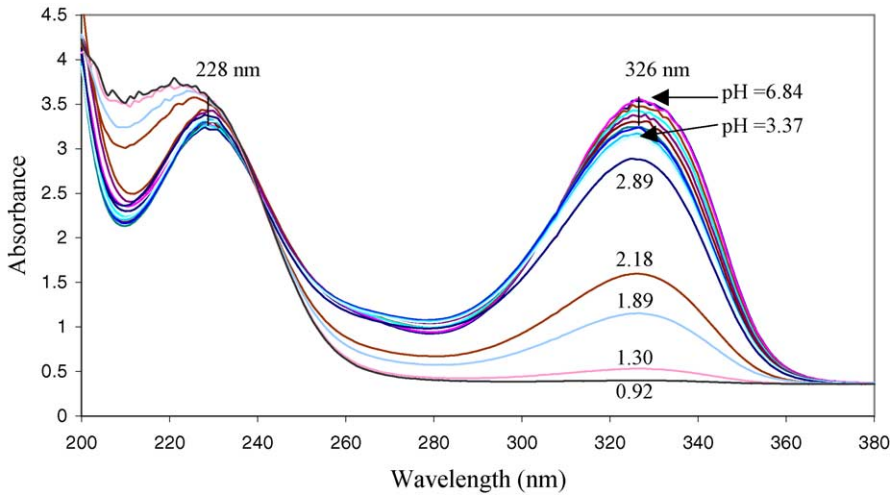


Fig. 2. Near ultraviolet spectra of ranitidine in IPA at various pH ($T = 25\,^{\circ}C$).

tensity of 1045 cm^{-1} peak fluctuates for different runs of an identical sample. The fluctuations were due to the changes in size distribution of particles. In order to alleviate the problem, the powder had to be ground to a narrow size distribution but this may cause solid–solid transformation in polymorphic systems. The other approach is to use the ratio of two peaks including a characteristic peak and an inert peak that is the same for both forms (Radatus and Murthy, 1997). In this study, peaks at 1045 cm^{-1} and 1075 cm^{-1} were chosen as characteristic and inert peaks, respectively. Plotting the absorbance ratio of these two peaks showed a linear relation with the weight percent of Form 2 in the solid mixture with $R^2 = 0.9983$. Fig. 5a and b illustrate the absorbance of single peaks and their ratio, respectively. The regression results were used for the quantification of Forms 1 and 2 in the solid state.

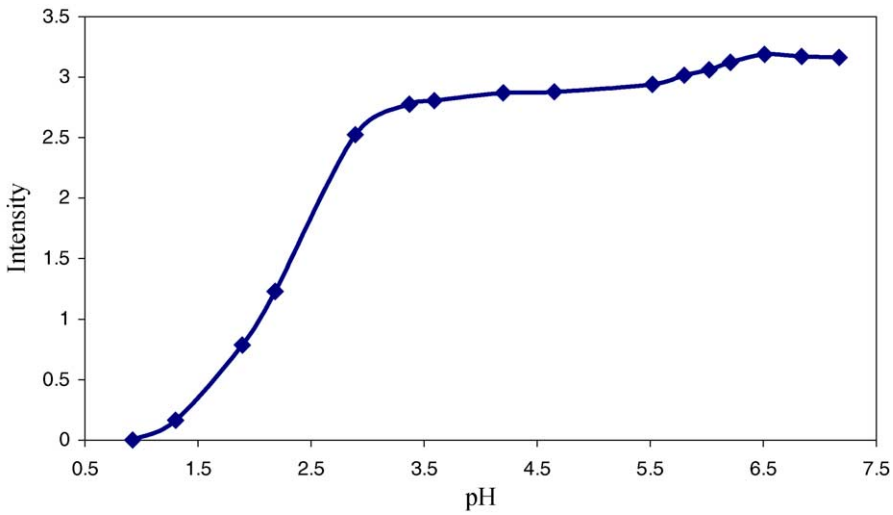


Fig. 3. The intensity of 326 nm peak vs. pH, the baseline has been tared to zero.

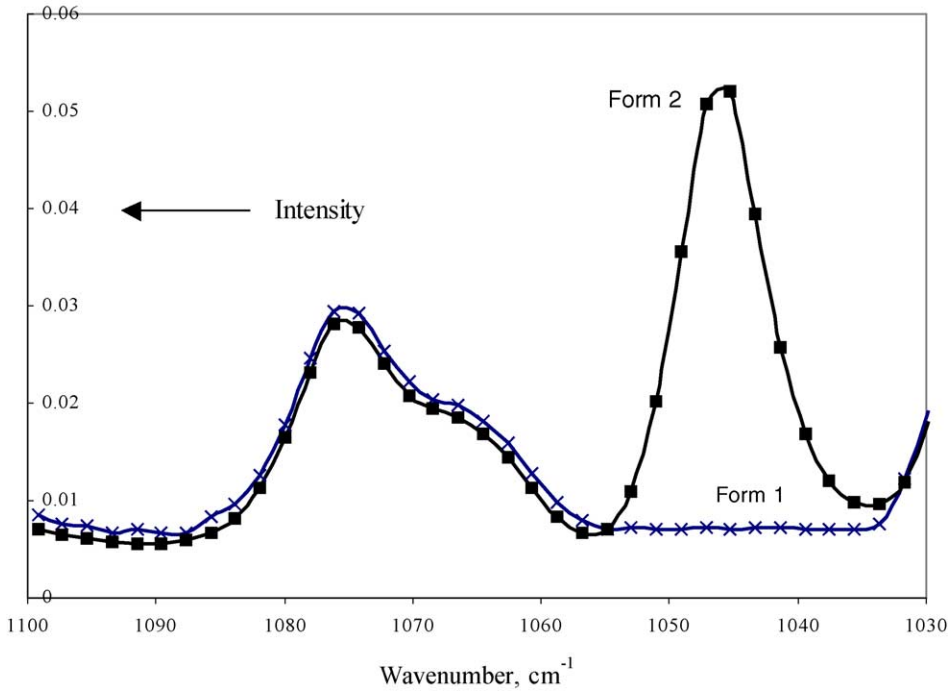


Fig. 4. The ATR-FTIR spectra of polymorphic forms of RAN-HCl.

3.3. Solubility data

The results of solubility measurements in different solvents are given in Tables 1–3. Ranitidine hydrochloride is sparingly soluble in isopropanol and *n*-propanol but very soluble in methanol. Interpolation of the solubility values at 42 °C shows that the solubility of ranitidine hydrochloride in *n*-propanol and methanol are approximately 4 times and 540 times more than the solubility in isopropanol, respectively. It was also

Table 1
Solubility of ranitidine hydrochloride solid forms in methanol

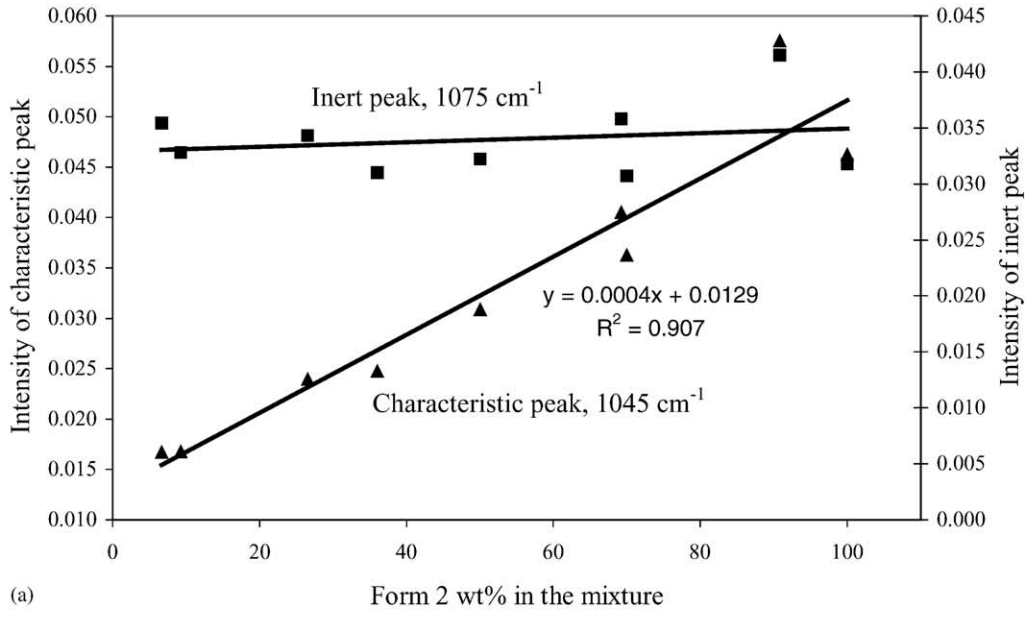
Form 1		Form 2	
Temperature (°C)	Solubility (g solute/100 g solvent)	Temperature (°C)	Solubility (g solute/100 g solvent)
12.4	12.965	7.9	10.466
17.1	17.873	14.8	17.101
26.7	36.034	29.9	47.834
28.5	40.026	32.1	56.406
31.0	46.943	34.9	68.133
43.0	92.868	41.5	98.104

Table 2
Solubility of ranitidine hydrochloride solid forms in isopropanol

Form 1		Form 2	
Temperature (°C)	Solubility (g solute/100 g solvent)	Temperature (°C)	Solubility (g solute/100 g solvent)
24.2	0.052	25.2	0.061
31.2	0.081	30.0	0.085
32.0	0.084	34.0	0.114
35.0	0.104	37.9	0.149
42.8	0.172	42.0	0.180

Table 3
Solubility of ranitidine hydrochloride solid forms in *n*-propanol

Form 1		Form 2	
Temperature (°C)	Solubility (g solute/100 g solvent)	Temperature (°C)	Solubility (g solute/100 g solvent)
21.3	0.179	22.4	0.213
26.7	0.255	25.6	0.279
33.2	0.417	32.1	0.422
38.1	0.628	39.2	0.731
42.8	0.788	43.5	0.995



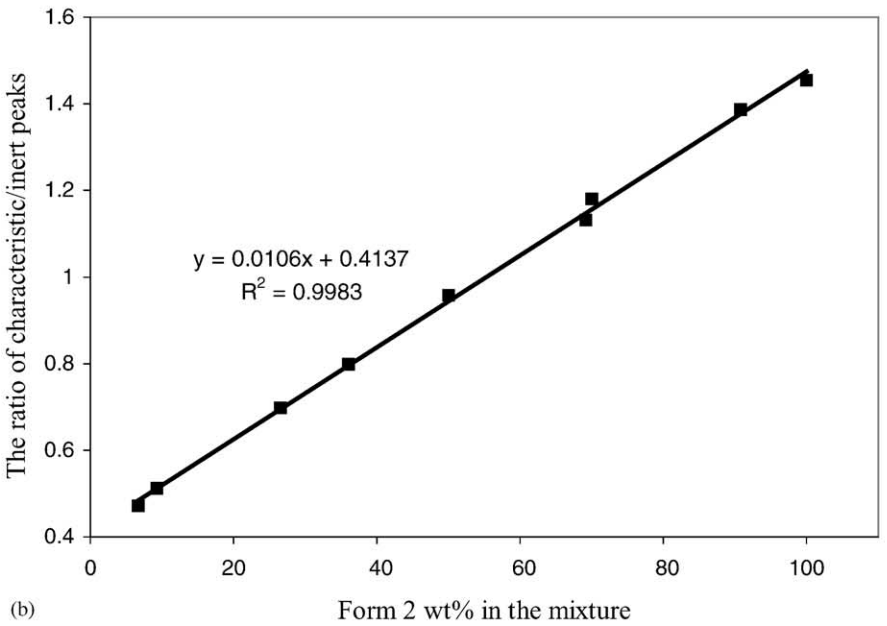


Fig. 5. The standard curves of ATR-FTIR.

found that as the polarity of solvent increases the solubility of ranitidine hydrochloride also increases:

solubility: water > methanol > MIBK > *n*-propanol > isopropanol

polarity: water > methanol > MIBK > *n*-propanol > isopropanol

where MIBK is methyl isobutyl ketone. Changing the pH of anhydrous isopropanol with hydrochloric acid

and sodium hydroxide in the range of 4.0–6.5 did not change the solubility of ranitidine hydrochloride. So, the solubility does not change with pH.

Tables 1–3 also show that Form 1 has a lower solubility than Form 2 and the difference between the solubility of the two forms increases with temperature.

Some other thermodynamic properties can also be calculated from the solubility data. The Van't Hoff equation shows that the logarithm of mole fraction of a solute is a linear function of heat and entropy of solution:

$$\ln x_2 = \frac{\Delta H_{\text{sol.}}}{RT} + \frac{\Delta S_{\text{sol.}}}{R} + c \quad (1)$$

where x_2 is the mole fraction of solute in the solvent, $\Delta H_{\text{sol.}}$ the heat of solution, $\Delta S_{\text{sol.}}$ the entropy of solution, T the corresponding absolute temperature, R the universal gas constant and c is a constant. Mole fraction, x_2, can be calculated using the solubility data in the following equation:

$$x = \frac{S \times \text{MW}_{\text{solvent}}}{100 \times \text{MW}_{\text{solute}}} \quad \text{and then} \quad x_2 = \frac{x}{1+x} \quad (2)$$

where S is the solubility in terms of gram solute per 100 g of solvent and MW is the molecular weight (g/mol). Plotting $\ln x_2$ versus reciprocal of absolute temperature should result in a straight line with a slope of $\Delta H_{\text{sol.}}/R$.

The difference between the Gibbs free energy of the two forms, ΔG_{1-2}, can be calculated from the solubility data as is shown below:

$$\Delta G_{1-2} \cong RT \ln\left(\frac{S_1}{S_2}\right) \quad (3)$$

where S_1 and S_2 are the solubilities of Forms 1 and 2 at an absolute temperature T.

Table 4 presents the heats of solution of each form of ranitidine hydrochloride, calculated from solubility data, the difference between heats of solution and the Gibbs free energies at 25 °C. Although the heats of solution in different solvents are very different, it appears that the difference between the heats of solution, which is an indication of energy difference between the two solid forms, is independent of the type of the solvent. The differences in Gibbs free energies are close to each other.

3.4. Solution-mediated transformation

Table 5 shows the conditions and results of solution mediated-transformation studies. Transformation from Form 1 to Form 2 was not observed in any of the cases studied. This phenomenon was expected from the solubility data of the two solid forms. Since the solubility of Form 2 is more than Form 1, therefore it dissolves more. Therefore, the solution would be saturated with respect to Form 2 and supersaturated with respect to Form 1. This suggests that the solution-mediated transformation may occur from Form 2 to Form 1 and not the reverse. On the other hand, crystallization to Form 1 is very slow due to the low degree of supersaturation.

Table 5 shows that the solvent and the initial presence of Form 1 are important for transformation of Form 2 to Form 1. So, it may be concluded that the solution-mediated transformation is not an important issue in the production of RAN-HCl. Indeed, more important are the conditions that lead to the initial formation of each form during reactive crystallization (Murthy et al., 1995; Mirmehrabi et al., 2004a,b).

3.5. Effect of grinding and compressing

The grinding was performed at about 25 °C. The bulk solid density of Form 1 increased from 0.22 g/mL to 0.29 g/mL due to grinding. No transformation to Form 2 was observed, which is contrary to the results of Forster et al. (1998). Therefore, grinding is useful

Table 4
Heat of solution and the difference between energies of two forms of ranitidine hydrochloride

	Methanol		Isopropanol		*n*-Propanol	
	Form 1	Form 2	Form 1	Form 2	Form 1	Form 2
Heat of solution (J/mol)	5645	5760	6061	6185	6617	6765
$\Delta H_{\text{sol.}1-2}$ (J/mol)	115		124		148	
ΔG_{1-2} at 25 °C (J/mol)	−282		−300		−274	

Table 5
Solution-mediated transformation results

Initial form	Process time	Media	Final form room $T \sim 23$°C	Final form $T = 48$ °C
Form 1	7 h	Anhydrous IPA	Form 1	Form 1
		2.5 wt.% water in IPA	Form 1	Form 1
	1 week	Anhydrous IPA	Form 1	
		2.5 wt.% water in IPA	Form 1	
Form 2	7 h	Anhydrous IPA	Form 2	Form 2
		2.5 wt.% water in IPA	Form 2	Form 2
	1 week	Anhydrous IPA	Form 2	
		2.5 wt.% water in IPA	Form 2	
50/50 wt.% Form 1/Form 2	7 h	Anhydrous IPA	50/50 wt.% F1/F2	50/50 wt.%
		2.5 wt.% water in IPA	50/50 wt.% F1/F2	50/50 wt.%
	1 week	Anhydrous IPA	66/44 wt.% F1/F2	
		2.5 wt.% water in IPA	50/50 wt.% F1/F2	

for increasing the bulk solid density of Form 1 ranitidine hydrochloride without any risk of solid–solid transformation. The same experiments were performed on Form 2 and no conversion was observed using solid-state FTIR analysis. The bulk solid density of Form 2 increased from 0.27 g/mL to 0.36 g/mL due to grinding.

Approximately 2.0 g of RAN-HCl of each solid form were used for tableting. Solid–solid transformation was not observed in any of the cases. This finding confirms the observation of Agatonovic-Kustrin et al. (2000).

3.6. Dissolution rate

Four concentrations were prepared to develop the spectrophotometric calibration curve. The intensity at 228 nm for 58.78 mg/L, 70.52 mg/L, 86.31 mg/L and

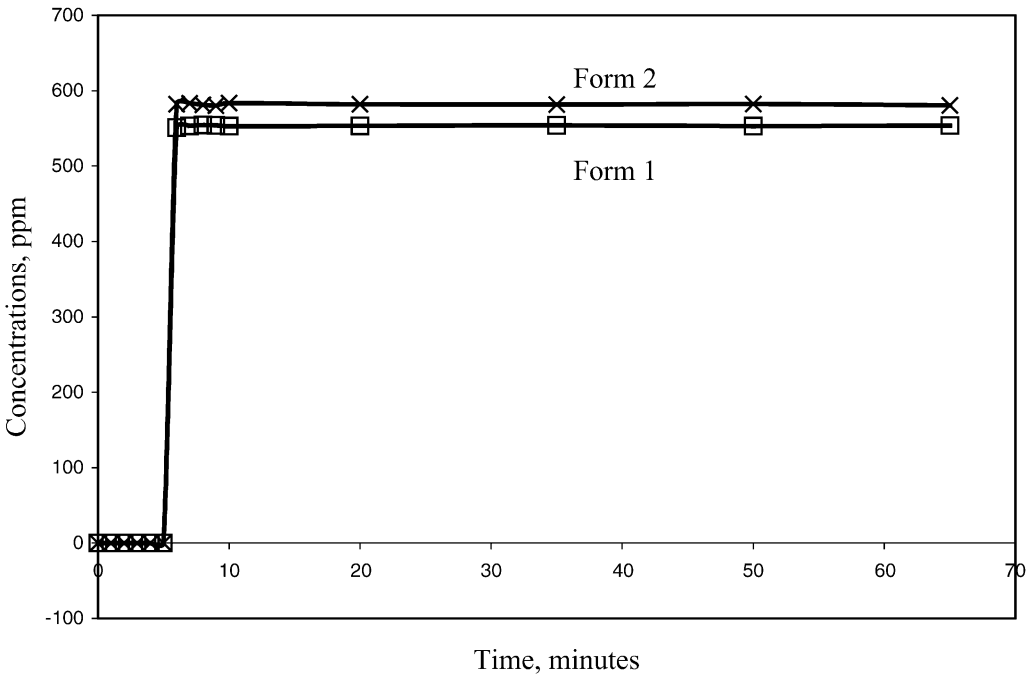


Fig. 6. Dynamic solubility of ranitidine hydrochloride in isopropanol.

99.87 mg/L RAN-HCl in IPA were 3.0252, 3.3832, 3.8893 and 4.3155, respectively. Fig. 6 illustrates the dissolution rate of both forms in isopropanol. The first sample that was taken 1 min after adding the solid has the same concentration as the last one taken after 1 h. The graph also confirms that the solubility of Form 2 is more than the solubility of Form 1.

The rationale for this part of study was to see if there were any difference between the dissolution rate of the two forms and consequently any difference in their bioavailability. In general, higher solubility results in higher dissolution rate. Form 2 has slightly higher solubility in IPA. It was, however, observed that the dissolution rates of both forms in IPA were the same. It is expected that the dissolution rate of both forms in water (bioavailability) would be similar.

3.7. Modeling the solubility by UNIQUAC

For non-ideal solutions we have (Prausnitz et al., 1999):

$$\ln\frac{f_2^{\mathrm{L}}}{f_2^{\mathrm{S}}} = \frac{\Delta H_{\mathrm{fus}}}{RT_{\mathrm{tp}}}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) - \frac{\Delta c_{\mathrm{p}}}{R}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) + \frac{\Delta c_{\mathrm{p}}}{R}\ln\frac{T_{\mathrm{tp}}}{T} \tag{4}$$

where f_2^{L} and f_2^{S} are pure sub-cooled liquid and pure solid fugacities of solute molecules, respectively, and T_{tp} is the triple point temperature which can be considered as melting point. ΔH_{fus} is heat of fusion and Δc_{p} is the difference between heat capacities of liquid and solid forms of solute at temperature T and R is the universal gas constant. The ratio of fugacities is also related to:

$$x_2\gamma_2 = \frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}} \tag{5}$$

where γ_2 is activity coefficient and x_2 is the molar solubility of solute in the binary solution. For ideal solutions, the activity coefficient of the solute is equal to unity so that the equation will be deduced to:

$$\ln\frac{1}{x_2^{\mathrm{ideal}}} = \frac{\Delta H_{\mathrm{fus}}}{RT_{\mathrm{tp}}}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) - \frac{\Delta c_{\mathrm{p}}}{R}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) + \frac{\Delta c_{\mathrm{p}}}{R}\ln\frac{T_{\mathrm{tp}}}{T} \tag{6}$$

and

$$x_2 = \frac{x_2^{\mathrm{ideal}}}{\gamma_2} \tag{7}$$

Replacing the thermal parameters of solute in Eq. (6) gives the ideal solubility of the solute in terms of mole fraction. Table 6 shows the thermal parameters of both forms.

To model the solubility, the UNIQUAC equation was used. The activity coefficient in UNIQUAC has two parts: combinatorial and residual. The combinatorial part describes the dominant entropic contribution and the residual part is due to intermolecular forces and is responsible for enthalpy of mixing (Abrams and Prausnitz, 1975). The UNIQUAC equation for two component systems is as follow:

$$\ln\gamma_2 = \ln\frac{\Phi_2}{x_2} + \frac{z}{2}q_2\ln\frac{\theta_2}{\Phi_2} + \Phi_1\left(l_2 - \frac{r_2}{r_1}l_1\right) - q_2'\ln(\theta_2' + \theta_1'\tau_{12}) + \theta_1' q_2'\left(\frac{\tau_{12}}{\theta_2' + \theta_1'\tau_{12}} - \frac{\tau_{21}}{\theta_1' + \theta_2'\tau_{21}}\right) \tag{8}$$

$$\Phi_2 = \frac{r_2x_2}{r_1x_1 + r_2x_2} \qquad \theta_2 = \frac{q_2x_2}{q_1x_1 + q_2x_2}$$
$$\theta_2' = \frac{q_2'x_2}{q_1'x_1 + q_2'x_2} \tag{9}$$

Table 6
Temperature, enthalpy of melting and heat capacities of ranitidine hydrochloride solid forms

Form	$T_{\mathrm{melt.}}$ (°C)	$\Delta H_{\mathrm{melt.}}$ (J/g)	$c_{\mathrm{p}} = \alpha_0 + \alpha_1 T + \alpha_2 T^2 + \alpha_3 T^3$ (J/g °C), range of 25–130 °C			
			α_0	α_1	α_2	α_3
Form 1	135.6	116.6	1.846	−0.01	9×10^{-5}	-3×10^{-7}
Form 2	137.8	101.6	1.602	3.9×10^{-3}	-7×10^{-5}	-3×10^{-7}

$$\tau_{12} = \exp\left(-\frac{a_{12}}{T}\right) \quad \tau_{21} = \exp\left(-\frac{a_{21}}{T}\right)$$
$$l_1 = \frac{z}{2}(r_1 - q_1) - (r_1 - 1)$$
$$l_2 = \frac{z}{2}(r_2 - q_2) - (r_2 - 1) \tag{10}$$

a_{12} and a_{21} are adjustable parameters of the UNIQUAC equation and r, q and q' are pure component constants, which depend on the molecular size and can be calculated from Van der Waals volume and area. Due to lack of availability of Van der Waals volume and area of RAN-HCl, the functional group approach presented by Fredenslund et al. (1975) was adopted.

$$r = \sum_{i=1}^{m} n_i \times R_i \tag{11}$$

$$q = \sum_{i=1}^{m} n_i \times Q_i \tag{12}$$

where m is the number of functional groups in the molecule, which is 11 for ranitidine hydrochloride and n is the repeating number of each functional group in the molecule. The group data were taken from Hansen et al. (1991). The values of n, R and Q are given in Table 7. Using this table and Eqs. (11) and (12), the r and q parameters for ranitidine hydrochloride were calculated equal to 15.29 and 12.88, respectively. Furthermore, Van der Waals volume and area were calculated using the following equations (Bondi, 1968):

$$Q_{\mathrm{VdW}} = 15.17 \times r \tag{13}$$

$$R_{\mathrm{VdW}} = 2.5 \times 10^9 \times q \tag{14}$$

where Q_{VdW} and R_{VdW} are the Van der Waals volume and area, respectively. From these equations, $Q_{\mathrm{VdW}} = 231.95\,\mathrm{cm^3/mol}$ and $R_{\mathrm{VdW}} = 3.22 \times 10^{10}\,\mathrm{cm^2/mol}$ were calculated, for ranitidine hydrochloride. R_{VdW} and Q_{VdW} of solvents were obtained from Yaws et al. (1999) and consequently r and q were calculated from Eqs. (13) and (14).

The optimization procedure was based on the minimization of the error between calculated and experimental values of activity coefficients.

$$\min_{a_{12},a_{21}} \text{error} = \sum_{k=1}^{d} (\gamma_{2,\mathrm{k,exp.}} - \gamma_{2,\mathrm{k,calc.}})^2 \tag{15}$$

where d is the number of experimental data points, $\gamma_{2,\mathrm{k,exp.}}$ and $\gamma_{2,\mathrm{k,calc.}}$ are the experimental and calculated equilibrium activity coefficients of the solute. The experimental activity coefficient, $\gamma_{2,k,\mathrm{exp.}}$ and $\gamma_{2,\mathrm{k,calc.}}$ were found as follows.

1. Calculate the ideal mole fractions from Eq. (6) at temperatures that the solubility of solids is available.
2. Calculate the experimental mole fractions from Eq. (2) and solubility data.
3. Calculate experimental activity coefficients from Eq. (7) using the calculated and experimental mole fractions.
4. Write a program in MATLAB™ software using *fmincon* function of MATLAB™ and give all the experimental mole fractions, activity coefficients and temperatures. The program will change the adjustable parameters to minimize the result of Eq. (15) and reports the adjustable parameters.

Furthermore these adjustable parameters will be used for calculating the solubility at various temperatures using UNIQUAC equation. Tables 8 and 9 show the adjustable parameters of UNIQUAC that were calculated from the solubility data. The adjustable parameters can be further used in simulation software for predicting other properties of the employed chemicals or for predicting the equilibrium in

Table 7
Functional groups and the group volume and area parameters of ranitidine hydrochloride

	R	Q	Number of groups in the molecule (n)
CH_3	0.9011	0.8480	3
CH_2	0.6744	0.5400	4
CH	0.4469	0.2280	1
$CHNO_2$	1.5540	1.2480	1
C=CH	0.8886	0.6760	1
CH_3NH	1.4337	1.2440	1
CH_2NH	1.2070	0.9360	1
CH_2S	1.3863	1.0600	1
Tetra hydro furan (THF)	0.9183	1.1000	1
CH_2N	0.9597	0.6320	1
HCl	1.1000	1.0560	1

Table 8
Adjustable parameters of UNIQUAC equation; subscript 1 refers to solvent and 2 refers to ranitidine hydrochloride Form 1

Solvent	r	q	q'	a_{12}	a_{21}	E%	T range (°C)
Methanol	1.43	1.43	0.96	−64.85	314.16	0.89	12.4–43.0
Isopropanol	2.78	2.51	0.89	−33.72	352.08	1.07	24.2–42.8
n-Propanol	2.78	2.51	0.89	−8.07	204.74	3.53	21.3–42.8

Table 9
Adjustable parameters of UNIQUAC equation; subscript 1 refers to solvent and 2 refers to ranitidine hydrochloride Form 2

Solvent	r	q	q'	a_{12}	a_{21}	E%	T range (°C)
Methanol	1.43	1.43	0.96	−54	331.8	1.52	7.9–41.5
Isopropanol	2.78	2.51	0.89	38.91	196.01	2.64	25.2–42.0
n-Propanol	2.78	2.51	0.89	49.73	122.1	1.26	22.4–43.5

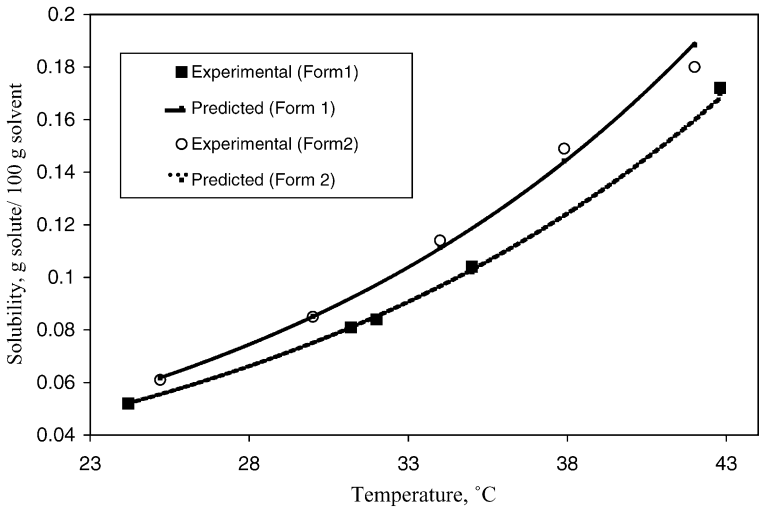


Fig. 7. Experimental and predicted (by UNIQUAC) solubility of ranitidine hydrochloride solid forms in isopropanol.

multi-component systems. The reported errors in these tables are the absolute deviation between the calculated solubility using UNIQUAC and the experimental data:

$$\text{error percent} = \text{average} \sum_{k=1}^{d} \left(\left| \frac{S_{\text{k,exp.}} - S_{\text{k,calc.}}}{S_{\text{k,exp.}}} \right| \right) \times 100 \qquad (16)$$

where S_k is the solubility at a temperature corresponding to point k. Fig. 7 illustrates the experimental and calculated solubility of ranitidine hydrochloride solid forms in isopropanol.

4. Discussions

Spectrophotometeric studies showed that pH has an important influence on the degree of reaction between ranitidine base and hydrogen chloride in crystallization media. A pH between 4.5 and 6.5 will assure the production of RAN-HCl. It was also shown that using just two peaks of infrared spectra is reliable for determining the composition of solid forms of ranitidine hydrochloride. There is no need for grinding the solids in order to compensate for the variation of the particle size. This analytical method can be further extended to other polymorphic and tautomeric systems.

Solubility of Form 1 was found to be less than Form 2. The difference between the solubilities of two solid forms increases at the higher temperatures. Thermodynamic parameters calculated from solubility data indicated that the difference between energies of two solid forms is almost independent of the type of solvent employed. Solution-mediated transformation showed a weak conversion from Form 2 to Form 1. No transformation was observed from Form 1 to Form 2. So, in order to isolate a special tautomer, efforts must be focused on the initial formation of each solid form rather than the transition between them.

Grinding can be considered a safe method for increasing the bulk solid density of ranitidine hydrochloride without any risk of solid–solid transformation. Compression in tableting process also does not induce conversion of solid forms. At the end, the UNIQUAC and group contribution parameters were used to model the strongly non-ideal equilibrium system of ranitidine hydrochloride in pure solvents.

Acknowledgements

The authors would like to thank Ms. Luisa Grappolini for help in thermodynamics calculations.

References

Abrams, D.S., Prausnitz, J.M., 1975. Statistical thermodynamics of liquid mixtures. A new expression for the excess Gibs energy of partly and completely miscible systems. AIChE J. 21, 116–128.

Agatonovic-Kustrin, S., Wu, V., Rades, T., Saville, D., Tucker, I.G., 2000. Ranitidine hydrochloride X-ray assay using a neural network. J. Pharm. Biomed. Anal. 22, 985–992.

Bondi, A., 1968. Physical Properties of Molecular Crystals, Liquids and Gasses. Wiley, New York.

Canadian Pharmacists Association, 2000. Ranitidine HCl. Webcom Limited, Toronto, pp. 1772–1774.

Chiavone, F.O., Rasmussen, P., 2000. Modeling of salt solubilities in mixed solvents. Braz. J. Chem. Eng. 17, 117–131.

Cholerton, T.J., Hunt, J.H., Klinkert, G., Smith, M.M., 1984. Spectroscopic studies on ranitidine—its structure and the influence of temperature and pH, J. Chem. Soc. Perkin Trans. II, 1761–1766.

Crookes D.J., 1987. Process for Forming Form 2 Ranitidine Hydrochloride. US Patent 4 672 133.

Forster, A., Gordon, K., Schmierer, D., Soper, N., Wu, V., Rades, T., 1998. Characterization of two polymorphic forms of ranitidine-HCl. Int. J. Vib. Spec. 2, Section 2.

Fredenslund, A., Jones, R.L., Prausnitz, J.M., 1975. Group-contribution estimation of activity coefficient in nonideal liquid mixtures. AIChE J. 21, 1086–1099.

Grant, D.W.J., Higuchi, T., 1990. Solubility Behavior of Organic Compounds, Techniques in Chemistry. Wiley, Toronto.

Hansen, H.K., Rasmussen, P., Fredenslund, A., Schiller, M., Gmehling, J., 1991. Vapor–Liquid Equilibria by UNIFAC Group Contribution. 5. Revision and Extension. I & EC Res. 30, 2352–2355.

Khanna, J.M., Kumar, N., Khera, B., Khanna, M., 1997. Process for the Manufacture of Form 1 Ranitidine Hydrochloride. US Patent 5 621 120.

Mirmehrabi, M., Rohani, S., 2004. Measurement and prediction of the solubility of stearic acid polymorphs by the UNIQUAC equation. Can. J. Chem. Eng., in press.

Mirmehrabi, M., Rohani, S., Murthy, K.S.K., Radatus, B., 2004a. Characterization of tautomeric forms of ranitidine hydrochloride: thermal analysis, solid-state NMR, X-ray. J. Crystal Growth 260, 517–526.

Mirmehrabi, M., Rohani, S., Murthy, K.S.K., Radatus, B., 2004b. Improving the filterability and solid density of ranitidine hydrochloride Form 1. J. Pharm. Sci. 93, 1692–1700.

Murthy, K., Radatus, B.K., Sidhu, K.P.S., 1995. Reissued 2002. Process for Production of an Improved Form of Form 1 Ranitidine Hydrochloride having Improved Filtration and Drying Characteristics, Canadian Patent 2 120 874.

Ngooi, T.K., Antczak, C., Tindall, J.L.A., McGolrick, J.D., 1998. Preparation of Form 1 Ranitidine Hydrochloride. Canadian Patent 2 099 530.

Pinhoa, S.P., Macedob, E.A., 2002. Experimental measurement and modelling of KBr solubility in water, methanol, ethanol, and its binary mixed solvents at different temperatures. J. Chem. Therm. 34, 334–360.

Prausnitz, J.M., Lichtenthaler, R.N., Azevedo, E.G., 1999. Molecular thermodynamics of Fluid-Phase Equilibria, third ed. Prentice-Hall, Upper Saddle River, NJ.

Price, B.J., Clitherow, J.W., Bradshaw, J., 1978. Aminoalkyl Furan Derivatives. US Patent 4 128 658.

Radatus, B., Murthy, K.S.K., 1997. Unpublished work. Brantford Chemicals Inc.

Schickaneder, H., Nikolopoulos, A., 1997. Process for Preparing Form 1 Ranitidine Hydrochloride. US Patent 5 663 381.

Sertsou, G., Agatonovic-Kustrin, S., Rades, T., 1999. The Use of DRIFTS to analyse binary mixtures of two polymorphic forms of ranitidine-HCl using only one specific peak. Int. J. Vib. Spec. 5, Section 3.

Yaws, C.L., Wang X.M., Satyro, M.A., 1999. Solubility parameters, liquid volume, and Van Der Waals volume and area, in: Yaws C.L. (Eds.), Chemical Properties Handbook: Physical, Thermodynamic, Environmental, Transport, Safety, and Health Related Properties for Organic and Inorganic Chemicals, McGraw Hill, New York, pp. 340–363.