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Response surface analysis of solution-mediated polymorphic transformation of buspirone hydrochloride

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Abstract

Buspirone hydrochloride has several polymorphs including Form 1 and Form 2. The solution-mediated transformation of Form 2 to Form 1 has been studied in this research. The interconversion of two polymorphs can occur in the salt formation step which is the last step for producing this drug. In addition, the effect of co-solvent and rate of addition of acid to the solution were investigated on the extent of interconversion of Form 2 to Form 1. It has been found that pH, co-solvent ratio and amount of solvent have more influence on polymorphic interconversion. A factorial design approach was used to carry out a response surface analysis to identify the more important factors affecting the interconversion of polymorphs and find the optimum experimental conditions for the production of the desired polymorph. Quantitative characterization of the product was done by XRPD, FT-IR, SEM, DSC and TSI-PSD.

Keywords: Design of experiment; Response surface analysis; Polymorphism; Interconversion; Buspirone hydrochloride

1. Introduction

Any crystallization process must cross the nucleation barrier. It is generally assumed that, as the molecules start to assemble in a supersaturated solution, they form clusters that may lead to lasting nuclei. For polymorphic systems nuclei of all the observed polymorphs are probably formed [1]. Each type of nucleus would structurally resemble the crystal into which it will eventually develop. In the pharmaceutical industry, different polymorphs are usually prepared by crystallization from solution employing various solvents, temperature regimes, etc. [2]. The supersaturation may be achieved by cooling, addition of an anti-solvent, chemical reaction between soluble species, or variation of pH to produce less soluble acid or base from the salt or vice versa.

In this study, polymorphic interconversion of buspirone hydrochloride (BUS-HCl; *N*-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl]-1,1-cyclopentanediacetamide monohydrochloride) with respect to various parameters such as the solvent type and amount, pH, impurity and co-solvent ratio were investigated. BUS-HCl is a white crystalline water-soluble anti-anxiety drug. BUS-HCl is produced through three reaction steps. The last step is salt formation which is presented in Fig. 1. This step is very important for crystal formation of final product. The first two steps involve two reactions that may result in the formation of impurities in the form of unreacted raw materials and/or reaction by-products in the final stage.

Extensive polymorph screening on BUS-HCl has shown that close to 90% of the experiments result in the two main polymorphs of this compound, namely Form 1 with a melting point at 188 °C and Form 2 with a melting point at 203 °C. Based on thermal analysis and solubility measurements that have been performed by the present principal authors [3,4], these two crystal structures are enantiotropes and the transformation temperature from Form 1 to Form 2 is at 95 °C.

This study is focused on the effect of various parameters on the polymorphic interconversion of BUS-HCl. A 2^4-factorial design method design was used to plan and analyze the experiments with respect to Form 1 formation. It was found that pH, solvent composition, co-solvent ratio and impurity, played the most prominent role. The morphology of crystals, filterability, crystallization time, size distribution and quantitative analysis of final products have also been investigated.

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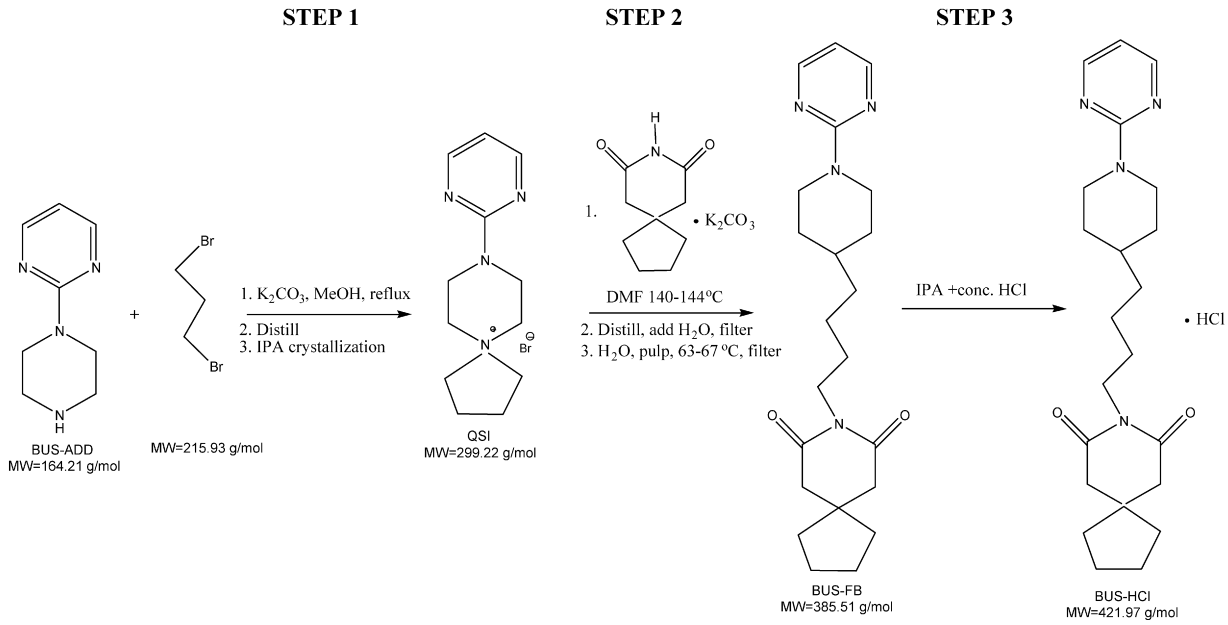

Fig. 1. The reaction steps in producing buspirone hydrochloride.

2. Materials and methods

2.1. Materials

Buspirone-free base (BUS-FB) was supplied by Apotex PharmaChem Inc. (Brantford, Ont.). Other chemicals were purchased from Caledon (Georgetown, Ont.) and EMD (Gibbstown, NJ).

2.2. Experiment method

In all the experiments, 7 g of BUS-FB was used in a predetermined amount of isopropyl alcohol (IPA). The experiments were carried out in a 100 ml double-jacketed glass vessel (Bellco, NJ) equipped with a stirrer (AC Tech, MN). Mixing was achieved with a magnetic stirrer at constant speed for all experiments. In order to produce Form 2, the experimental procedure of US patent 4,810,789 was adopted [5]. By altering some parameters used in the US patent 4,810,789, the transformation of BUS-FB to Form 1 of BUS-HCl was investigated. In all the experiments conducted, the initial temperature was kept at 50 °C and the solution was then cooled to 15 °C or ≤5 °C depending on the conditions studied. The solution temperature was controlled using a water bath system (RTE 220, Neslab instrument Inc., NJ). The solid crystals formed in the solution were separated from the solvent using vacuum filtration and washed with IPA. The particle size distribution measurements were carried out using TSI-PSD-3603 apparatus.

Thermal analysis was done using a Mettler Toledo 822^e DSC operating with Version 9.01 Star^e software (2006). Samples of 4–15 mg were prepared in a covered aluminium crucible having pierced lids to allow escape of volatiles. The heating rate of 10 °C/min was employed. The sensors and samples were under nitrogen purge during the experiments and the flow rate of nitrogen was 30–50 ml/min. The uniform size distribution was ensured by gently grinding the samples. In addition, FT-IR results confirmed that there was no interconversion during the sample preparation.

The FT-IR spectra were recorded on a solid-state Fourier transformation infrared spectrometer (Bruker Vector 22) equipped with OPUS v3.1. The samples were analyzed in transmission mode through a diamond window. The number of scans was 32 over the 450–4000 cm^{-1} spectral region with a resolution of 2 cm^{-1}. The background was collected in the same range for air. The XRPD spectra were collected on a Rigaku-MiniFlex powder diffractometer, using Cu Kα (λ for Kα = 1.54059 Å) radiation obtained at 30 kV and 15 mA. The scans were run from 3.0° to 90.0° 2θ, increasing at a step size of 0.02° with a counting time of 2 s for each step. For X-ray sample preparation, uniform mixtures of final product were prepared by gently grinding and weighing to a total amount of 50 mg. FT-IR was used to make sure there was no interconversion due to sample preparation. An optical microscope (Zeiss) with a magnification of 50–500, equipped with a digital camera and Northern Eclipse v6.0 imaging software, was used for visual analysis. Also the scanning electron microscope (SEM) was used for morphological analysis (Hitachi VP-SEM). The samples were gold-sputtered.

A series of unseeded experiments were performed to determine the effects of pH, solid to solvent ratio, impurity and addition of co-solvent, on the interconversion of Form 2 to the more stable Form 1. In all the experiments care was taken to prevent any impurity contamination. The following experiments were conducted:

1. Rapid addition (5 ml/min) of HCl to BUS-FB/IPA solution at 50 °C and maintaining the solution at a stable desirable pH for 2–3 h. The pH range studied was from 0.4 to 3.9.
2. Gradual addition (0.05 ml/min) of HCl to BUS-FB/ IPA solution at 50 °C to achieve two different pH's, an extremely acidic condition in the range of 0.4–0.55 and a moderately acidic condition with pH in the range of 3.4–3.6.

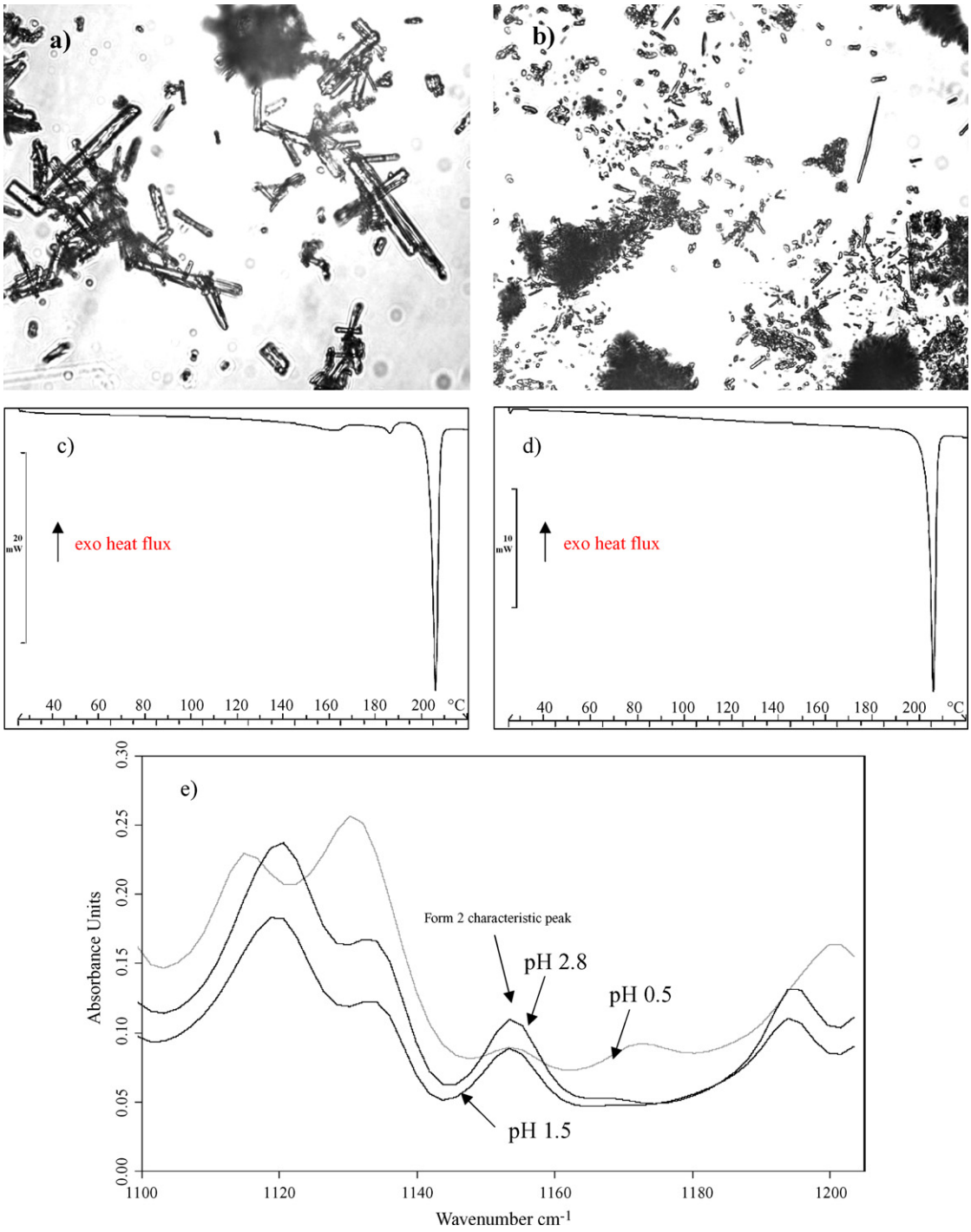

Fig. 2. Particle morphology, thermal analysis and FT-IR of BUS-HCl. (a) At pH 3.85, (b) at pH 0.5 (all pictures were taken at a magnification 50×), (c) DSC result for pH 0.5 (heating rate: 10 °C/min), (d) pH 3.85, and (e) FT-IR result for different pH (Section 3.1.1.1).

3. *Effect of solute concentration*. The amount of solute (BUS-FB) added was kept constant at 7 g but the amount of solvent (IPA) was altered from 50 g to 55 g, 60 g, 65 g and 70 g. In all the experiments, acid was added rapidly to the solution until pH was maintained within the range of 3.4–3.6.
4. *Effect of pH and variable solvent ratios*. A procedure similar to the preceding case was used but the pH was reduced to the range of 0.45–0.55.
5. *Effects of impurity*. Two types of impurities were tested, the first one being the QSI (8-(2-pyrimidinyl)-8-aza-5-azoniaspiro[4,5] decane bromide) (see Fig. 1) and the second was BUS-FB.

   (a) Different amounts of QSI ranging from 0.5% to 1.5% of the total amount of solid was added and then mixed with 50 g of IPA. The acid was added rapidly to the solution

and pH was maintained within the range of 3.4–3.6 in all the experiments.

(b) Impurity testing for BUS-FB was performed by rapid addition of acid to the solution of 7 g of BUS-FB and 50 g of IPA until the pH was reduced to 3.4–3.6. At this point, extra BUS-FB was added in an attempt to neutralize the solution to the target pH of 3.4–3.6. The amount of extra BUS-FB added was measured by weighing the BUS-FB beaker before and after adding it to the extremely acidic solution.

6. *Effect of co-solvent*. Water was added to the IPA in different amounts ranging from 3% to 12% by weight. Acid was added rapidly to the solution and the pH was maintained within the range of 3.4–3.6 in all the related experiments.

3. Experimental results and discussion

Studies investigating the characteristics of each polymorph had been performed by Sheikhzadeh et al. [3] using DSC, FT-IR and XRPD. Thermal analysis using the DSC showed an endotherm at 189 °C which is the melting point of Form 1 and another endotherm at 203 °C which is its melting point of Form 2. To prevent the effect of particle size distribution it is best to use the ratio of the characteristic peak and a reference peak (inert peak) common to both polymorphs [4]. The band associated with C–N stretching appears in the region 1130–1270 cm^{-1} in Form 2 with a small shoulder. Form 2 exhibits a unique absorption band at 1153 cm^{-1}. For Form 2, peaks at 1153 cm^{-1} and 1193 cm^{-1} were chosen as characteristic and reference peaks for quantization by FT-IR, respectively. X-ray powder diffraction (XRPD) showed that Form 1 has specific peaks at the following 2θ angles: 6.7°, 8.5°, 12.6°, 17.6°, 28.2°, 33.6°, and 44.8°. On the other hand, the unique 2θ angles for Form 2 are 7.4°, 10.0°, 18.9°, 20.0°, 21.7°, 29.3°, and 30.3° [3].

3.1. Polymorphic outcome and crystal morphology

3.1.1. Effect of rate of addition of HCl to BUS-FB/IPA solution

3.1.1.1. Rapid addition. Addition of HCl to the supersaturated solution at 50 °C and leaving the acidic solution for 2–3 h at a pH in the range of 3.4–3.6 resulted in the formation of Form 2 as the main product. Several experiments were conducted using the experimental procedure presented in [5] but altering the pH from 3.85 to 0.45.

When the pH was in the range of 3.4–3.6, the solution was pale yellow. As the pH decreased, the solution became more yellow and at a pH of 0.5 the solution had a brownish-yellow color. The induction time for all the experiments varied between 10 min and 30 min after the temperature of the bath—circulator was reduced to 15 °C. The product formed at pH 3.4 was filtered faster than the product formed at a pH 0.5. Optical microscopy showed that the crystals formed at a pH 0.5 were smaller, very sticky and more susceptible to agglomeration. Fig. 2a and b illustrates the microscopic pictures obtained at both pH. Fig. 2a shows Form 2 rode shape crystals which indicate the existing of

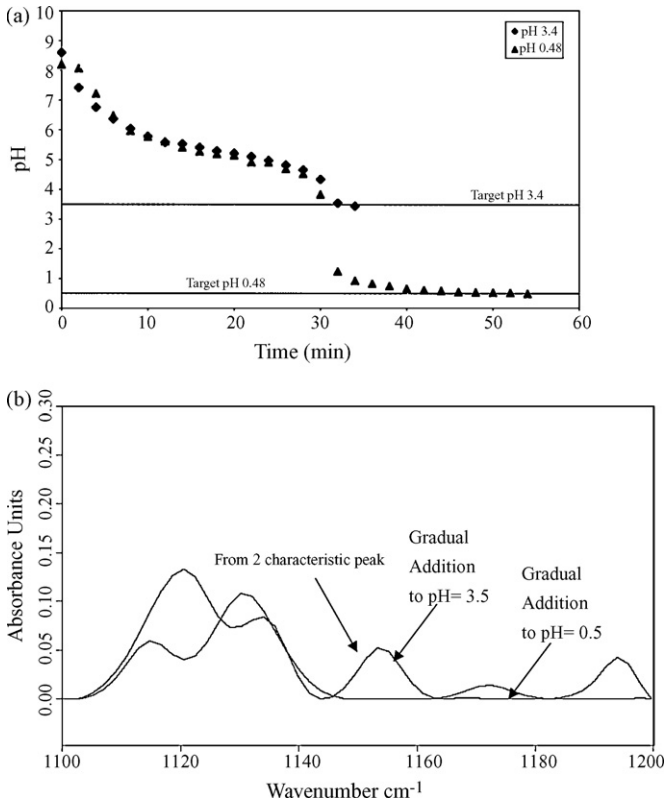

Fig. 3. Gradual addition of acid: (a) pH profile for BUS-FB/IPA solution and (b) FT-IR results (Section 3.1.1.2).

Form 2. However, Fig. 2b has flat and shorter crystals too which corresponds to Form 1.

Thermal analysis of the samples showed that there were significant differences between the samples produced at different pH. The DSC analysis showed that at a pH of 0.5 there was a small endothermic peak at 189 °C which indicates the presence of Form 1 in the sample. Fig. 2c indicates that there is a mixture of Form 1 and 2 due to the high acidity of the solution, pH 0.5. Fig. 2d (corresponding to a pH 3.85), however, indicates the presence of Form 2 only.

FT-IR analysis (Fig. 2e) also confirms the above results suggesting that as the pH decreases the extent of interconversion of Form 2 to Form 1 increases (the characteristic peak of Form 2 located at wavelength 1153 cm^{-1} decreases).

3.1.1.2. Gradual addition. In these experiments, acid was added at a rate of 0.05 ml/min until a target pH was reached. Fig. 3a illustrates the pH profile as a function of time during the gradual addition of the acid. It can be observed from the figure that the solution is very sensitive to the addition of acid after a pH of approximately 4.4 where a huge drop of pH can be observed.

Form 2 was obtained at a pH of 3.5 and Form 1 at pH 0.5. Further analysis using FT-IR, DSC and XRPD showed the same trends obtained during the rapid addition of acid. This proves that the rate of acid addition to the solution of BUS-FB/IPA does not affect the interconversion and the determining factor is the pH. Fig. 3b shows the FT-IR spectra of the two samples during gradual addition of HCl.

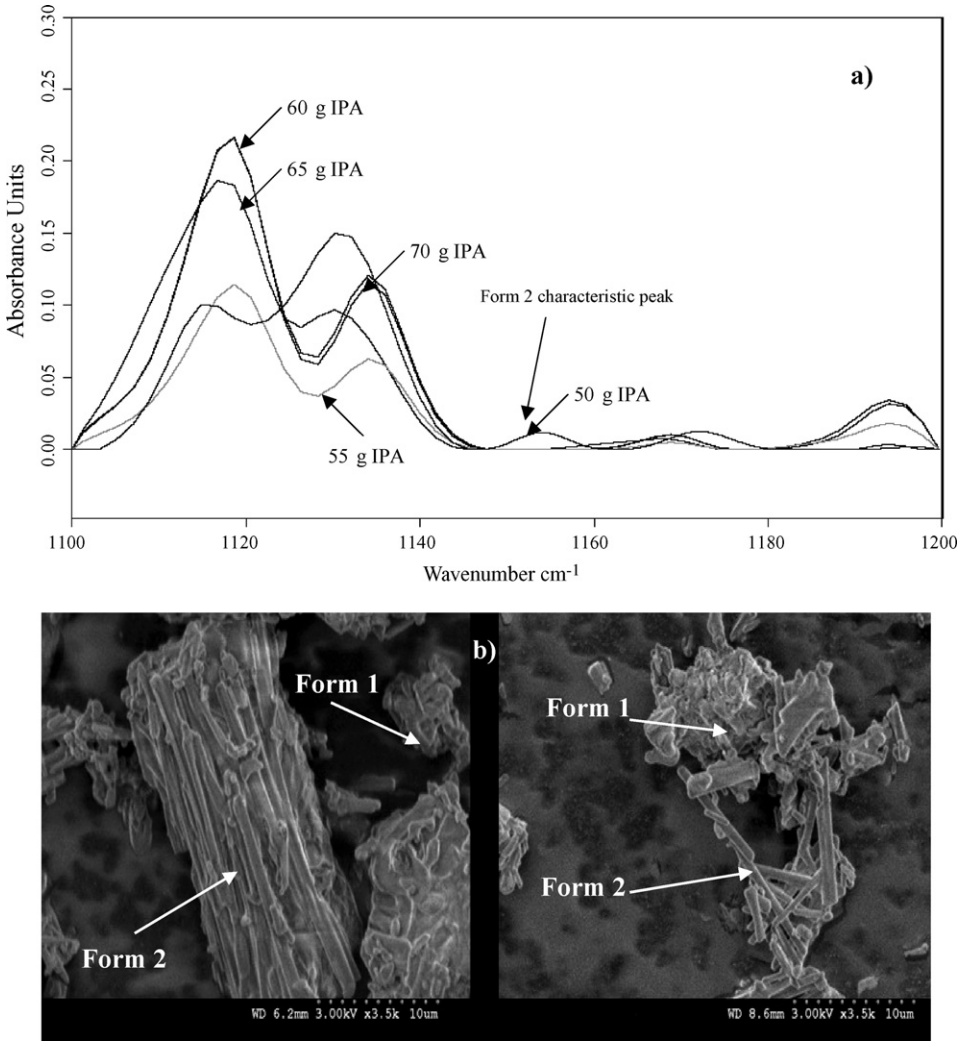

Fig. 4. Effect of initial solute concentration in one solvent. (a) The FT-IR spectra of samples of BUS-HCl that have been produced at a pH of 0.5 but with different amounts of IPA as a solvent. (b) SEM pictures of crystals produced at pH 0.5 and 50 g of IPA (Section 3.1.2.1).

3.1.2. Effect of initial solute concentration or supersaturation

3.1.2.1. In the presence of a single solvent. Form 2 of BUS-HCl is produced by the addition of HCl to a solution of 7 g of BUS-FB in 50 g of IPA until a pH of 3.4–3.6 is reached [3]. In order to investigate the effect of initial solute concentration on the polymorphic outcome, 7 g of BUS-FB was added to 50 g, 55 g, 60 g, 65 g and 70 g of IPA, in two sets of experiments. In the first set of experiments the final pH was maintained in the range of 3.4–3.6. In the second set, the final pH was maintained at 0.5.

In the first set of experiments, the optical micrographs did not show an effect on the crystal shape and size. The powder obtained from this set of experiments was characterized as white, non-sticky with no tendency to agglomeration. Thermal analysis of the samples proved that Form 2 was produced and there was no interconversion.

In the second set of experiments, slight interconversion to Form 1 was observed. DSC and FT-IR results (Fig. 4a) confirmed the presence of Form 1. SEM pictures shown in Fig. 4b confirm the presence of large agglomerates containing mixtures of both forms. Form 1 has random and smaller size crystals while Form 2 has rod shaped crystals. The crystals produced at pH 0.5 and IPA content greater than 50 g did not show the characteristic peak of Form 2 in the FT-IR spectra suggesting the formation of pure Form 1. It was difficult to generate clear SEM micrographs due to high charging effects. When the voltage was increased to above 5 kV melting occurred. This could be due to high acidic conditions. In addition, agglomeration was intensified possibly due to the hydrogen bonding.

3.1.2.2. In the presence of a co-solvent. According to Sheikhzadeh et al. [6], BUS-HCl is more soluble in water than in IPA. The effect of solute concentration in a mixture of water and IPA was investigated in this series of experiments. The amount of water was changed in the range of 3%, 4%, 5%, 7.5%, 10% and 12%. Fig. 5a–c illustrates the spectra produced by the XRPD, the FT-IR and DSC, respectively, for the crystals produced at different water contents. Fig. 5a shows that the crystals produced at 3% and 7.5% of water in IPA were pure Form 2, whereas, at water content of 10% and 12%, the extent of interconversion to Form 1 was high.

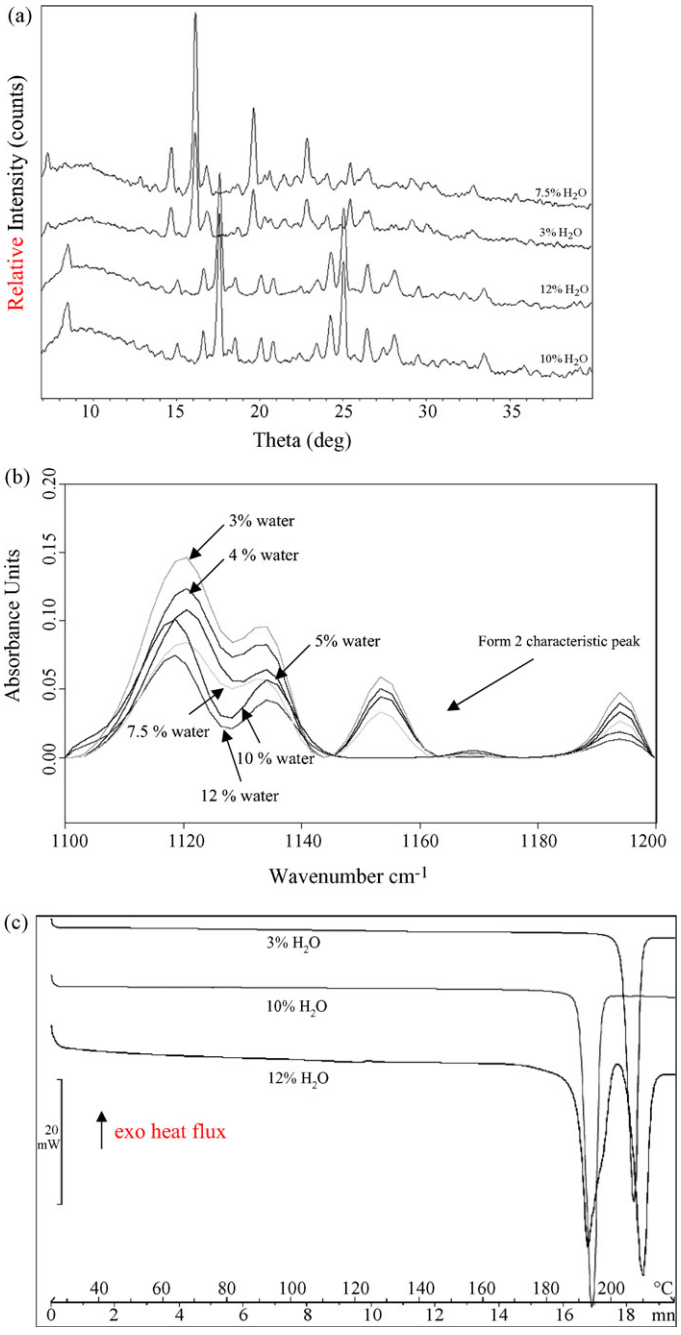

Fig. 5. Effect of initial solute concentration in presence of different co-solvent content: (a) XRPD, (b) FT-IR, and (c) DSC (heating rate: 10 °C/min) (Section 3.1.2.2).

Further analysis of the samples using FT-IR spectra confirmed the results obtained from the XRPD. Fig. 5b demonstrates that as the water content increases from 3% to 7.5%, the absorbance peak of the characteristic peak of Form 2 at 115 cm^{-1} tends to decrease. This indicates gradual interconversion of Form 2 to Form 1 at water content of greater that 10%.

The DSC results demonstrated the impact of increasing the water content in the solvent. From Fig. 5c we can observe that at 3% water content, the solid produced is pure Form 2, since only one peak appeared at a melting temperature of approximately 203 °C. However, at water content of 10%, pure Form 1 was produced (an endothermic peak occurred at 189 °C). The solids produced from the above two conditions were quite stable since they resulted in only one endothermic peak. On the hand, the solid produced at a water content 12% showed an unstable behavior resulting in two endothermic peaks at 189 °C (Form 1) and at 203 °C (Form 2, melting and recrystallization to Form 2).

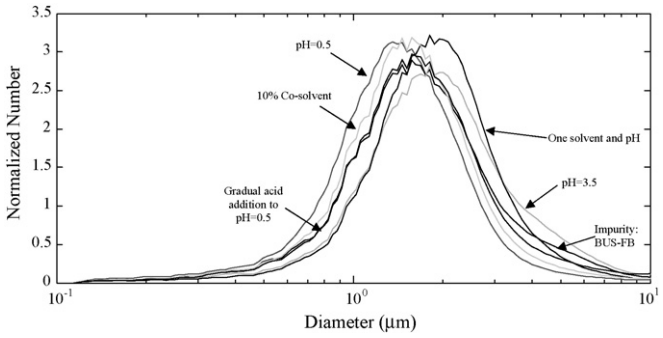

Fig. 6. Volume distribution of samples produced in different experimental conditions.

The morphology of the crystals produced at water content equal to or greater than 10% was different than solids produced at lower water contents. At higher water contents, the crystals were yellowish-beige color large agglomerates and very hard to break. The powder produced at water content lower than 10% was white-beige color. For the quantitative analysis of the amount of Form 1 produced in the sample, Sheikhzadeh et al. [4] proposed equations to predict the amount of Form 1 produced from XRPD, DSC and FT-IR spectra. Table 1 depicts the estimation models for quantitative analysis of the powder mixture.

The induction time, which is the onset of nucleation, with a single solvent (IPA) was between 20 min and 30 min. However, for the mixture of two solvents (IPA and water), nucleation started after 1 h. Besides, to initiate nucleation, the temperature had to be reduced to 5 °C. At water content greater or equal to 10%, temperature had to be reduced to 0 °C and the induction time increased to a few days. Table 2 summarizes the results obtained at different water content.

3.1.3. The effect of impurity

The first stage of synthesis of BUS-HCl involves the formation of BUS-ADD (8-azaspiro[4,5]decane-7,9-dione, see Fig. 1) which is then transformed to QSI, and further transformed to BUS-FB. BUS-FB is then acidified to make BUS-HCl. In each stage there could be some traces of these compounds that because of the similarity of their molecular structure to BUS-HCl could affect polymorphic outcome.

Two types of impurities were tested in this study, the first was QSI with a maximum impurity of 1.5% and the other impurity was BUS-FB which was used to neutralize the solution to pH 3.5 if excess HCl was added during the reaction. The samples produced with different amounts of QSI impurity ranging from 0.5% to 1.5% did not cause any polymorphic interconversion.

In the case of BUS-FB as an impurity, the pH of the solution was reduced to 0.3–3.5 and then extra BUS-FB was added to increase the pH to 3.4–3.6. Table 3, summarizes the amounts

Table 1
Comparison of different quantitative analysis [4]

Device	Equation	"x" definition	R^2
XRPD	$y^a = 0.2425x - 11.367$	Form 1 characteristic peak intensity	0.9097
	$y = -0.1555x + 95.861$	Form 2 characteristic peak intensity	0.9876
	$y = 0.0208x - 37.395$	Form 1 characteristic peak area	0.9437
	$y = -0.0083x + 98.127$	Form 2 characteristic peak area	0.9184
DSC**	$y = 118.16x + 10.641$	Form 1/Form 2 (normalized peak area)	0.9046
	$y = 1.5884x + 7.3161$	Form 1 normalized peak area	0.9417
FT-IR	$y = -237.09x + 202.30$	Form 2 characteristic peak/reference peak	0.9866

** The heating rate is 10 °C/min.
[a] y is the extent of interconversion of Form 1 in percentage.

Table 2
Summary of the results obtained using different amounts of co-solvent

Water (%)	Interconversion observed	Induction time	Yield of crystallization (%)	T_{cloudy} (°C)	% Form 1 (FT-IR data)
3	No	2 h	64.3	≈10	0
4	No	2–2.5 h	59.3	≈10	0
5	No	2–2.5 h	44.8	9.5	0
7.5	No	3 h	34.4	2	0
10	Yes	5 days	29.5	<0	95
12	Yes	≈10 days	16.5	<0	85.2

Table 3
Amount of BUS-FB needed for different excess acid

pH at excess acid	Target pH (3.4–3.6)	Amount of BUS-FB (g)
0.33	3.53	6.03
0.51	3.43	3.18
1.35	3.47	0.48
1.42	3.45	0.37
1.54	3.45	0.28
1.9	3.56	0.2

of BUS-FB required to neutralize solutions of different pH. XRPD and thermal analysis showed no polymorphic interconversion.

3.2. Crystal size distribution

Vacuum filtration was used to separate the solid precipitate from the solution. The filtration time differed according to the condition at which the particles were formed. The normalized number distribution obtained for different samples using TSI-PSD are shown in Fig. 6.

One of the main factors affecting the filtration rate of slurry is particle size and sticky behavior of the particles possibly due to agglomeration. It can be observed from Fig. 6 that the crystals produced at pH 3.5 and in the presence of BUS-FB as an impurity, have the smallest diameter ranging from 10 μm to 40 μm. This indicates that solid crystals formed were mainly Form 2. These crystals were long and needle-like and showed low tendency to agglomerate and were not sticky. The solid crystals formed at pH 0.45–0.5 and at a water content of 10%, were either pure Form 1 or a mixture of Form 1 and Form 2. The mean diameter of these crystals was between 95 μm and 300 μm with high degree of agglomeration.

4. Surface response analysis by factorial design

Factorial design is widely used in the design of experiments involving several factors where it is necessary to study the joint effect of the several variables on a response surface [7]. In order to analyze the results of our experiments on the extent of interconversion, the statistical analysis approach available in the Design Expert software Version 7 (Stat-Ease Inc., Minneapolis, USA) was used. The desired goal was to determine the optimum operating conditions for the extent of interconversion to Form 1. This objective can be used to design experiments in such a way to maximize (pure Form 1) or minimize (pure Form 2) the extent of polymorphic interconversion.

Table 4
Parameters range and designation for the experimental design calculation

Factor coded	Name	Unit	Type	Low actual	High actual	Low coded	High coded	Mean
A	pH	–	Numeric	0.50	3.6	−1	1	2.050
B	Solvent	g	Numeric	50.00	70.00	−1	1	60.00
C	Co-solvent	%	Numeric	3.00	12.00	−1	1	7.50
D	Impurity	%	Numeric	0.50	1.50	−1	1	1.00
Response	Form 1 interconversion	%	Numeric	0	100	−1	1	50

Table 5
BUS-HCl polymorph interconversion design experiments

Run number	Factor				Interconversion extent (%)
	A	*B*	*C*	*D*	
1	−1	−1	−1	−1	74.5
2	1	−1	−1	−1	0
3	−1	1	−1	−1	100
4	1	1	−1	−1	0
5	−1	−1	1	−1	90
6	1	−1	1	−1	85.2
7	−1	1	1	−1	95
8	1	1	1	−1	85.2
9	−1	−1	−1	1	74.5
10	1	−1	−1	1	0
11	−1	1	−1	1	100
12	1	1	−1	1	0
13	−1	−1	1	1	95
14	1	−1	1	1	85.2
15	−1	1	1	1	100
16	1	1	1	1	80

A: pH; *B*: solvent amount; *C*: co-solvent amount; *D*: impurity.

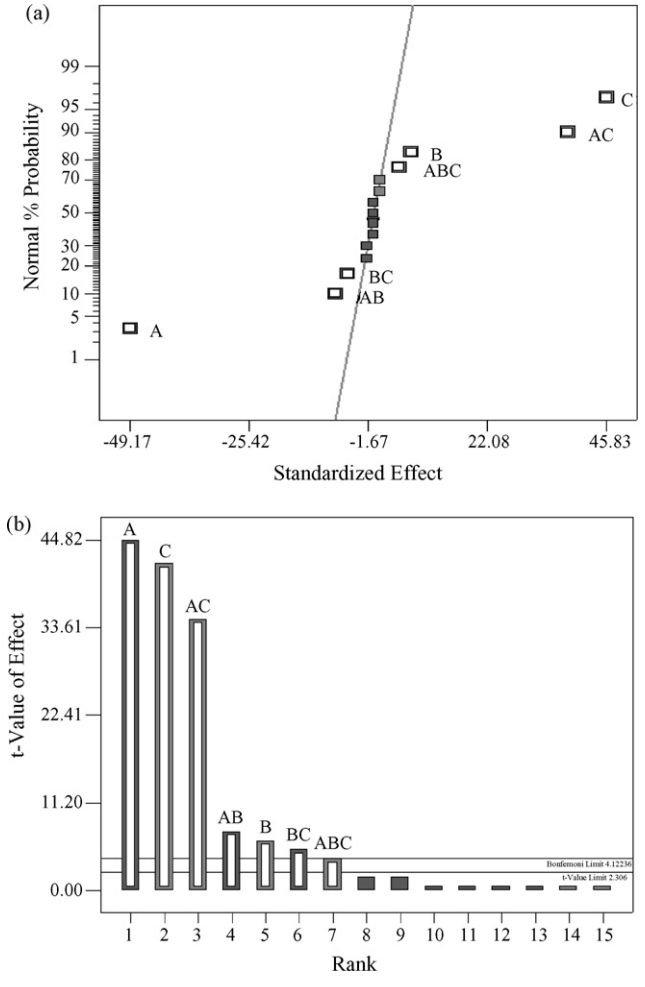

Fig. 7. The effects for the 2^4-factorial method by: (a) normal probability plot, and (b) Pareto plot.

Table 6
Analysis of the equations for the prediction of the extent of interconversion to Form 1 (coded mode)

Factor	Coefficient estimate	95% CI[a] low	95% CI high	Degree of freedom
Intercept	66.54	65.27	67.8	1
A (pH)	−24.59	−25.85	−23.32	1
B (solvent)	3.49	2.22	4.75	1
C (co-solvent)	22.91	21.65	24.18	1
AB	−4.14	−5.4	−2.87	1
AC	19.04	17.77	20.3	1
BC	−2.89	−4.15	−1.62	1
ABC	2.24	0.97	3.5	1

[a] Confidence interval.

Four different factors and their influence on the extent of BUS-HCl interconversion were evaluated using a 2^4-full factorial design. The four factors designated by A, B, C, and D were final pH, amount of solvent, amount of co-solvent, and amount of impurity (BUS-FB), respectively. For each factor, the lower and higher levels were represented by a 1 or a −1 sign, which are called coded parameters. The information on all factors, their minimum and maximum in actual and coded formats are presented in Table 4.

Table 7
Equations for prediction of the extent of interconversion to Form 1 in coded and actual format

Coded format	$y = 66.54 - 24.59A + 3.49B + 22.91C - 4.14AB + 19.04AC - 2.89BC + 2.24ABC$
Actual format	$y = (-9.46) - 5.86(\text{pH}) + 1.87(\text{solvent (g)}) + 7.30(\text{co-solvent (\%)}) - 0.51(\text{pH})(\text{solvent (g)}) + 0.80(\text{pH})(\text{co-solvent (\%)}) - 0.13(\text{solvent (g)})(\text{co-solvent (\%)}) + 0.032(\text{pH})(\text{solvent (g)})(\text{co-solvent (\%)})$

y is the extent of interconversion to Form 1 in percentage.

Table 8
Response surface analysis for different combinations of factors

Optimization condition	pH: 0.5–3.6; solvent: 50–70 g; co-solvent: 0–12%; impurity: 0.5%		pH: 0.5; solvent: 50–70 g; co-solvent: 0–12%; impurity: 0.5%	pH: 3; solvent: 50–70 g; co-solvent: 0–12%; impurity: 0.5%	pH: 2; solvent: 50 g; co-solvent: 0–12%; impurity: 0.5%
Run	Run 1	Run 2	Run 3	Run 4	Run 5
Desired value of objective function (%)	100% pure Form 1	50% Form 1	100% pure Form 1	50% Form 1	75% Form 1
pH	0.5	3.09	0.5	3	2
Solvent (g)	50	51.22	68.5	69	50
Co-solvent (%)	12	11.91	1	4.13	8.98
Impurity (%)	0.5	0.5	0.5	0.5	0.5
Actual value of objective function (%)	91.2	50	98.3	51.5	67.3

The design matrix and the response data obtained from a single replicate of the 2^4 are shown in Table 5. Sixteen experiments were conducted in the different combination of factors.

The normal probability plot of the estimates of each effect is shown in Fig. 7a. All of the effects that lie along the line are negligible, whereas the large effects are far from the line. The main effects appear to be due to factors *A* (pH), *C* (co-solvent) and *AC*. The effects of *AC* and *C* are positive whereas that of *A* is negative. Also *B* (solvent portion), *AB*, *BC* and *ABC* have less prominent effect on the extent of interconversion to Form 1. Fig. 7b presents the entire factors in the Pareto chart which sorts the parameters from highest to lowest value.

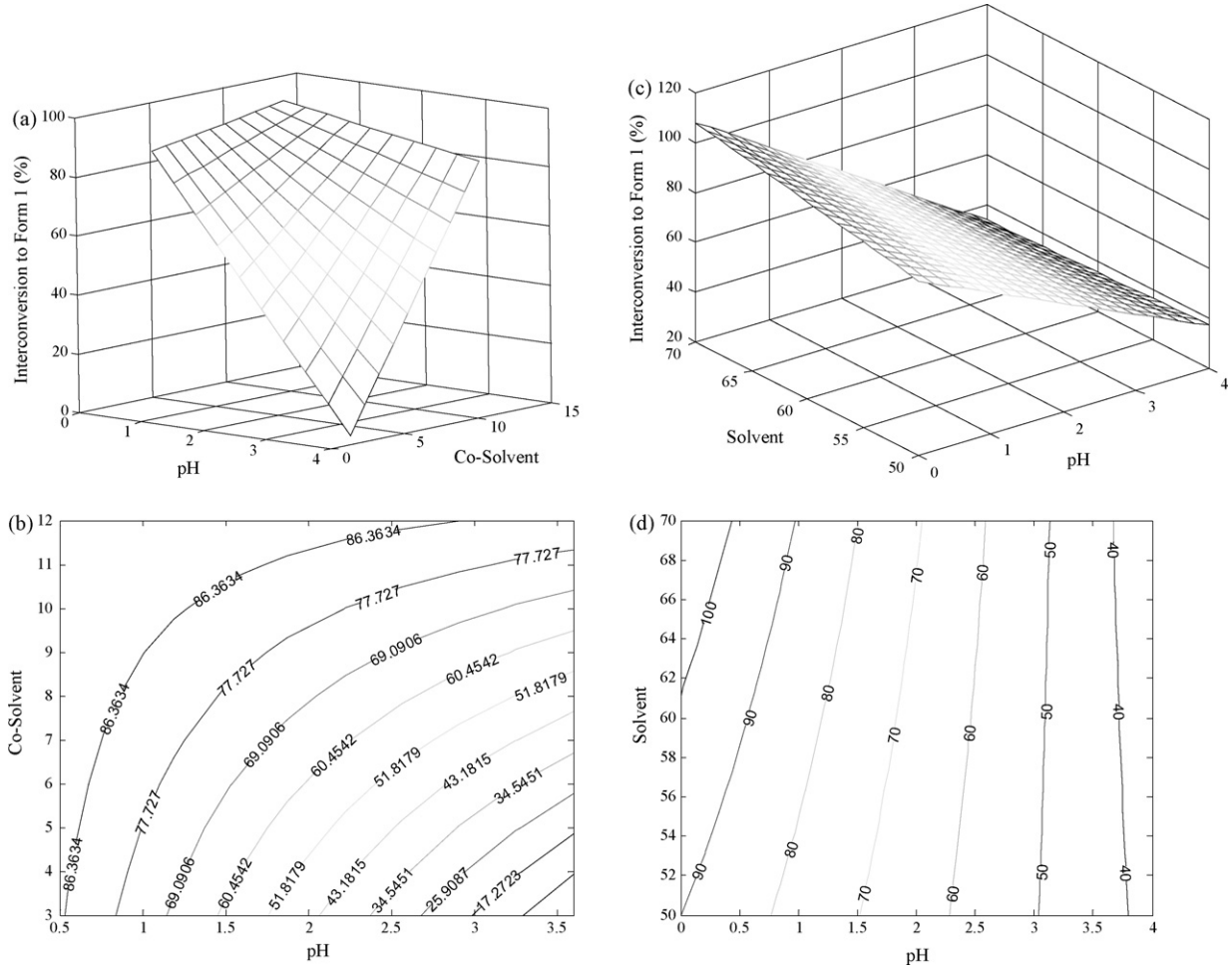

Fig. 8. Surface response and contour plot: (a and b) pH and co-solvent are changing and solvent amount is 60 g and impurity is 0.5%; (c and d) pH and solvent are changing and co-solvent amount is 7 g and impurity is 0.5%.

The interaction information was used to provide a model for predicting the extent of interconversion to BUS-HCl Form 1. The analysis of variance for this model and the prediction model in actual and coded format are shown in Tables 6 and 7.

Fig. 7a and b shows that the impurity does not have a strong effect on the extent of interconversion even when it is involved in significant interaction with other factors. *A* (pH effect) and *C* (anti-solvent) and interaction between them and a slight effect of solvent portion are the key factors affecting the extent of interconversion.

Table 8 shows the optimization results. The objective function was to minimize the difference between the pre-specified and calculated the extent of inter conversion to Form 1. In all calculations (which are referred to as 'runs'), the amount of impurity was set to its minimum value (0.5%). In the first two runs, pH, solvent and co-solvents amount were changed in a predefined manner. For lower interconversion to Form 1, higher pH and solvent and lower co-solvent were needed.

Table 7 lists the equations to calculate the extent of interconversion to Form 1. Table 8 provides a snapshot of the required values of factors considered in the optimization to achieve a desired extent of interconversion to Form 1. In some cases the desired extent of interconversion cannot be achieved as is shown in Table 8.

Fig. 8a shows the response surface for the model at an impurity value at 0.5%, and taking the average value of the solvent (60 g). From the response surface, it can be concluded that for higher extent of interconversion to Form 1, lower pH and higher amount of co-solvent are needed. Fig. 8b shows the contour plot. The same procedure was applied by fixing the co-solvent value to the mean value (7 g), and varying the solvent and pH. Fig. 8c shows the corresponding surface response. At maximum solvent and minimum pH, it is theoretically possible to obtain 100% to Form 1. In practice, however, achieving 100% conversion to Form 1 is not possible, due to the model deviation from the real data. Fig. 8d depicts the corresponding contour plot.

5. Conclusions

Using the procedure mentioned in Ref. [5], pure Form 2 buspirone hydrochloride was produced and the solid was characterized as a white fluffy powder with good filterability. In this study, the effect of final pH in the salt formation step, HCl addition rate, solvent ratio, co-solvent and impurity were investigated on the extent of interconversion of BUS-HCl forms. In addition, the effect of various process variables on product morphology and size distribution of buspirone hydrochloride was studied.

It was found that pure Form 1 can be obtained by decreasing pH from 3.5 to 0.45–0.5 and increasing the IPA content to more than 50 g but less than 70 g. Under these conditions, the product was a white and sticky solid that tended to form agglomerates due to the fine nature of the crystals. Pure Form 1 was produced at water content $\geq$10%. This, however, led to the long induction time. It was observed that the percent yield of crystallization was lowest at water content of 12% which could have been due to the difficulty of the formation of crystals and the very slow nucleation rate. The solid crystals were fine, bright yellowish in color and hard agglomerates.

A factorial design approach was used to identify the most significant factors for the interconversion of Form 2 to Form 1. It was found that pH, the amount of co-solvent and the combination of these two factors had the strongest effect on the extent of interconversion. The prediction model that can estimate the extent of interconversion to From 1 was obtained successfully.

References

[1] J. Bernstein, Polymorphism in Molecular Crystals, Oxford University Press, New York, 2002, pp. 29–49.
[2] H.G. Brittain (Ed.), Polymorphism in Pharmaceutical Solids, Marcel Dekker, New York, 1999.
[3] M. Sheikhzadeh, S. Rohani, A. Jutan, T. Manifar, Pharm. Res. 23 (2006) 1043–1050.
[4] M. Sheikhzadeh, S. Rohani, A. Jutan, T. Manifar, J. Pharm. Sci. 96 (2007) 569–583.
[5] R.J. Behme, T.T. Kensler, D.G. Mikolasek, Process for buspirone hydrochloride polymorphic crystalline form conversion, USA Patent 4,810,789 (1989).
[6] M. Sheikhzadeh, M. Taffish, S. Rohani, Int. J. Pharm. 338 (2007) 55–63.
[7] D.C. Montgomery, Design and Analysis of Experiments, John Wiley and Sons Inc., New York, 2001.