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RESEARCH PAPER

Supersolubilization and Amorphization of a Model Basic Drug, Haloperidol, by Interaction with Weak Acids

Saumya Singh • Tapan Parikh • Harpreet K. Sandhu • Navnit H. Shah • A. Waseem Malick • Dharmendra Singhal • Abu T. M. Serajuddin

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ABSTRACT

Purpose To present a novel approach of greatly enhancing aqueous solubility of a model weakly basic drug, haloperidol, by using weak acids that would not form salts with the drug and to attain physically stable form of amorphous drug by drying such aqueous solutions.

Method Aqueous solubility of haloperidol in presence of increasing concentrations of four different weak organic acids (malic, tartaric, citric, fumaric) were determined. Several concentrated aqueous solutions with differing drug-to-acid molar ratios were dried in vacuum oven, and dried materials were characterized by DSC, powder XRD, dissolution testing, and stability study.

Result Acids were selected such that they would not form salts with haloperidol. Haloperidol solubility increased greatly with increased concentrations of malic, tartaric and citric acids, reaching >300 mg/g of solution. In contrast to the haloperidol HCl aqueous solubility of 4 mg/g, this may be called supersolubilization. Fumaric acid did not cause such solubilization as it had low water solubility. Dried solids formed dispersions of amorphous haloperidol in acids that were either amorphous or partially crystalline. Amorphous haloperidol was physically stable and had better dissolution rate than HCl salt.

Conclusion A novel method of drug solubilization in aqueous media by acid–base interaction is presented. Physically stable amorphous systems of drugs may also be prepared by using this organic solvent-free approach.

KEY WORDS acid–base interaction · amorphous system · basic drug · dissolution rate · haloperidol · solubility · weak acid

INTRODUCTION

Majority of new chemical entities (NCE) synthesized by the pharmaceutical industry during the past 2 decades were found to be very poorly soluble in aqueous media (1–3). It is estimated that more than two-thirds of the compounds currently emerging from the drug discovery pipeline have solubility <100 μg/ml (4,5) and thus, according to the definition of the United States Pharmacopeia (6), they may be considered insoluble or practically insoluble. Even when they are considered insoluble, there is no limit how low the aqueous solubility of drugs can be; compounds with solubility <1 μg/ml, and even <0.1 μg/ml, are commonly selected for development. The development of such compounds into bioavailable oral dosage forms has become very challenging. Some of the technologies generally applied to increase dissolution rate and thereby bioavailability are: particle size reduction (7–9), salt formation (10), conversion to amorphous form (11–13), solid dispersion (14,15), and solubilization in lipids or lipid-surfactant mixtures (16–18). However, each of these techniques has its own limitations. There is a practical limit how low the particle size can

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S. Singh • T. Parikh • A. T. M. Serajuddin (✉)
College of Pharmacy and Health Sciences, St. John's University
8000 Utopia Parkway, Queens, New York 11439, USA
e-mail: serajuda@stjohns.edu

H. K. Sandhu • N. H. Shah • A. W. Malick • D. Singhal
Hoffmann-La Roche, 340 Kingsland Street
Nutley, New Jersey 07110, USA

Present Address:
S. Singh
SSCI, A Division of Aptuit Inc., 3065 Kent Avenue
West Lafayette, Indiana 47906, USA

be reduced by conventional means, the lower limit usually being about 3 to 5 μm. Even if the particle size is reduced to the submicron range by nanomilling (7,8), there are difficulties with redispersion of such particles in aqueous media once they are dried and developed into solid dosage forms (19). The salt formation, which requires an ionizable functional group on the pharmacophore, may not be feasible for neutral as well as very weakly basic and very weakly acidic compounds (10). Even when salts are formed, the solubility of the salts for many compounds could still be very low and may prove ineffective to provide the desired enhancement in dissolution rate and bioavailability. For example, it has been reported that the aqueous solubilities of hydrochloride and mesylate salt forms of a basic drug ziprasidone were 80 and 890 μg/ml (20), respectively, and such low solubility could not overcome the issues of incomplete and variable bioavailability for the drug (21). There is also a potential that the salts may undergo pH-mediated precipitation in the gastrointestinal tract and thus prove ineffective to achieve the desired absorption enhancement (10). The development of amorphous forms and solid dispersions also has many manufacturing challenges and stability issues (4,15). There has been a great interest in recent years in the development of lipid-based drug delivery systems; however the technology is still emerging and there is incomplete understanding how different components of lipid-based drug delivery systems interact and perform (5,16). In many cases, the usefulness of the lipid-based drug delivery system may be further limited by their inability to solubilize the entire dose of drug in the volume of a single soft or hard gelatin capsule suitable for oral administration (22).

Because of various limitations of currently available technologies to overcome formulation issues with poorly water-soluble drugs, there is a need for newer strategies and newer approaches. The present report describes a novel approach of greatly increasing the solubility of a basic drug in an aqueous medium by interaction with acidic species that would not normally form salts with it. Haloperidol, a basic compound with the pK_a value of 8.0 and the intrinsic solubility of 2.5 μg/ml (23), was used as the model drug. It was reported that haloperidol formed salts with hydrochloric acid, methanesulfonic acid and phosphoric acid (dihydrogen phosphate salt), and no salt could be prepared when relatively weaker acids, such as citric acid, tartaric acid, acetic acid, fumaric acid, and so forth, were used (23,24). The primary objectives of the present study were to determine what would be the solubility if the pH of an aqueous solution of haloperidol is lowered by adding excessive amounts of weak non-salt forming acids and what would be the physical state of haloperidol if such solutions are dried. It was also of interest to determine how the haloperidol-organic acid mixtures prepared by drying aqueous solutions would redissolve in aqueous media.

Theoretical Considerations

When a basic drug is dissolved in water, the following equilibrium exists:

$$BH^+ + H_2O \overset{K}{\leftrightarrow} B + H_3O^+ \tag{1}$$

or

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \tag{2}$$

Kramer and Flynn (25) showed that the interrelationship of the solubility of a base, B, and its salt form, BH^+, as a function of pH may be described by two independent curves, one where the free base is the equilibrium species and the other where the salt is the equilibrium species (Fig. 1a). The change in solubility of basic and acidic drugs as a function of pH has also been reviewed extensively by different authors (10,26,27). As shown by the line A to B in Fig. 1a, when an acid is added gradually to the aqueous suspension of a basic drug to decrease pH, the solubility increases. Below a certain pH, called pH_{max} or the pH of maximum solubility, the crystallization of salt form ensues, where the solubility as a function of pH may be described by the line B→C in Fig. 1a. The free base and the salt are, respectively, the equilibrium species at pH above and below the pH_{max}, and only at the point of pH_{max}, both the free base and the salt can coexist as equilibrium species or solid phases.

The solubility expressed by the line A→B above the pH_{max} and the line B→C below the pH_{max} in Fig. 1a may be expressed, respectively, by Eqs. 3 and 4 below:

$$\begin{aligned} S_{Tbase(pH>pHmax)} &= [B]_S + [BH^+] = [B]\left(1 + \frac{H_3O^+}{K_a}\right) \\ &= [B]_S(1 + 10^{pKa-pH}) \end{aligned} \tag{3}$$

$$\begin{aligned} S_{T\ salt(pH<pH\,max)} &= [BH^+]_S + [B] = [BH^+]\left(1 + \frac{K_a}{H_3O^+}\right) \\ &= [BH^+]_S(1 + 10^{pH-pKa}) \end{aligned} \tag{4}$$

Equation 3 is essentially a modified version of the classical Henderson-Hasselbach equation, according to which the solubility of a basic compound should increase indefinitely if its pH is gradually lowered. In other words, the line A→B in Fig. 1a would extend indefinitely in the direction of B as the pH is decreased. However, as more and more of an acid, HX, is added to lower pH, the concentration of counterion, X^-, in solution increases, and it is due to the effect of the solubility product, K'_{sp}, of the protonated drug, BH^+, and the ionized acid, X^-, that the line A→B breaks at point B or pH_{max} and the salt is formed.

The inter-relationship of various chemical species present below and above the pH_{max} of a basic drug, B, is shown schematically in Fig. 1b (28). From the equilibrium that exists below the pH_{max} for the salt of a basic drug in Fig. 1b, the

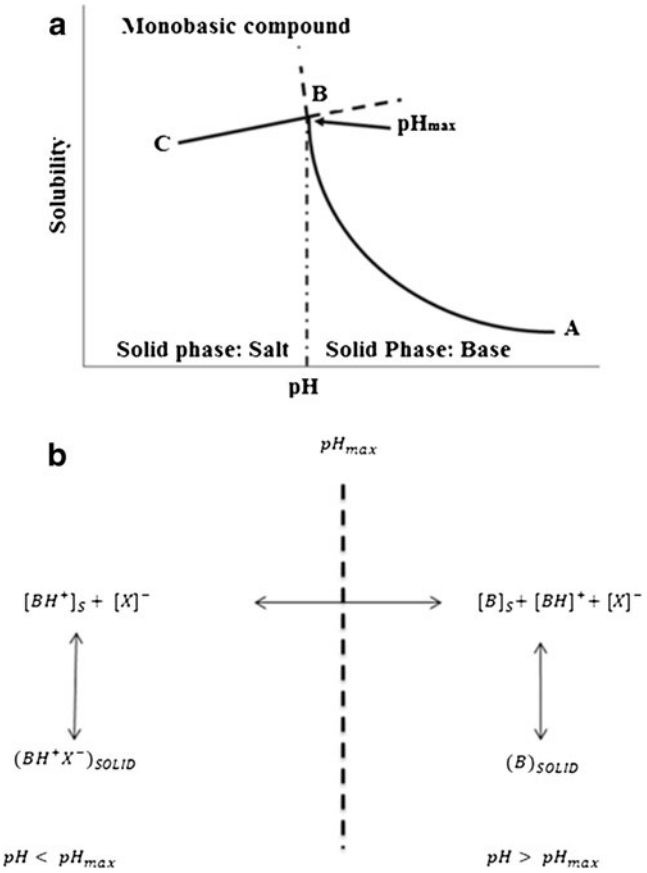

Fig. 1 Schematic representation of the interrelationship between the solubility of base and its salt form as a function of pH. (**a**) Line AB represents free base as equilibrium species above the pH_{max} and line BC represents salt as equilibrium species below the pH_{max} (reprinted with the permission from (28)). (**b**) Different species formed at pH above and below the $pH_{max;}$ when the pH of the suspension of a basic drug, B, is lowered by the addition of an acid, HX. The subscript 's' in $[BH^+]_s$ and $[B]_s$ indicates saturation.

apparent solubility product or K'_{sp} may be represented by the following equation:

$$K'_{sp} = [BH^+]_S[X^-] \quad (5)$$

If no excess counterion is present, $[BH^+]_S = [X^-]$, and, therefore, solubility of the salt $= \sqrt{K'_{sp}}$. The solubility of the salt will, however, decrease if the concentration of the counter ion in the saturated solution increases such that the K'_{sp} remains essentially constant. This is the reason for the observed decrease in solubility due to common ion effect when excess HCl or any other chloride species is added to the saturated solution of a hydrochloride salt.

According to the above-described pH-solubility interrelationships, with the addition of an acid the solubility of a basic drug increases with the decrease in pH and a salt is formed when the pH goes below the pH_{max}. In the present investigation, it was explored whether any deviation from or nonconformity with the classical pH-solubility interrelationship may be beneficially applied to the development of drug products. According to Fig. 1b, the acid added must remain fully ionized (X^-) below the pH_{max} to form a salt with the protonoted base (BH^+). If, say, the acid is not fully ionized and remains only partially unionized at $pH < pH_{max}$, the acid–base equilibrium described in Fig. 1b will no longer exist as it will lead to three species in solution ($[BH^+]$, $[X^-]$ and [HX]) rather than two ($[BH^+]$ and $[X^-]$) necessary to meet the K'_{sp} requirement of Eq. 5. Consequently, no salt will be formed. Indeed, depending on the pK_a, the acid may remain fully unioinized and $[X^-]$ may not even be present in a significant concentration. These considerations explain why some of the acids, such as citric acid, tartaric acid, acetic acid, etc., did not form salts with haloperidol as they were not fully ionized below the pH_{max} due to their relatively higher pK_a values than those forming salts (23). (Chemical properties and theoretical ionization curves of acids used and the theoretical pH-solubility profile of haloperidol are given in Supplementary Material)

Based on above considerations, the question arises: What will happen if the pH of the aqueous suspension of a weakly basic drug like haloperidol is lowered by adding weak acids that would not normally form salts? Since the salts will not be formed, it was of interest to know whether the solubility of the base would continue to increase according to Eq. 3. In case the solubility of the basic drug continues to increase in presence of added weak acids, how high the solubility will be and what will be the physical state of solids formed if the solutions are dried? To address these questions, the pH-solubility profiles of haloperidol were determined using citric acid (pK_a: 3.12, 4.76, 6.39), tartaric acid (pK_a: 3.11, 4.80), malic acid (malic acid: 3.40, 5.13) and fumaric acid (pK_a: 3.03, 4.54) as the representative weak acids. Aqueous solutions of selected haloperidol-acid mixtures were dried to determine their solid state properties, physical stability and dissolution rate.

MATERIALS AND METHODS

Materials

Haloperidol free base was obtained from Spectrum Chemicals (New Brunswick, NJ, USA). Haloperidol HCl salt was synthesized from the free base at our laboratory at St. John's University. The structure of the salt prepared was confirmed by elemental analysis, melting point determination and infrared spectroscopy. Tartaric acid was also obtained from Spectrum Chemicals. Citric acid was purchased from BDH (Radnor, PA, USA), and malic acid and fumaric acid were purchased from Sigma Aldrich (St. Louis, MO, USA). All solvents and other chemicals used were of analytical reagent

grade or better. Deionized water was used throughout the study.

Determination of Haloperidol Solubility *vs.* Acid Concentration

The phase solubility technique was used to determine solubility of haloperidol as a function of the concentration of acid in aqueous solution and the consequent change in pH. In preliminary experiments, suspensions of haloperidol in water were prepared and different weak organic acids were added to the suspensions to lower the pH. The drug concentration in solution increased as the increasing amounts of acids were added. Although the concentration of haloperidol in solution could be measured by HPLC analysis, it was, however, difficult to accurately determine how much organic acid was added and what its exact concentration in solution was. For this reason, solubility studies were repeated by dissolving weighed amounts of different acids (malic, tartaric, citric and fumaric) in accurately weighed amounts of water in 25-ml volumetric flasks and then adding excess haloperidol free base to each solution of acid. The suspensions were shaken in a water bath (25 ± 1°C) for predetermined periods of time using a Burrell wrist action shaker (Burrell Scientific, Pittsburgh, PA, USA). After equilibration, the pH of each suspension was measured, the entire content was centrifuged, and the supernatant was filtered through the polypropylene membrane syringe filter of 0.45 μm pore size (VWR Scientific, Bridgeport, NJ, USA). A weighed amount of the filtrate was diluted to the appropriate analytical range by using a 1:1-mixture of methanol and 0.1 NHCl prior to analysis by an UV-Visible spectrophotometer (Beckman DU 650i, Beckman Coulter Inc. Brea, CA, USA) at the detection wavelength of 247 nm. This enabled determination of how much haloperidol dissolved per g of solution. By subtracting the weight of haloperidol dissolved from the weight of aliquot (solution) used and then based on the ratio of acid to water in the solution, it was possible to ascertain how much haloperidol, acid and water were present per g of solution. Such determination of solubility was conducted in triplicate.

Preparation of Dry Solids

Various solutions of haloperidol in water in presence of weak acids were dried to study physical states of the solids formed. The compositions of solutions prepared are given in Table I. The amounts of acid and water for the solutions were kept constant while the amounts of haloperidol varied such that there were varying molar ratios between haloperidol and acids. The highest haloperidol to organic acid ratio was selected based on the phase solubility study such that haloperidol dissolved completely in acid solutions. The solutions were then spread on petri dishes and dried in vacuum ovens at 55°C for 7 days.

Table I Molar Ratios and Weights of Haloperidol and Weak Organic Acids Selected to Prepare Dry Solid Systems

Weak organic acid	Molar ratio Drug: acid	Haloperidol (g)	Acid (g)	Water (g)
Malic acid	0.05:1	0.14	1	1
	0.10:1	0.28	1	1
	0.14:1	0.39	1	1
	0.16:1	0.45	1	1
	0.18:1	0.50	1	1
	0.29:1	0.81	1	1
Tartaric acid	0.04:1	0.10	1	1
	0.08:1	0.20	1	1
	0.10:1	0.25	1	1
	0.12:1	0.30	1	1
	0.15:1	0.38	1	1
	0.24:1	0.60	1	1
Citric acid	0.02:1	0.04	1	1
	0.06:1	0.11	1	1
	0.08:1	0.14	1	1
	0.10:1	0.18	1	1
	0.12:1	0.22	1	1

Characterization of Dry Solids

Thermal Analysis

Differential scanning calorimetric (DSC) analysis was conducted for haloperidol (free base), weak organic acids (malic, citric and tartaric) and the dry solid mixtures of haloperidol and weak organic acids prepared. The analysis was carried out by Perkin-Elmer DSC-7 (Perkin Elmer, Inc. San Jose, CA, USA) using ~4 mg of each sample weighed into a standard aluminum pan. A heating rate of 10°C/min over the temperature range of 25–180°C under an extra dry grade nitrogen purge (20 cc/min) was applied.

Thermogravimetric (TG) analysis of dry solids was conducted by using a Perkin-Elmer thermogravimetric analyzer (Pyris 1 TGA, Perkin Elmer, Inc. San Jose, CA, USA) to determine whether there is any weight loss from the samples. For each analysis, ~2 mg of sample was weighed into a tared crucible and then heated from 25°C to150°C at the heating rate of 10°C/min.

Powder X-Ray Diffraction Analysis

The powder X-ray diffraction (XRD) patterns of the haloperidol free base, the weak organic acids used and the dry solid mixtures of haloperidol and weak organic acids

prepared were recorded using Shimadzu X-ray Diffractometer, model XRD-6000, with Ni CuKα as the X-ray source (Shimadzu, Kyoto, Japan). Continuous scans were recorded at a voltage of 40 kV, 30 mA having a scan rate of 2°C/min across the scan range of 10–60°2θ and step size of 0.02° taking scan axis as θ/2θ. Samples were prepared into thin films by "sideways filling method" on the glass micro sample holder.

Dissolution Study

Since haloperidol has pH-dependent solubility and the pH values of gastrointestinal (GI) fluids changes in different regions of the GI tract, a multi-step dissolution test was conducted for various dried haloperidol-organic acid mixtures. Compositions of different solid systems used for dissolution testing are given in Table II. The amount of haloperidol in each sample was kept constant at 0.15 g, while the molar ratio between the drug and each acid varied. For this reason, the amount of acid used as well as the total weight of drug and acid per sample decreased when the molar ratio between haloperidol and acid increased. Haloperidol hydrochloride (0.165 g, equivalent to 0.15 g free base) served as the control. All samples were filled in size 00 capsules (multiple capsules were used when necessary) and their dissolution was studied at 37 ± 1°C using an USP dissolution apparatus II (Distek Inc, North Brunswick, NJ, USA) at 50 RPM. In step 1, 250 ml of 0.01 N HCl (pH ~ 2) was used as the dissolution medium and 3 ml of aliquot was withdrawn at each of 5, 15, 30, 60, 90 and 120 min time points. A sinker was used to keep each capsule submerged in the dissolution medium. Immediately after the 120-min sampling, the step 2 dissolution was conducted, where the pH was changed to 4.5 by adding the appropriate amount 1 N NaOH and the dissolution was continued up to 150 min. The dissolution at step 2 was followed by the step 3, where the pH was adjusted similarly to 6.8 and samples were withdrawn at 180, 210 and 240 min time points. Aliquots withdrawn at different time points were replenished by adding equivalent volumes of dissolution medium. Samples were filtered through polypropylene membrane syringe filter of 0.45-μm pore size (VWR Scientific) and analyzed for haloperidol after appropriate dilution using UV-Visible spectrophotometer at the wavelength of 247 nm.

Table II Molar Ratios and Contents of Haloperidol and Different Acids in Solid Systems Used for Dissolution Testing

Weak organic acid	Molar ratio Drug: acid	Haloperidol (g)	Acid (g)	Total weight (g)
Malic acid	0.05:1	0.15	1.07	1.22
	0.10:1	0.15	0.54	0.69
	0.14:1	0.15	0.38	0.53
	0.16:1	0.15	0.33	0.48
	0.29:1	0.15	0.19	0.34
Tartaric acid	0.04:1	0.15	1.50	1.65
	0.08:1	0.15	0.75	0.90
	0.12:1	0.15	0.50	0.65
	0.15:1	0.15	0.39	0.54
	0.24:1	0.15	0.25	0.40
Citric acid	0.02:1	0.15	3.75	3.90
	0.06:1	0.15	1.36	1.51
	0.10:1	0.15	0.83	0.98
	0.12:1	0.15	0.68	0.83

Physical Stability Testing

Since it was found that the solids prepared by drying aqueous solutions of haloperidol and organic acids could be amorphous, additional studies were conducted to determine whether haloperidol would revert back to its crystalline form. Solids with the highest molar ratios between haloperidol and different acids were used and the compositions of mixtures are given in Table III. For this purpose, the solids were finely ground by using the glass mortar and pestle, and 250 mg of each sample was stored in open glass vials inside desiccators at 60% RH and room temperature (~25°C). The humidity in desiccators was maintained by using the saturated solution of $MgCl_2.6H_2O$. The relative humidity and the temperature were monitored continuously by using a hygrometer (Daigger scientific, Vernon Hills, IL, USA). After 6 months, samples were analyzed using powder XRD and DSC to detect any phase changes in dry solid systems upon storage in presence of moisture.

RESULTS

Determination of Haloperidol Solubility *vs.* Weak Acid Concentration

Haloperidol is a very poorly water-soluble basic compound having the pK_a value of 8.0 and the intrinsic (free base) solubility value of 2.5 μg/ml (23). Figure 2 shows that the solubility of haloperidol in aqueous solutions can be increased greatly by using such weak organic acids as malic

Table III Molar Ratios and Weights of Haloperidol and Weak Organic Acids Used in Solid System for Stability Testing

Acid	Molar ratio Drug: acid	Haloperidol (g)	Acid (g)
Malic acid	0.29:1	0.81	1
Tartaric acid	0.24:1	0.60	1
Citric acid	0.12:1	0.22	1

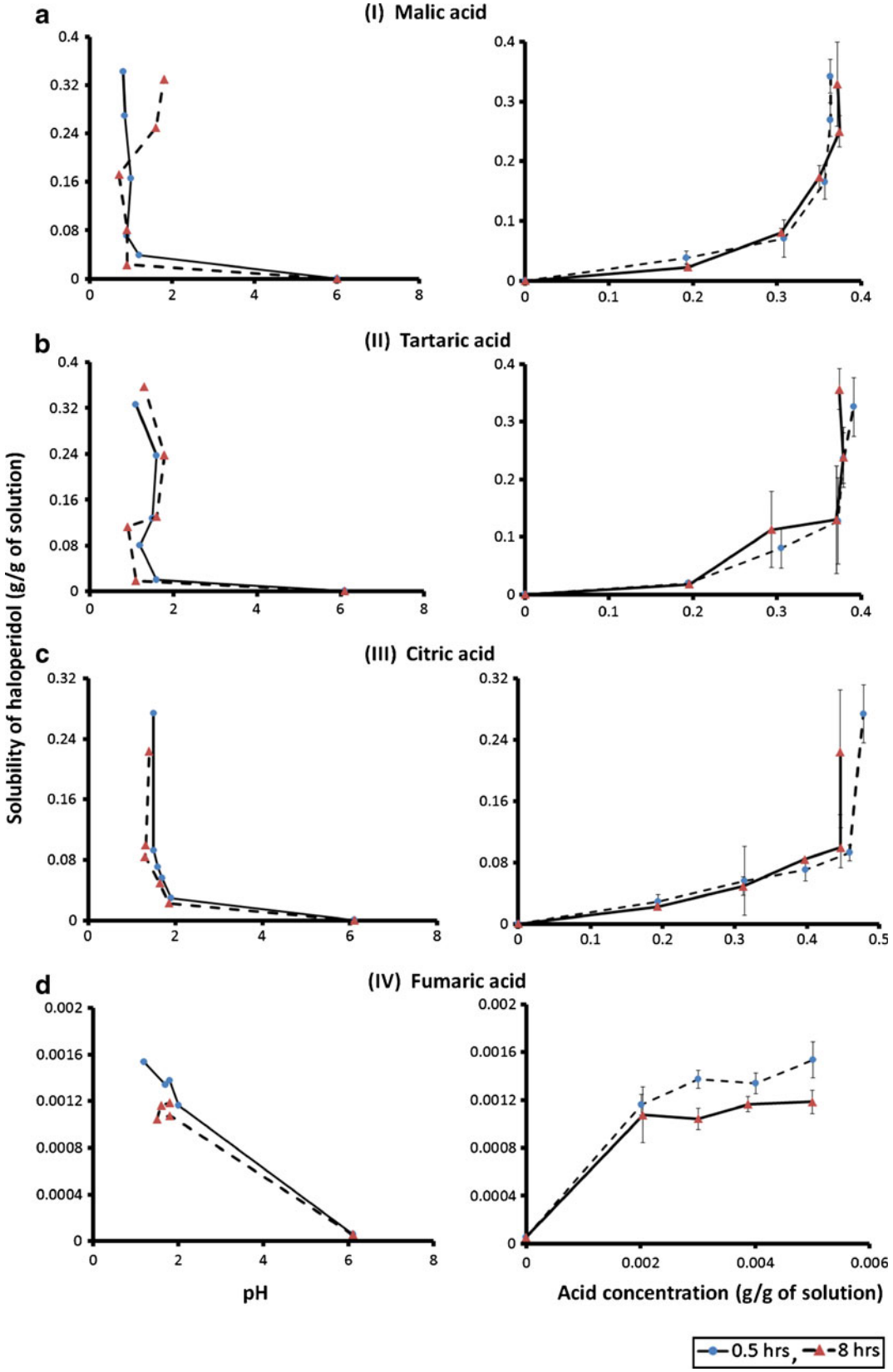

Fig. 2 Solubility profiles of haloperidol as function of pH and weak organic acids after 0.5 and 8 h of equilibration: (**a**) malic acid; (**b**) tartaric acid, (**c**) citric acid and (**d**) fumaric acid. For each acid, *left panel* shows the increase in solubility of haloperidol (g/g of solution) with the change in pH, and *right panel* shows the solubility of haloperidol (g/g of solution) with increasing amount of acid concentration in solution. Each data point in *right panel* represents the average (± s.d.) of three determinations.

acid, tartaric acid and citric acid as solubilizing agents. The increase of haloperidol solubility in presence of fumaric acid was, however, much lower. As the concentration of acid in solution increased, the pH decreased and the concentration of haloperidol in solution increased. For these reasons, the haloperidol solubility in presence of each acid is plotted in Fig. 2 in two different ways: First, as a function of the decrease in pH (left panel for each acid) and, second, as a function of the increase in organic acid concentration in solution (right panel for each acid). For the purpose of generating left panels, increasing amounts of each organic acid were added to aqueous suspensions of haloperidol and the drug solubility (g/g of solution) as a function of pH was determined. However, since the amounts of acids added to lower pH were not measured, the exact amounts of acid and water present per g of solution could not be calculated in this method. Therefore, for right panel in Fig. 2, solutions of acids with the predetermined ratios of acid to water were prepared and the drug solubility in these solutions was determined. In this way, concentrations of all components in solution (haloperidol, acid and water) could be measured or calculated. For example, if the drug concentration in a solution was 300 mg/g, the remaining 700 mg would be the combined weight of water and the acid present per g of the solution. Then, if a 1:1 w/w ratio of acid and water was used to determine haloperidol solubility, the concentrations of drug, acid and water in the final solution were, respectively, 300, 350 and 350 mg per g of solution. From such data, the drug solubility could be calculated as functions of the weight of the solution as well as the amounts of acid and water.

With the addition of malic, tartaric and citric acids, the apparent pH of solutions initially decreased to values around 1.5 to 2.0 and then remained practically constant. These are only apparent pH values as the solutions were highly concentrated and viscous, and small variations in pH observed for different data points at relatively low pH may not be meaningful. Although the pH remained almost constant in this range, the solubility of haloperidol increased with the increase in concentrations of acids in solutions. These results are shown by left panel for each acid in Fig. 2. The right panel for each acid in Fig. 2 showed that the haloperidol solubility (g of haloperidol per g of solution) increased nonlinearly with the increases in acid concentration.

During the determination of pH-solubility profiles in Fig. 2, it was also observed that there was an almost immediate solubilization of haloperidol in acidic solutions reaching saturation solubility in <30 min, and, as indicated by the data at the two time points (0.5 *vs.* 8.0 h) in Fig. 2, no further change in solubility was observed when haloperidol was equilibrated for 8 h. The aqueous solubility of haloperidol in presence of malic, tartaric and citric acids at 8 h were, respectively, 0.33, 0.36 and 0.23 g/g of solution. In presence of fumaric acid, it was much lower (~0.0015 g/g of solution or1.5 mg/mL).

The solubility values in Fig. 2 are expressed as g of haloperidol per g of solution. However, since the saturated solutions contained haloperidol, acids and water, they do not reflect the drug concentration in term of the amount of water present. Indeed, it is mentioned in Table I that as much as 0.81 g of haloperidol was dissolved per g of water during the preparation of haloperidol-malic acid amorphous solid systems. Therefore, it was of interest to calculate from the data presented in Fig. 2 what were the maximum solubility of haloperidol per g of water that could be obtained in malic, tartaric and citric acid solutions. A haloperidol solubility of 0.33 g/g of solution was reached in 8 h in presence of 0.37 g of malic acid (Fig. 2a, right panel), and from these two values, the amount of water per g of solution was calculated to be 0.30 g. Thus knowing the amounts of haloperidol, acid and water present per g of solution, the maximum solubility of haloperidol in presence of malic acid was calculated to be 1.1 g per g of water. The maximum solubility values of haloperidol in presence of tartaric acid and citric acid were similarly calculated to be, respectively, 1.3 and 0.8 g per g of water. These values in presence of malic, tartaric and citric acids represent enormously large increases in solubility in comparison with the aqueous solubility of 1, 4 and 30 mg/ml (or g), respectively, for phosphate, hydrochloride and mesylate salts of haloperidol reported by Li *et al.* (23). Compared to the intrinsic solubility of 2.5 μg/ml for the haloperidol base, the increase was 300,000 to 500,000 times larger. It is difficult to imagine whether the aqueous solubility of a basic drug may be increased to such a high degree by any other solubilization or complexation techniques. For these reasons, the increase in haloperidol solubility in presence of certain weak acids may be considered as supersolubilization.

To compare solubilization capacities of malic, tartaric and citric acids, the solubility of haloperidol was plotted in Fig. 3 as molar concentration of haloperidol dissolved as a function of the molar concentration of each acid present in solution. It is apparent that the solubilization capacities of acids were dependent on their concentrations in solution; as the concentration of acids increased, their solubilization capacities also increased. After the acids reached certain molar concentrations (>0.002 mol/g of solution), the slopes of the solubility profiles increased sharply, and apparently the increase in the solubility did not seem to follow a particular stoichiometric ratio. As shown in Table IV, there was apparently not a single complexation constant for each acid. From the highest slopes of 0.38, 0.28 and 0.37 obtained for, respectively, malic, tartaric and citric acids, it appears that one mole of haloperidol may be dissolved in approx. 2.5 to 3 moles of acids. The limiting factor in the increase in solubility of haloperidol in presence of acids appeared to be the aqueous solubility of acids themselves. Malic, tartaric and citric acids have high aqueous solubility

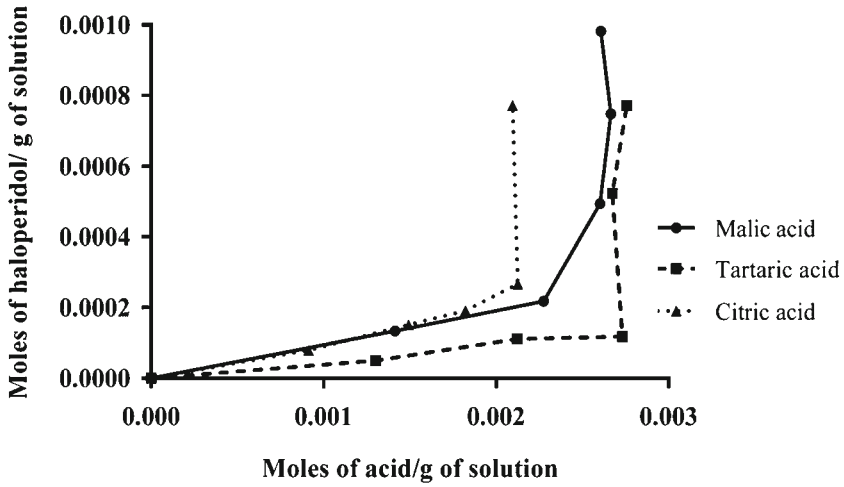

Fig. 3 Increase in molar concentration of haloperidol with the increase in molar concentration of weak organic acids.

values of 1.2, 1.5, and 1.6 g/g of water, respectively. Since they could be dissolved at high concentrations in water, they could also solubilize higher amounts of drug in a particular volume of solution. In contrast, fumaric acid has the poor solubility of 0.05 g/g of water, which resulted in the poor solubilization of haloperidol. For this reason, further studies with fumaric acid were discontinued.

Characterization of Dry Solids

Thermal Analysis

The solid mixtures obtained by drying aqueous solutions of haloperidol with weak organic acids were characterized by DSC analysis. The results for mixtures of haloperidol with one of the acids, malic acid, are given in Fig. 4. The DSC scans of haloperidol and malic acid showed melting peaks at 151 and 131°C, respectively, and no other thermal events were observed, thus indicating crystallinity of the compounds. However, in the solids prepared by mixing haloperidol with malic acid, relatively broad and shallow melting peaks were observed at low haloperidol to acid molar ratios (0.05:1 and 0.1:1) (Fig. 4). Since an excess of malic acid was present at these haloperidol to weak acid molar ratios, the observed melting peaks were due to the presence of the unreacted crystalline malic acid in the mixtures. As the haloperidol-to-malic acid molar ratio was further increased, more haloperidol was available to interact with the excess acid. As a result, the melting endotherm of malic acid disappeared, indicating the loss in crystallinity of samples. Similar results were also obtained for the mixtures of haloperidol with tartaric acid and citric acid (DSC Scans are given in Supplementary Material); there was a gradual decrease in melting endotherms of solid mixtures as the molar ratios of haloperidol to acids increased and the endotherms practically disappeared at the highest haloperidol to acid ratios used.

Since the presence of any residual moisture in the dry mixtures may influence their physical and chemical stability, the TG analysis was conducted on dry solids to determine whether there was any weight loss due to dehydration. There was no significant change in weight (<0.2% w/w) at the temperature range of 50–150°C, indicating that the samples were completely dry and there was no bound or unbound water present in the dried materials (the TGA scans not shown).

Powder X-Ray Diffraction (XRD)

Powder XRD patterns of haloperidol, malic acid and dry haloperidol-malic acid mixtures are shown in Fig. 5. The scan of the neat haloperidol showed a distinct peak at 20.5° 2θ; however, it overlapped with the peak of malic acid at the same position. Therefore, the low intensity peaks at position

Table IV Non-Stoichiometric Increase in Molar Ratio of Haloperidol: Weak Organic Acids

Molar ratio Haloperidol: malic acid	Slope	Molar ratio Haloperidol: tartaric acid	Slope	Molar ratio Haloperidol: citric acid	Slope
0.0001: 0.0010	0.10	0.00005: 0.0013	0.04	0.00008: 0.0009	0.09
0.0002: 0.0023	0.10	0.00011: 0.0021	0.05	0.00015: 0.0015	0.10
0.0005: 0.0026	0.19	0.00012: 0.0027	0.04	0.00019: 0.0018	0.11
0.0007: 0.0026	0.28	0.00052: 0.0027	0.20	0.00027: 0.0021	0.13
0.0009: 0.0026	0.38	0.00077: 0.0028	0.28	0.00077: 0.0021	0.37

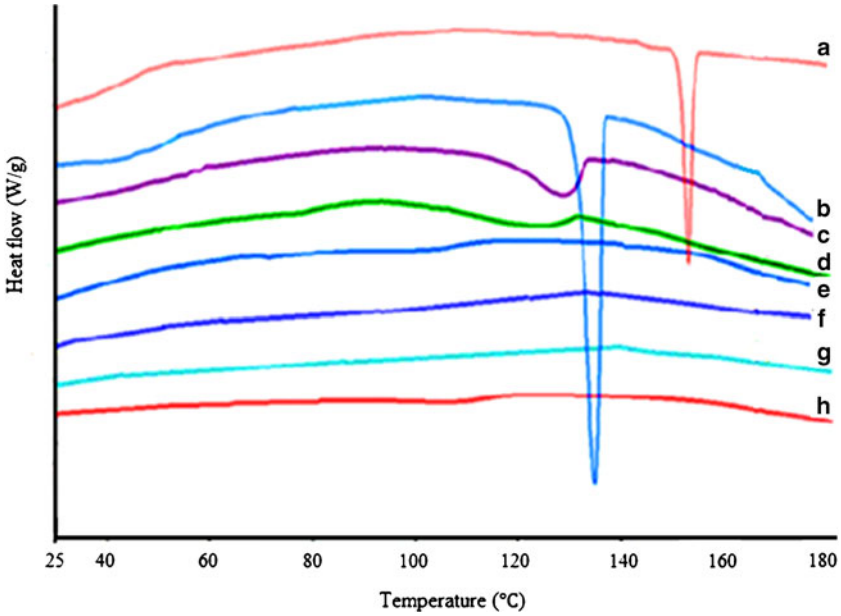

Fig. 4 DSC scans of (**a**) haloperidol, (**b**) malic acid, and haloperidol- malic acid combinations of (**c**) 0.05:1, (**d**) 0.1:1, (**e**) 0.14:1, (**f**) 0.16: 1, (**g**) 0.18:1 and (**h**) 0.29:1 molar ratios between haloperidol and malic acid.

15, 25 and 28°2θ were considered to interpret the powder XRD scans. It may be observed in Fig. 5 that the characteristic powder XRD peaks of haloperidol disappeared in all molar ratios, indicating that haloperidol converted to the amorphous form. Malic acid maintained some crystallinity when it was present in excess, *i.e.*, at lower haloperidol to acid ratio in the mixture. As the ratio of haloperidol to malic acid increased, there was more haloperidol available to interact with the acid, and, therefore, all powder XRD peaks disappeared, showing that both haloperidol and malic acid became amorphous. The absence of the powder XRD diffraction peaks of haloperidol-malic acid mixtures was in agreement with the loss of DSC endotherms observed in Fig. 4. Similar absence of haloperidol powder XRD peaks and gradual decrease in acid peaks were also observed for dried haloperidol-tartaric acid and haloperidol-citric acid mixtures (powder XRD scans not shown).

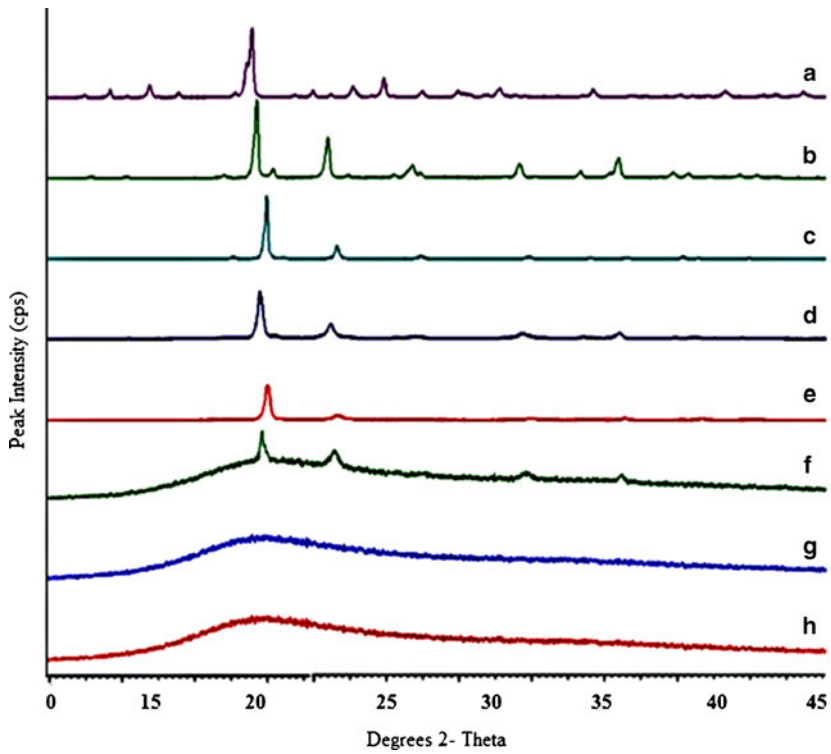

Fig. 5 Powder XRD patterns of (**a**) haloperidol, (**b**) malic acid, and haloperidol-malic acid combination with molar ratios of (**c**) 0.05:1, (**d**) 0.1:1, (**e**) 0.14:1, (**f**) 0.16:1, (**g**) 0.18:1 and (**h**) 0.29:1 showing conversion of crystalline haloperidol and malic acid into amorphous form with the increase in molar ratio.

Dissolution Study

Step dissolution profiles of dry solid forms of haloperidol-malic acid, haloperidol-tartaric acid and haloperidol-citric acid mixtures are given in Fig. 6 (a, b and c, respectively). Since haloperidol HCl is the chemical form present in the marketed dosage forms, its dissolution profiles were also determined for comparison. For all haloperidol-acid dried mixtures, the onsets of dissolution at pH 2 were much faster than those of the hydrochloride salt. It may be observed in Fig. 6 that at relatively low haloperidol to acid ratios, >85% drug dissolved in 15 min, indicating very rapid dissolution rates of the mixtures. When haloperidol-acid molar ratios were high, there was incomplete drug dissolution, although

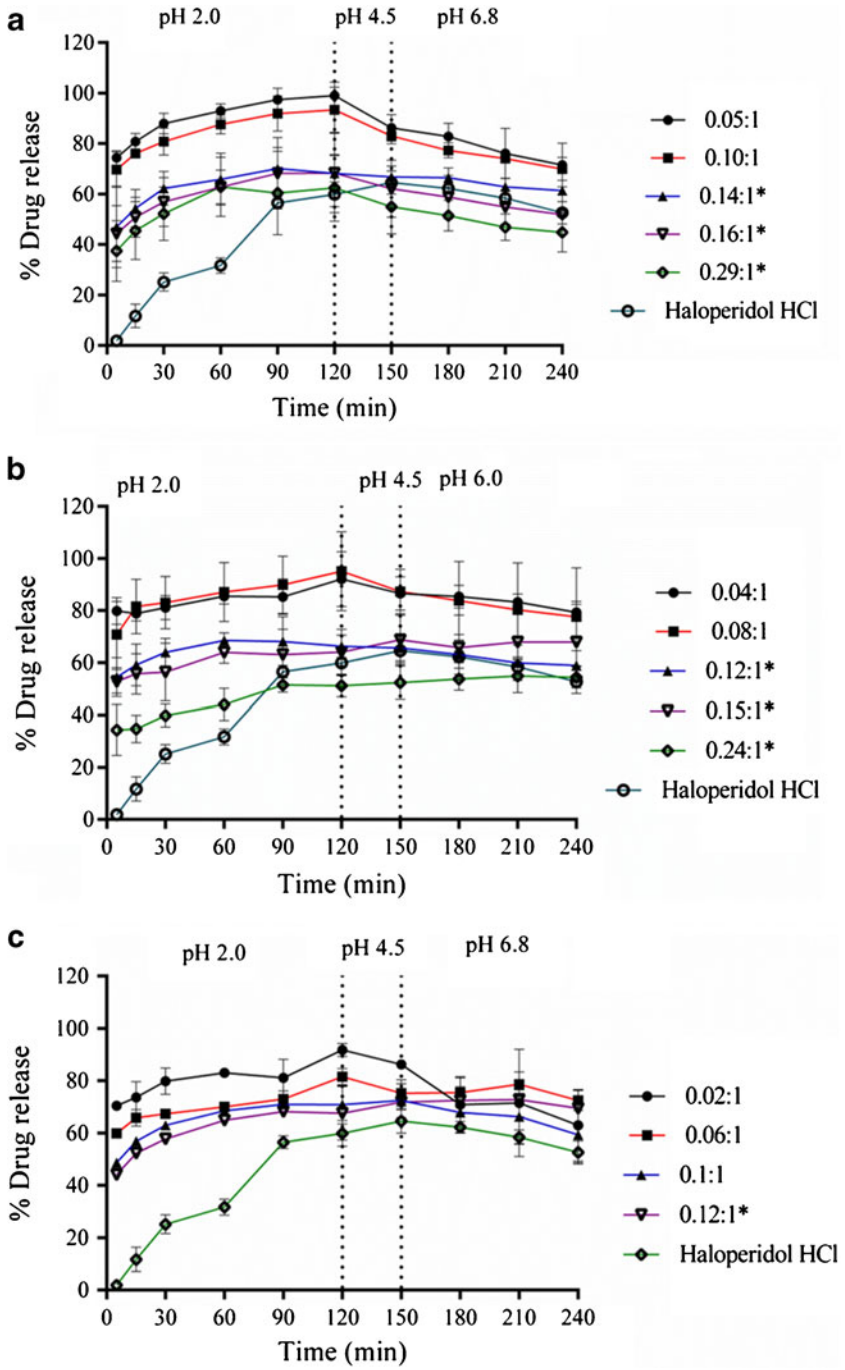

Fig. 6 Comparitive step dissolution profiles of amorphous haloperidol from combinations with (**a**) malic acid, (**b**) tartaric acid, and (**c**) citric acid. Results for different haloperidol to acid ratios are given, and the dissolution profile of haloperidol HCl is shown for comparison. The asterisk represents the molar ratios that existed as sticky viscous mass during dissolution testing. Each point refers to mean ± S.D ($n = 3$).

the initial rates were still high. It was observed that a viscous sticky mass, apparently amorphous haloperidol free base adhered to bottoms and sides of dissolution vessels, thus resulting in incomplete drug dissolution. The dry solids contained highly water-soluble weak acids and the poorly water-soluble free base. It is possible that when the acids dissolved from the dried mixture, part of the amorphous free base did not disperse completely in aqueous media in case of the high drug-to-acid ratios due to its viscous nature. No attempt was made to optimize formulations by adding surfactants or other dispersing agents in the drug-acid mixtures; further studies to overcome issues with the dispersion of drug are continuing in our laboratory. When the pH of dissolution medium was changed from ~2 in step 1 to 4.5 in step 2, there was no significant change in haloperidol concentration in solution and there was no precipitation of drug. This is because, based on the pH-solubility profile, the solubility of haloperidol at pH4.5 is relatively high. The drug concentration either remained unchanged or a small decrease in drug concentration in dissolution media was observed in step 3 at pH6.8. However, considering that the solubility of haloperidol at pH 6.8 is is extremely low (~2.5 μg/ml) (24), the solutions were supersaturated and there was no substantial precipitation of drug.

Physical Stability Testing

DSC scans and powder XRD patterns of different haloperidol-organic acid mixtures listed in Table III were determined initially and after 6 months of storage at 60% RH and 25°C. No change DSC scans and powder XRD patterns was observed, indicating that solid state properties of the mixtures, especially their amorphous nature, were not affected by storage at relatively high humidity (see Supplementary Material).

DISCUSSIONS

In accordance to physicochemical considerations discussed earlier, no haloperidol salt could be formed with malic acid, tartaric acid, citric acid and fumaric acid. This is in agreement with the previous reports by Li *et al.* (23) and Greco *et al.* (24) that relatively stronger acids like HCl, methanesulfonic (mesylic) acid and phosphoric acid are necessary to form salts with haloperidol. As discussed earlier under Theoretical Considerations, the pH must be below pH_{max} and the added acid fully ionized to form a salt. According to the pH-solubility relationship of haloperidol reported by Li *et al.* (23), the pH_{max} values for phosphate, hydrochloride and mesylate salts are, respectively, around pH5, 4.8 and 4.5. Phosphoric acid, mesylic acid and HCl are fully ionized at and below pH_{max} and this is the reason for the formation of haloperidol salts by these acids. It is not known what would be pH_{max} values if malic acid, tartaric acid and citric acid were to form haloperidol salts. If we assume that the apparent K'_{sp} values of such salts would be similar to that of the mesylate salt, it may be assumed that the pH_{max} would be around 4.5. However, a theoretical calculation in the present investigation indicated that malic acid, tartaric acid and citric acid, based on their first pKa values (3.40, 3.11 and 3.12, respectively) (29), would be only partially ionized at around pH4.5 and the ionization further decreases as the pH decreased with the addition of acids. The pH values of the final solutions containing haloperidol and various weak organic acids were below 2. Even if the acids were to form salts with haloperidol, the salts would dissociate as the added acid would be unionized at such a low pH. This is the reason why malic acid, tartaric acid and citric acid never formed salts. Based on these arguments, it may be concluded that the supersolubilization of haloperidol in presence of these acids observed in the present investigation was not due to salt formation. Figure 2 shows that the maximum solubilization of haloperidol was obtained at pH <2. However, based on the pKa values, the ionization of the acids at pH <2 is negligible, and, therefore, the increased solubilization of haloperidol is not due to the protonation of haloperidol (BH^+) as the dissolved acids are not capable of donating protons to fully protonate the base.

Further research is continuing in our laboratory to elucidate the mechanism of supersolubilization by weak acids. Since malic acid, tartaric acid and citric acid are highly soluble in water (>1 g/g), they may be dissolved in water at high concentrations, and at such concentrations, the acid solutions serve as super solvents for solubilizing haloperidol. Additional studies in our laboratory showed that similar solubilization may also be observed for other basic compounds. It appears that certain interactions that could be van der Waal's type or hydrogen bonding are responsible for the supersolubilization. It also appears that such interactions increase as concentrations of acids in solution increase, which is evident from the greater solubilization of haloperidol by acids on a mole to mole basis with the increased acid concentration. If any complex is formed between haloperidol and acids, there do not appear to be any definite stoichiometric ratios (Table IV) since the solubilization capacities of acids increased with the increase in their concentrations in solutions. It can be observed in Fig. 3 that the increase in solubility of haloperidol (moles/g of solution) did not follow any general stoichiometry with increasing concentrations of weak organic acids.

The pH-solubility considerations suggest that the amorphous materials produced by drying aqueous solutions of the haloperidol in concentrated solutions of acids should

also be physically stable. Since haloperidol does not form salts with the acids, there will not be any conversion to the solids into crystalline salts. On the other hand, the possibility of any conversion of the material into the haloperidol base may also be insignificant in the highly acidic microenvironment (pH <2) of the systems.

CONCLUSION

There are many reports in the literature showing that certain organic and inorganic acids may form salts with basic drugs, while others do not. Similarly, certain bases may form salts with acidic drugs, while others do not. When acids or bases do not form salts with, respectively, basic and acidic drugs, they are not considered further for the development of those drugs. By using haloperidol as a model basic drug, the present report demonstrates that the non-salt forming acids may be used advantageously in drug product development. It has been reported in the literature that the aqueous solubility of the marketed hydrochloride salt form of haloperidol is only 4 mg/ml and the maximum solubility that could be obtained for a haloperidol salt was ~30 mg/ml (mesylate salt). The present study shows that the aqueous solubility of haloperidol can be increased as high as >300 mg/g of solution by using such non-salt forming weak acids as malic acid and tartaric acid. In term of the water content, the solubility could be as high as 1.3 g of haloperidol per g of water (*see* solubility in presence of tartaric acid). Further, the drug converted to amorphous forms when such aqueous solutions of drug and acids were dried. Thus, the study also provides an organic solvent-free process of producing amorphous solid formulations of poorly water-soluble basic drugs. Studies are currently ongoing in our laboratory to optimize dissolution properties of such solid systems.

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