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Research Paper

Investigation of Solubility and Dissolution of a Free Base and Two Different Salt Forms as a Function of pH

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Purpose. To evaluate the effect of pH on solubility and dissolution rates of a model weak base, haloperidol, and two different salt forms, hydrochloride and mesylate.
Methods. pH-solubility profiles were determined by using haloperidol base, haloperidol hydrochloride, and haloperidol mesylate as starting materials; concentrated or diluted HCl or NaOH solutions were added to aqueous suspensions of solids to adjust pH to desired values. Intrinsic dissolution rates were determined using intrinsic dissolution apparatus under various pH-stat conditions. Further, approximation of diffusion layer pH was estimated from that of 10% w/w slurries of drug substances in dissolution media, which were used to correlate with intrinsic dissolution rates of haloperidol and its salt forms under different pHs.
Results. pH-solubility profiles of haloperidol base and its HCl salt were similar, while when the mesylate salt was used as starting material, it exhibited a higher solubility between pH 2 and 5. The higher solubility of the mesylate salt at pH 2–5 is attributed to its higher solubility product (K_{sp}) than that of the hydrochloride salt. The pH-solubility profiles indicated a pH_{max} (pH of maximum solubility) of ~5, indicating that the free base would exist as the solid phase above this pH and a salt would be formed below this pH. Below pH 1.5, all solubilities were comparable due to a conversion of haloperidol base or the mesylate salt to the HCl salt form when HCl was used as the acidifying agent. These were confirmed by monitoring the solid phase by differential scanning calorimeter. When their dissolution rates are tested, dissolution rates of the mesylate salt were much higher than those of the free base or the HCl salt, except at very low pH (<2). Dissolution rates of free base and HCl salt also differed from each other, where that of HCl salt exhibits higher dissolution rates at higher pHs. A direct correlation of dissolution rate with solubility at diffusion layer pH at the surface of dissolving solid was established for haloperidol, its hydrochloride, and mesylate salts.
Conclusions. Using pH-solubility and pH-dissolution rate interrelationships, it has been established that diffusion layer pH could be used to explain the observed rank order in dissolution rates for different salt forms. A non-hydrochloride salt, such as a mesylate salt, may provide advantages over a hydrochloride salt due to its high solubility and lack of common ion effect unless at very low pH.

KEY WORDS: basic drug; diffusion layer pH; dissolution; haloperidol; hydrochloride; intrinsic dissolution rate; mesylate; pH; salt forms.

INTRODUCTION

A common approach to improve dissolution of a compound is by forming salts. Early work on dissolution rates of pharmaceutical salts and its impact on bioavailability have been nicely reviewed by Berge *et al.* (1). There are many reports in the literature on the selection of optimal salt forms of new drug candidates (2–4). However, the process of a systematic screening of various potential salt forms of a compound for the identification of an optimal one with desirable physicochemical and biopharmaceutical properties is still hindered by the lack of a comprehensive understanding of their solubility and dissolution behavior. The selection of an optimal salt form purely based on physicochemical properties such as crystallinity, thermal properties, hygroscopicity, and stability may be inadequate due to its inappropriate biopharmaceutical attributes, such as solubility and dissolution rate. Although several investigators attempted to address solubility and dissolution issues in reference to salt selection (4–7), questions that have not been adequately addressed are the following: How will solubility and dissolution of nonhydrochloride salts be influenced after oral ingestion by gastric pH? Will a nonhydrochloride salt provide any advantage over a hydrochloride salt? or will it convert into a hydrochloride salt in the presence of HCl in the stomach without providing a significant advantage? In this report, attempts were made to

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address these questions by using different salt forms of a model drug: haloperidol.

MATERIALS AND METHODS

Materials

Haloperidol free base was obtained from Sigma-Aldrich Co. (St. Louis, MO, USA), and its hydrochloride and mesylate salts were synthesized at Novartis Pharmaceuticals Corp. (East Hanover, NJ, USA). Purified and deionized water (Millipore, Bedford, MA, USA) were used in this study. Other reagents used include hydrochloric and methylsulfonic acids from Sigma-Aldrich (St. Louis, MO, USA). All solvents and other chemicals were of analytical reagent grade.

Thermal Analysis

Differential scanning calorimetry (DSC) was used to characterize haloperidol free base, its hydrochloride and mesylate salts. The solid phase after pH-solubility experiments were also characterized. All thermal analysis were carried out using TA Instruments (New Castle, DE, USA) Model 2920 differential scanning calorimeter. Samples (~5 mg) were placed in a flat crimped aluminum pans and heated at a rate of 10°C/min under N_2 purge (50 ml/min). Potential changes in drug substance, such as salt forms, hydration state or polymorphs were monitored.

Determination of pH-Solubility Profile

pH-solubility profiles of haloperidol were determined at 37°C by phase-solubility techniques (8). Initially, excess solids (free base, hydrochloride or mesylate salts) were added to a 10-ml vial containing 5 ml of water. Solubility at different pH values were determined by stepwise titration with HCl or NaOH solutions. After each addition of acid or alkali, the suspension was equilibrated for over 24 h, the pH value was recorded, and an aliquot was removed and filtered using a 0.45-μm AcroDisc filter (Fisher Scientific, Fairlawn, NJ, USA). Haloperidol solutions were analyzed by UV spectrophotometer (HP2940) by diluting them to appropriate analytical ranges. The detection wavelength was 250 nm, and a linearity range between 0.25 to 100 μg/ml was used.

Intrinsic Dissolution Experiments

Intrinsic dissolution rate experiments were conducted in a rotating disk apparatus. Disks of haloperidol drug substances were prepared by directly compressing 200 mg of free base and hydrochloride or 500 mg of haloperidol mesylate in a die at a pressure of 1 ton for 30 s using a hydraulic press (Carver Press, Fred Carver, NJ, USA). The exposed surface area for the resulting disk was 0.5 cm^2. A regular USP dissolution apparatus maintained at 37 ± 0.5°C was used for the dissolution study. Each dissolution vessel contained 500 mL of aqueous dissolution medium maintained at various unbuffered conditions (constant pH at 1.0, 2.0, 3.0, 5.0, and 7.0) by titration of dilute HCl or NaOH solutions. The disk holder (die) was half-immersed into the dissolution medium and rotated at 200 rpm. Samples were withdrawn automatically at 15, 30, 45, 60, 75, 90, 105, and 120 min, filtered, and then analyzed by an online HP 8452A UV Diode Array Spectrophotometer (Agilent, Palo Alto, CA, USA) at the detection wavelength of 250 nm.

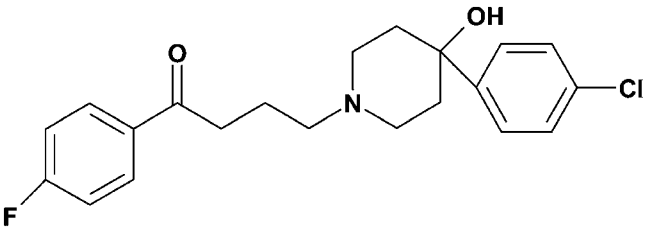

Fig. 1. Chemical structure of haloperidol free base.

Diffusion Layer pH Measurement

Diffusion layer pH of haloperidol free base and its salts were measured by suspending 100 mg of drug substance in 1 ml of each dissolution medium in which the intrinsic dissolution experiments were conducted. The slurry contains 10% w/v solid content and the pH measured were used to approximate the pH at the surface of solid as the diffusion layer thickness approaches zero ($pH_{h=0}$) (8).

RESULTS AND DISCUSSION

pH-Solubility Profiles

Figure 1 shows the structures of haloperidol, a model compound used in this study. Its pK_a value and intrinsic solubility (solubility of nonprotonated form) are 8.0 and 2.5 μg/ml, respectively (Fig. 2). Figure 2 gives the pH solubility profiles of haloperidol when the free base form and the hydrochloride salt were used as starting materials for the determination of solubility, where pH was adjusted by using solutions of HCl or NaOH, as necessary. There is generally a good agreement between the experimental values (symbol) and theoretical prediction (line). Figure 3 gives the pH-solubility profile using haloperidol mesylate as starting material by adjusting pH with HCl or NaOH solutions.

Equations elucidating pH-solubility interrelationships of salt and free base forms of basic compounds were first described by Kramer and Flynn (9). Subsequently, there have been many other reports on both experimental and theoretical aspects of the solubility of basic drugs as a function of pH

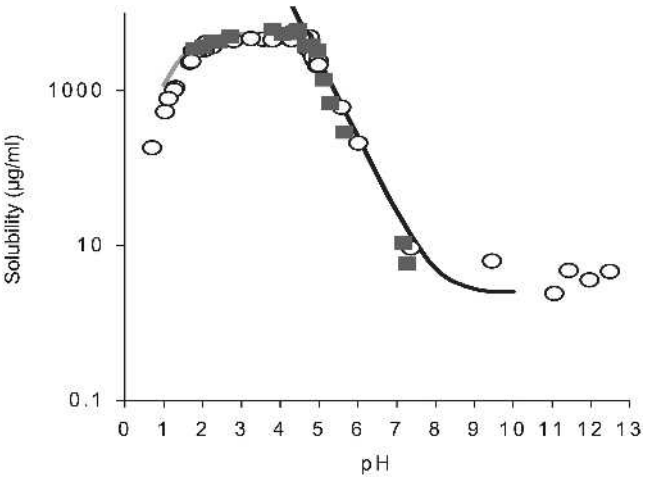

Fig. 2. pH-solubility profile for haloperidol free base (■) and its HCl salt (○).

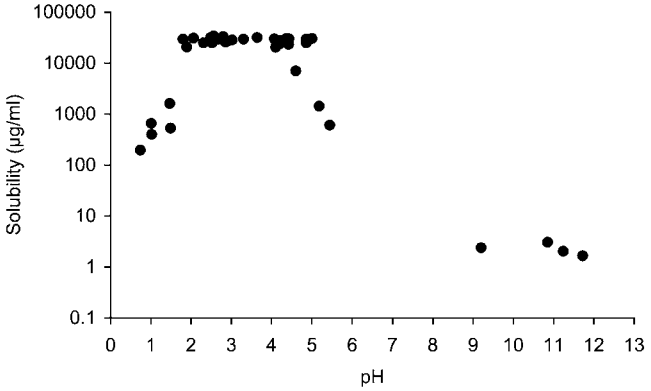

Fig. 3. pH-solubility profile for haloperidol mesylate (●).

(6,10). Essentially, when a basic compound or its salt is dissolved in water, the following equilibrium exists:

$$BH^+ + H_2O \overset{K_a}{\Leftrightarrow} B + H_3O^+ \quad (1)$$

Or,

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \quad (2)$$

where BH^+ and B represent, respectively, protonated and free base forms of the compound. Therefore, when the salt form is the saturation or equilibrium species, that is, when the salt exists as the solid phase during the determination of the pH-solubility profile, the total solubility (S_T) in the aqueous solution is:

$$S_{T,salt} = [BH^+]_S + [B] = [BH^+]_S \left(1 + \frac{K_a}{[H_3O^+]}\right) \quad (3)$$

where S represents saturation species. On the other hand, when the free base is the saturation species,

$$S_{T,base} = [BH^+] + [B]_S = [B]_S \left(1 + \frac{[H_3O^+]}{K_a}\right) \quad (4)$$

Equations 3 and 4 represent two independent pH-solubility curves and the point where the two curves intersect is generally defined as pH_{max}, the pH of maximum solubility. Therefore, the $S_{T,salt}$ in Equation 3 is for the solubility below pH_{max} and may also be denoted by $S_{T,pH<pHmax}$ to differentiate it from $S_{T,base}$ in Eq. (4). The S_T in Eq. (4) is for the solubility above pH_{max} and may thus be denoted by $S_{T,pH>pHmax}$. Depending on pK_a, intrinsic solubility of the base and solubility of the salt, pH_{max} values may vary. For example, pH_{max} will increase by one unit when any of the following factors changes: an increase in pK_a by one unit, a 10-fold increase in intrinsic solubility, or a 10-fold decrease in the solubility of salt. Therefore, all these factors have profound impact on salt formation.

Figure 2 shows that pH-solubility profiles are similar whether hydrochloride salt or free base was used as starting material. The pH_{max} of haloperidol, where the free base and salt curve intercepts, is around 5, this indicates that when the salt is used as the starting material, it converts to free base if the pH of a suspension is raised above 5. In the same way, the free base converts to the hydrochloride salt when the pH of its suspension is lowered below 5. Therefore, similar species, both in solid phase and in solution, remained in equilibrium at any particular pH irrespective of the use of hydrochloride salt or free base as the starting material, and this explains the similarity in the two profiles. On the other hand, when haloperidol mesylate was used as the starting material, the solubility measured was much higher than that of the hydrochloride salt (Fig. 3). For example, the solubility of the mesylate salt in the pH region of 3 to 5 was in the range of 25 to 29 mg/ml, while that of the hydrochloride salt was in the same pH region is 4.2 to 4.3 mg/ml. This is due to the high solubility of mesylate salt and therefore the higher buffer capacity provided by mesylate. The profile at pH > 5 in Fig. 3 is, however, similar to those in Fig. 2, as the solid phase converted to the free base at pH higher than the pH_{max}. The conversion between different forms is monitored by DSC, which will be discussed at later section.

It may also be noted that in both Figs. 2 and 3, solubility decreased gradually at low pH, when HCl was used to titrate the pH to less than 1.5. This is due to the common ion effect on solubility of the HCl salt. The difference in solubility between hydrochloride and mesylate salts and the common ion effect may be explained based on solubility products of the salts (11). When the pH of an aqueous suspension (slurry) of a free base is lowered by the addition of an acid, the following relationship exists:

$$[B]_S + [BH^+]\uparrow + [X]\uparrow \Leftrightarrow (B)\ \text{solid} \quad (5)$$

where X^- represents the anion species from the acid added. As indicated by the arrows, concentrations of the protonated compound and the counterion increase with the addition of acid. This continues until the concentration of $[BH^+]$ exceeds the salt solubility, at which point the salt, (BH^+X^-) solid, nucleates. Eventually, all the solid base converts to solid salt and the equilibrium shifts to:

$$(BH^+X^-)\ \text{solid} \Leftrightarrow [BH^+]_S + [X^-] \quad (6)$$

The apparent solubility product (K'_{sp}) can be derived from Eq. (6) as follows:

$$K'_{sp} = [BH^+]_S\,[X^-] \quad (7)$$

In the absence of excess counterion (X^-), $[BH^+]_S = [X^-]$, and therefore, solubility $= \sqrt{K'_{sp}}$.

Otherwise, $[BH^+]_S = K_{sp}/[X^-]$. From the relatively flat solubility profiles of hydrochloride and mesylate salts between pH 3 and 5 (Figs. 2 and 3), the apparent K_{sp} values of the two salts were calculated to be 1.6×10^{-4} M and 2.0×10^{-3} M, respectively. Such a difference in solubility products explains the difference in solubility of various salt forms of a particular compound.

Because HCl solution was used to titrate the pH, counter ion X^- in this case was Cl^-. The decrease in solubility of haloperidol at pH below 3 (Fig. 2) is due to a gradual increase in chloride ion concentration as the pH was lowered. For the mesylate salt (Fig. 3), no decrease in solubility was observed until the pH was lowered to 1.5. This was because the pH was adjusted by using HCl and, therefore, no excess common ion initially existed for mesylate. Conversion from mesylate to

hydrochloride salt form at pH below 1.5 was confirmed by differential scanning calorimetric testing of the solid phase (Fig. 5). The pH at which solubility of the mesylate salt started to decline is related to both the amount of mesylate added at the start of the solubility testing and the amount of hydrochloride acid added to lower the pH (Eq. 8). When there was enough $[H^+][Cl^-]$ in the solution to convert all the mesylate drug substance, the conversion as indicated in Eq. (8) would occur, hydrochloride salt would be obtained at such pH.

$$(BH^+\,CH_3SO_3^-)_{solid} \Leftrightarrow [BH^+] + [CH_3SO_3^-] + [H^+] + [Cl^-] \Leftrightarrow (BH^+Cl^-)_{solid}\downarrow + CH_3SO_3H \quad (8)$$

As a consequence of this phase conversion and the consequent susceptibility of the converted solid phase to the common ion effect at lower pH, the solubility of the mesylate salt decrease with a further decrease with pH (Fig. 3; pH < 1.5). Despite the potential for phase conversion, the lack of influence of added HCl on the mesylate salt solubility over a wider gastric pH range (pH 2–5) provides an useful insight into potential advantages of using mesylate and possibly certain other salt forms over the hydrochloride salt.

Thermal Analysis

The differential scanning calorimetry curves of haloperidol free base, its hydrochloride and mesylate salts were shown in Fig. 4. Haloperidol free base has an onset of melting point approximately 151.4°C; that of its hydrochloride and mesylate salts are 230.8°C and 165.2°C, respectively.

Solid phase of haloperidol mesylate after pH-solubility study were also characterized, their DSC curves were shown in Fig. 5. Under pH ~1, the solid phase was characterized to had a similar melting point as that of its hydrochloride salt (Fig. 5A), indicating a conversion from mesylate to hydrochloride had occurred due to the addition of hydrochloride acid, at lower pH, the conversion was also facilitated by the lower K_{sp} of the HCl salt compared with that of the mesylate. When solid phase of mesylate under pH ~4 was tested, a typical DSC profile of mesylate was obtained (Fig. 5B), which confirmed that the high solubility observed between pH 2-5 was contributed by mesylate salt. At pH > pH_{max} (pH_{max} = 5), the pH-solubility curved is theoretically controlled by free base form. When the solid phase of mesylate was tested under pH 6.8, a free base DSC curve was evident (Fig. 5C).

The fact that different solid forms were observed under various pHs, when mesylate was used as starting material to prepare its pH-solubility profile is interesting, but not surprising. As discussed in the previous section, at pH above pH_{max}, free base is thermodynamically the most stable form, total solubility is determined by free base solubility and its ionized species (Eq. 4), whereas at pH below pH_{max}, the salt form is responsible for total solubility (Eq. 3), as the salt is thermodynamically the more stable form. Conversion from mesylate to hydrochloride salt is affected by both pH and chloride ion concentration. As indicated by Eq. (8), chloride ion will replace mesylate counterion under given pH when the K_{sp} of hydrochloride salt is lower than that of mesylate.

Intrinsic Dissolution Rates

Figures 6, 7, and 8 illustrate intrinsic dissolution profiles of haloperidol free base, hydrochloride salt and mesylate salt, respectively, as a function of pH. The individual rates in mg/min/cm^2 are tabulated in Table I. As shown in column 2 of Table I and in Fig. 6, the dissolution of haloperidol free base was highest at pH 2.0, followed by pH 3.1, 1.1, and 5.0, and the rate at pH 7 was so low that it was practically not measurable. In contrast, dissolution rates of the hydrochloride salt were highest at pH 3.1 and 5.0, followed by pH 7.0, 2.0, and 1.1. The

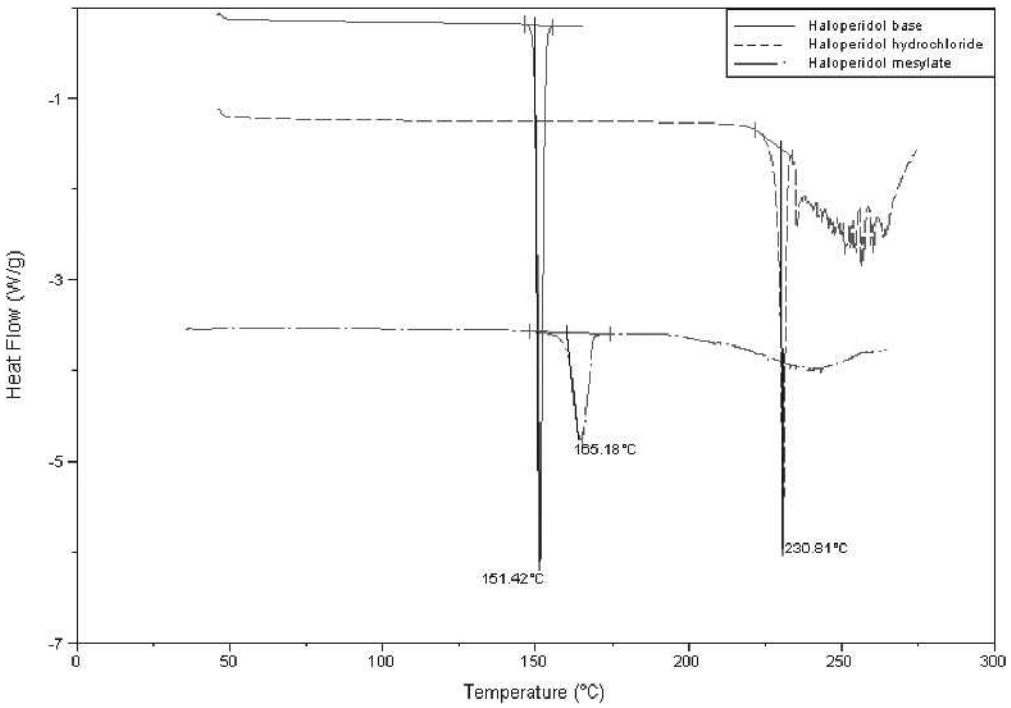

Fig. 4. Comparative DSC curves of haloperidol free base, its hydrochloride and mesylate salts.

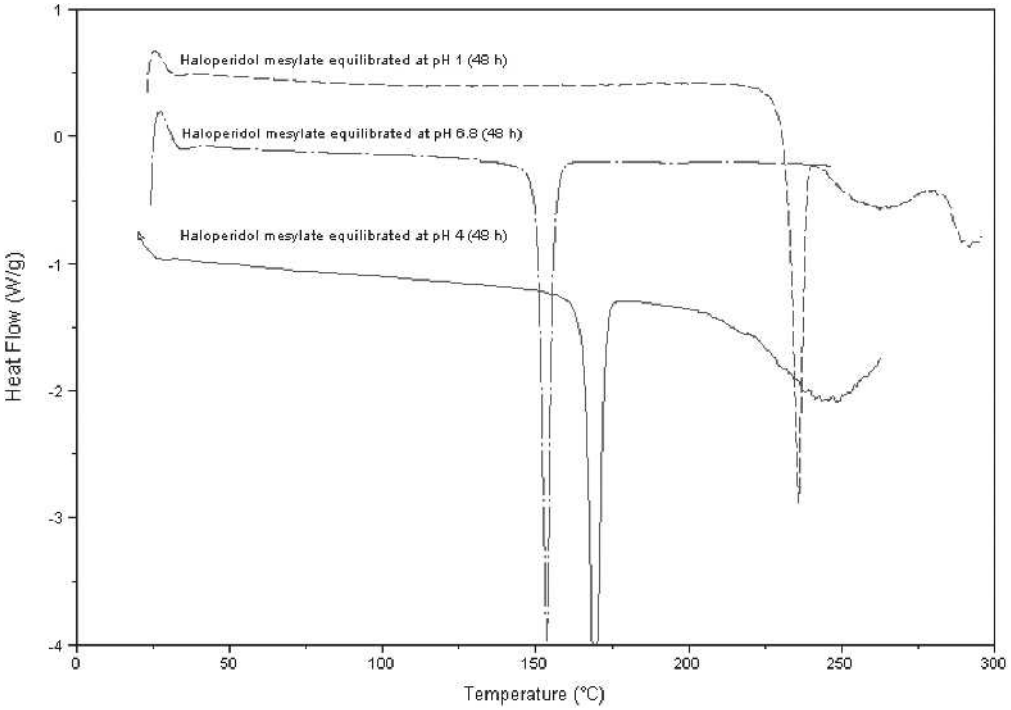

Fig. 5. Comparative DSC curves of solid forms of haloperidol mesylate equilibrated at pH 1 (A), pH 4 (B), and pH 6.8 (C).

dissolution rates of mesylate salt were similar and the highest in the pH range of 3.1 to 7.0, and then decreased at pH 2.0 and 1.1 in a gradual order. Further, the dissolution rates of the mesylate salt in the pH range 2.0 to 7.0 are greater than that of the hydrochloride salt by a factor of approximately 6, which is consistent to difference in their K_{sp}. These seemly random rank order of intrinsic dissolution rates of haloperidol free base, its hydrochloride and mesylate salts can be explained by theory of diffusion layer pH, which will be discussed in the following section.

The dissolution rate (J) of solid per unit surface area is given by:

$$J = \frac{D}{h}(C_S - C_b) \tag{9}$$

where D is the diffusion coefficient of the solute, h is the diffusion layer thickness during dissolution at the surface of solid, C_S is the saturation solubility of the solid in the dissolution medium, and C_b is its concentration in the bulk medium. For haloperidol base and salts, D may be considered to be constant, and, under identical dissolution conditions, h also remains constant. Therefore, under "sink" conditions (C_b < 10% of C_S), Eq. (9) is reduced to:

$$J \sim \frac{D}{h} C_S \tag{10}$$

As a consequence, a ratio J to C_S would also remain constant. However, as it is evident from column 3 in Table I, that is not the case, and the J/C_S ratios varied widely and without any definite order when Cs at the bulk pH is used for calculation.

Previous reports (4,12) demonstrated that it is not the solubility under a bulk pH condition, rather it is the solubility under pH condition at the solid surface in the diffusion layer ($C_{S,h=0}$), that controls dissolution rates of solids in reactive media. The pH at the dissolving surfaces of haloperidol base and salts ($pH_{h=0}$) were, therefore, responsible for the dissolution rates observed. This could be measured by a method described earlier (4,8) and the results are plotted in Fig. 9, where the pH as the diffusion layer thickness approaches zero ($pH_{h=0}$) of haloperidol base and its salts were approximated by concentrated slurry prepared from unbuffered dissolution media. As demonstrated in Fig. 9, diffusion layer pH could differ significantly from that of bulk pH, which can significantly influence drug solubility in the diffusion layer and, as a consequence, the dissolution rate. For instance, when the bulk pH varied between 3 and 7, $pH_{h=0}$ of the mesylate salt remained practically unchanged around pH 3. Because this pH is below the pH_{max}, where the drug solubility is high, the dissolution of the mesylate salt in the pH range of 3 to 7 is also

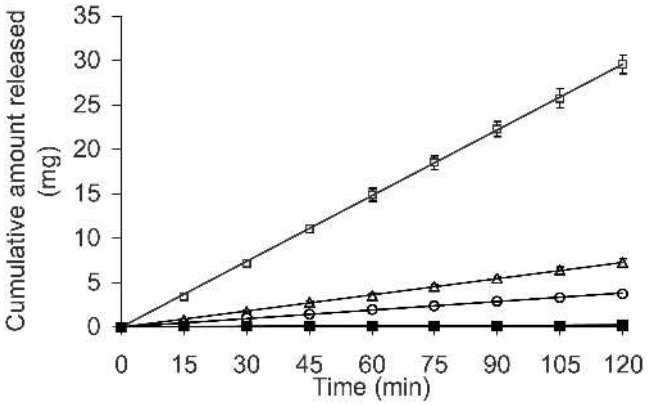

Fig. 6. Intrinsic dissolution rate of haloperidol free base at various pH (–○– pH 1.0, –□– pH 2.0, –△– pH 3.0, –■– pH 5.0). Data presented as mean ± SD; n = 6.

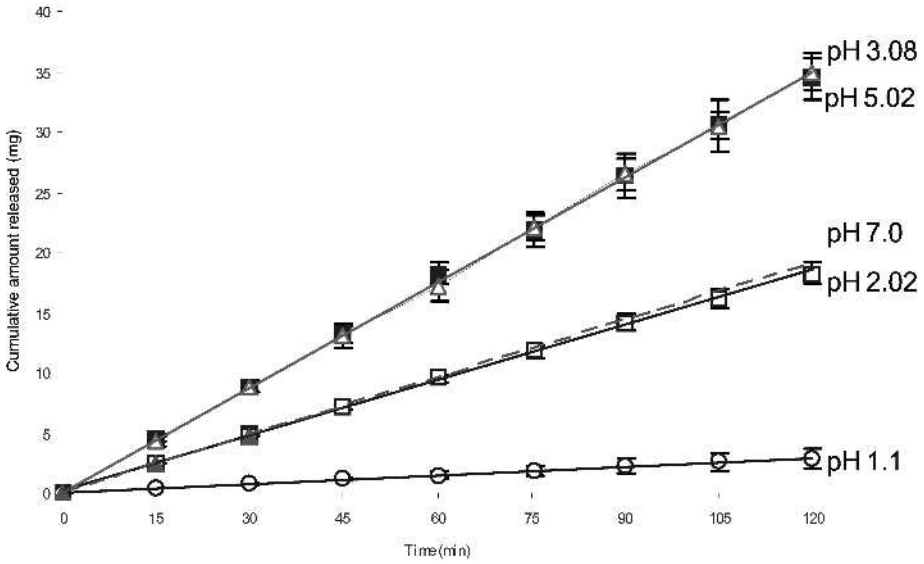

Fig. 7. Intrinsic dissolution rate of haloperidol HCl at various pH (–○– pH 1.0, –□– pH 2.0, –△– pH 3.0, –■– pH 5.0, –▲– pH 7.0). Data presented as mean ± SD; n = 6.

expected to be high. Essentially similar effect was also observed for the hydrochloride salt. On the other hand, the $pH_{h=0}$ in this bulk pH range is above the pH_{max} for the free base, and, therefore, the drug solubility in the diffusion layer and the dissolution rate would be lower.

Given the reason above, the dissolution rate to drug solubility ratios were recalculated using solubilities under pH conditions at solid surfaces. As shown in column 7 in Table I, $J/C_{S,h=0}$ values, calculated as a ratio between intrinsic dissolution rate (Table 1, column 2) and solubility at solid diffusion layer pH (Table I, columns 4 and 5), under different pH conditions and for different solid forms are very similar, slight deviations at other pH conditions could be due a difference in solute activity.

It may be concluded from Figs. 6 to 8 and the data in Table I that although the free base appeared to have a dissolution advantage at a lower pH, e.g., pH 2, the reverse is true at a higher pH, where dissolution rates a salt (hydrochloride or mesylate) could be higher by several orders of magnitude. This is due to the much higher solubility in their diffusion layer pH of the salt forms compare to that of free base. On the other hand, at pH 1.l, all the three forms had similar dissolution rates, this can be explained by the fact that the free base and its hydrochloride and mesylate salt forms have similar diffusion layer pH under this pH. As discussed earlier in pH-solubility section, conversion to HCl salt could help to explain the similarity in their dissolution rates.

In evaluating various free or salt forms of a drug candidate for selecting an optimal form for development, care must be given to studying dissolution rates at multiple conditions. It is also evident that a nonhydrochloride salt with higher drug solubility may have an advantage over the hydrochloride salt. The dissolution rate of haloperidol mesylate remained much higher than that of the hydrochloride salt at a wide

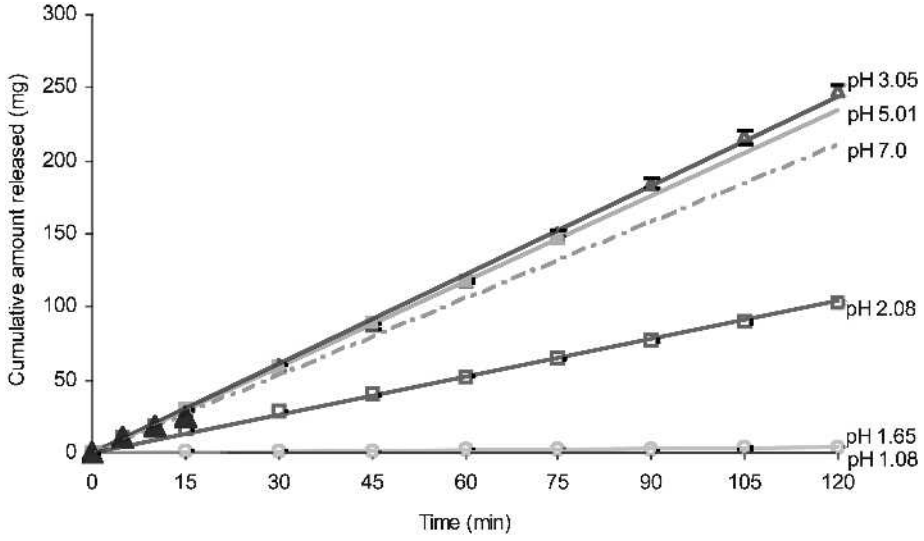

Fig. 8. Intrinsic dissolution rate of haloperidol mesylate at various pH (–○– pH 1.0, –□– pH 2.0, –△– pH 3.0, –■– pH 5.0, –▲– pH 7.0). Data presented as mean ± SD; n = 6.

Table I. Intrinsic Dissolution Rates of Haloperidol Free Base, Haloperidol Hydrochloride, and Haloperidol Mesylate as a Function of pH

pH of dissolution medium	Dissolution rate (J, mg min^{-1} cm^{-2})	Solubility at bulk pH (C_s, mg ml^{-1})	J/C_s (ml min^{-1} cm^{-2})	pH at solid surface ($pH_{h=0}$)	Solubility at solid surface ($C_{s,h=0}$, mg ml^{-1})	$J/C_{s,h=0}$ (ml min^{-1} cm^{-2})
Free base						
1.1	0.032	0.79	0.041	1.11	0.65	0.049
2.0	0.246	3.41	0.072	4.76	3.48	0.071
3.1	0.061	4.16	0.015	5.93	0.73	0.084
5.0	0.002	2.47	0.001	7.00	0.02	0.072
HCI salt						
1.1	0.025	0.79	0.032	0.88	0.56	0.044
1.5	0.062	2.50	0.025	1.37	1.20	0.052
2.0	0.155	3.41	0.045	1.85	2.84	0.055
3.1	0.292	4.16	0.070	3.01	4.16	0.070
5.0	0.291	2.47	0.118	4.89	4.28	0.068
7.0	0.157	0.02	7.140	4.85	2.82	0.056
Mesylate salt						
1.1	0.033	0.65	0.051	1.04	0.65	0.050
1.7	0.115	20.76	0.006	1.5	2.50	0.046
2.0	0.865	25.06	0.035	1.91	20.77	0.042
3.1	2.037	28.45	0.072	2.61	24.91	0.069
5.0	1.962	30.44	0.064	3.02	26.19	0.075
7.0	1.760	0.002	880.000	2.99	28.90	0.061

gastrointestinal pH range. The dissolution rate of the mesylate salt decreased only at pH below 2.

CONCLUSIONS

Depending on solubility products, different salt forms of a basic drug may have different aqueous solubilities. The current study shows that a non-hydrochloride salt, such as a mesylate salt, having aqueous solubility higher than that of a hydrochloride salt may have certain biopharmaceutical advantages. A non-hydrochloride salt is not as susceptible to the common ion effect due to the presence of HCl under gastric pH as a hydrochloride salt, unless it is converted to a hydrochloride salt form at a very low pH and abundance of chloride ion.

Although a free base may also exhibit superior dissolution rates at a low pH, the advantage disappears as the pH increases, and its dissolution rate under intestinal pH condition could indeed be much lower than that of its salt forms. If the total dose of a weak base is not dissolved in gastric pH, a

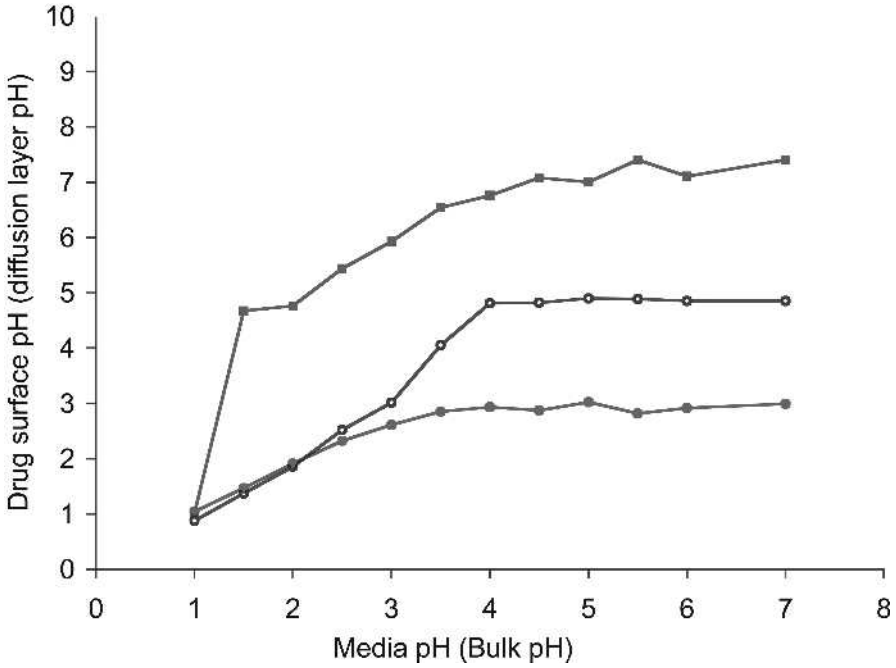

Fig. 9. pH at the surface of solid ($pH_{h=0}$) as a function of bulk pH of dissolution media (–●– haloperidol mesylate, –○– hydrochloride, and –■– free base).

salt form may well be preferred due to its ability to continuous higher dissolution at intestinal pH.

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