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Modifying the Diffusion Layer of Soluble Salts of Poorly Soluble Basic Drugs To Improve Dissolution Performance

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Abstract: The dissolution mechanism of soluble salts of poorly soluble bases can be complex because both the dissolution of the salt and precipitation of the free base can occur depending on the experimental conditions and properties of the molecule. The dissolution of three soluble salts of poorly soluble bases is described in this paper. Two of these compounds precipitate as free base under normal stomach pH conditions (pH from 2−4) during dissolution. This free base precipitation is a result of formation of free base on the surface of the dissolving salt. Diffusion Layer modulated (DLM) solids are defined and presented that can effectively counteract this precipitation mechanism. These DLM materials employ excipients in order to modify the pH or solubility conditions at the surface of the dissolving salt to minimize precipitation of the free base that can occur. Rotating disk dissolution data is presented which shows how these formulated solids can act to improve the dissolution profile for these materials.

Keywords: Dissolution; precipitation; supersaturation; salts; diffusion layer

Introduction

Solubility is a problem in the development of marketable formulations of poorly soluble drugs. Limited solubility can lead to formulations with inadequate oral bioavailability. A common approach to address this problem is to make water-soluble salts of poorly soluble (BCS II or IV) acidic or basic drugs in order to enhance their oral bioavailability.[1−3] This approach is successful in many cases.[4]

However, many times, despite its higher water solubility, the salt is no more bioavailable than the parent free acid or base. Occasionally, there are examples where the salt may have an even lower bioavailability than that of the parent drug.[5,6] The reason for the unpredictable bioavailability behavior of salts is due to the propensity of salts of poorly soluble drugs to undergo dissociation or "salt hydrolysis" upon contact with water in GI fluids. This phenomenon can lead to spontaneous precipitation of the corresponding free acid or the free base form of the drug salt if the pH generated during dissolution is not sufficient to maintain solubility of the free acid or free base.[7−9] This paper will focus on the

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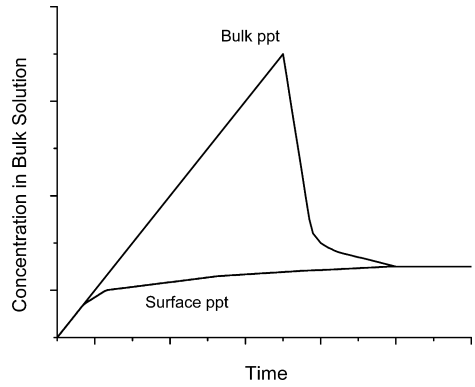

Figure 1. Schematic showing different dissolution profiles that might be obtained from two distinct precipitation mechanisms. When a soluble salt of a poorly soluble base dissolves in a medium where the free base is less soluble than the salt, precipitation can occur in the bulk dissolution fluid (upper curve) or on the surface of the dissolving salt (lower curve).

dissolution and precipitation mechanisms of soluble salts of poorly soluble basic drugs.

Precipitation Mechanisms. If precipitation of the free base occurs directly on the surface of a soluble salt of a poorly soluble basic drug, the dissolution rate will be significantly decreased, negatively impacting oral bioavailability. Therefore, this is an important topic to understand. Currently, there is no model for accurate prediction of how rapidly a supersaturated free acid or free base will precipitate under different conditions, and this can only be determined empirically.[10,11] It is proposed that there are two major mechanisms for precipitation resulting from salt hydrolysis. The first is a *bulk precipitation mechanism*, where material in solution precipitates as individual particles in the bulk fluid. The second mechanism is a *surface precipitation mechanism* where the free base form precipitates directly onto the surface of the dissolving salt within the dissolution diffusion layer.

The different dissolution profiles that might be produced by the two mechanisms are shown schematically in Figure 1. This figure shows the dissolution profiles of two soluble salts of poorly soluble bases with equal dissolution rates, but differing in their precipitation mechanisms. In this schematic figure, the dissolution experiment could be of any type, but the representation here is of a constant surface area rotating disk experiment for simplification.

The upper curve in Figure 1 shows that precipitation of the poorly soluble free base during dissolution of a soluble salt of a poorly soluble drug does not occur until a certain concentration in the bulk fluid is exceeded, perhaps even resulting in the dissolution of the entire dose. Above this critical concentration, however, precipitation of the free base can occur. Precipitation continues until the free base concentration approaches the bulk solubility limit of the poorly soluble basic drug. This mechanism results in the creation of a suspension of free base particles in the dissolution fluid—not directly at the surface of the dissolving soluble salt.

The lower curve in Figure 1 shows a distinctly different mechanism that can occur. Here, the dissolution of the soluble salt of a poorly soluble base starts off in a normal manner, but the solubility limit of the free base is quickly exceeded directly at the surface of the dissolving particle. In this case, precipitation occurs directly onto the surface of the salt particles, coating the drug salt surface with a layer of free base. Since, in this case, the free base is much less soluble, the dissolution slows considerably after this form conversion begins. As Figure 1 shows, the result of each of these mechanisms yields very different solution concentration profiles, which can translate into significant differences in intestinal drug absorption.

It is important to understand the difference between the two precipitation mechanisms (surface precipitation and bulk precipitation) that can occur with soluble salts of poorly soluble compounds because different formulation approaches may be required in order to block the undesired mechanism. By understanding the dissolution mechanism, the best formulation approach can be applied to maximize the dissolution effectiveness of the compound in the right environment. In our experience, the surface precipitation mechanism is very prevalent for the case of soluble salts of poorly soluble compounds, and this is the main focus of this paper.

In this paper, rotating disk dissolution data are reported for three different compounds at relevant stomach pH values between pH 2 and pH 4. Since salts of basic compounds are much more prevalent in the industry,[12] all three compounds discussed in this paper are soluble salts of poorly water-soluble basic drugs. The techniques discussed here can also be applied to free acids as well however. The measured rotating disk dissolution data demonstrates how these dissolution measurements can be used to better understand the dissolution mechanisms of these compounds. Once the dissolution mechanism is understood, approaches to enhance the dissolution by controlling the environment around the dissolving salt particles can be designed. Some examples of these approaches are shown. These examples demonstrate how simple approaches to alter the diffusion layer conditions can lead to a large increase in the amount of dissolved drug present in the bulk fluid. Cocompression of diffusion layer modifying excipients with salts of interest forms new particles that dissolve better with reduced precipitation. These materials demonstrate the marked impact that can be produced on the dissolution of salts of poorly soluble

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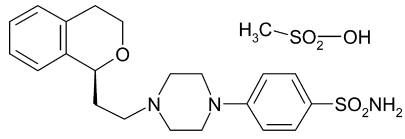
compounds. We term these cocompressed materials *diffusion layer modulated* (DLM) solids.

Experimental Section

Materials. Three salts of poorly soluble compounds were used in this study. All materials were manufactured by Pfizer research laboratories and were assayed for purity and potency. All three materials were anhydrous, crystalline solid forms with purities greater than 97% as determined by HPLC.

Solubility measurements were determined by shake flask techniques and assayed after 24 h using HPLC. The solid form was also assayed to ensure the salt form was intact. For delavirdine mesylate, the solid form does not survive this experimental protocol without changing, so the solubility is provided as a lower limit and was determined by quickly introducing the solid to aqueous solutions, filtering it through a syringe, dissolving and assaying the filtrate.

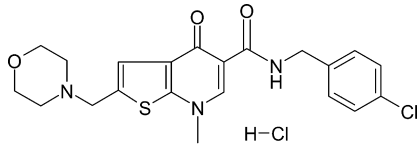
Sonepiperazole mesylate (CAS #170858-34-1) is a CNS active compound with the structure shown.[13]



Sonepiperazole mesylate

The mesylate salt is highly water-soluble with an aqueous solubility of about 37 mg/mL at 37 °C. The Ksp for this compound is 5.5×10^{-3} M^2. The free form of the compound is poorly soluble, with an intrinsic solubility of only about 6 μg/mL at 37 °C. The solubility profile for this compound shows that at a pH of 3.2, the solubility of the salt and free base are equivalent. Therefore, at a pH above 3.2, the salt solution becomes supersaturated with respect to the free form of the drug. Only a single anhydrous crystal form exists for this compound.

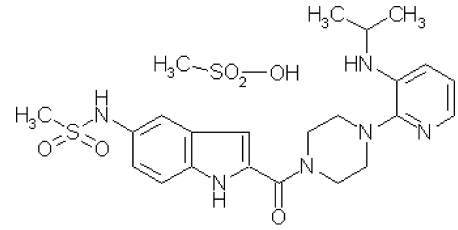
PNU-243672A is a broad spectrum antiviral to be used against the herpesvirus family with the structure shown.[14]



PNU-243672A

The HCl salt of the active compound is denoted by the "A" suffix. The aqueous solubility of the HCl salt is 13 mg/mL at 25 °C. The Ksp for the salt form is 7.7×10^{-4} M^2. The free base form of the compound has a pK_a of 4.0 and an intrinsic solubility of 30 μg/mL at 25 °C. The pH max occurs at 1.4 for the HCl salt. Multiple crystalline forms exist for PNU-243672A, but only the stable, anhydrous crystal form was used for these dissolution studies.

Delavirdine mesylate (CAS #147221-93-0) is a non-nucleoside reverse transcriptase inhibitor developed for the treatment of acquired immune deficiency syndrome, and its structure is shown.[15]



Delavirdine mesylate

There are many solid forms of delavirdine mesylate known.[16] In this study, all experiments were done on anhydrous form XI, which is the marketed crystal form. The mesylate salt form of delavirdine is highly water-soluble, but precipitates rapidly as the free base in water. The solubility of the salt form is greater than 300 mg/mL at 25 °C while the free base has a pK_a of 4.6 and an intrinsic solubility of about 0.8 μg/mL at 25 °C. This results in a pH_{max} value of about −1. Therefore, the salt solution is supersaturated with respect to the free base at all of the pH values of interest in this study.

Methods. The rotating disk dissolution (RDD) method was used for all studies. The method has been briefly described previously[17] and provides a constant surface area dissolution experiment similar to a Wood's apparatus[18] used for intrinsic dissolution rate measurement. Compacts for dissolution studies were prepared in the following manner. Disks (3/16 in.) of solid material for the dissolution studies were prepared by placing 5−40 mg of drug into a stainless steel die, 11/4 in. diameter ×1 in., which contained a 3/16 in. diameter hole (disk surface area of 0.178 cm^2). The powder was compressed with a 3/16 in. × 4 in. stainless steel rod using a press. The pressure on the powder was measured with a miniature load cell. A force of 1000 pounds was applied and held for 60 s. After this time, the die containing the drug

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compact was removed. This approach produces drug compacts with a solid fraction near one. The solid form integrity of representative compacts was assessed by removing the compacts from the die and running powder X-ray diffraction. No changes in crystallinity of crystal form were observed after compression. Avdeef has described an approach using pellets of a similar size for dissolution study.[19] The dissolution media used for these studies was 500 mL of dilute HCl or phosphate buffer, depending on the pH desired. The HCl was diluted to 10^{-2}, 10^{-3}, 10^{-4} M for nominal pH values from 2−4. Higher pH media (6−7) were made using 0.05 M phosphate buffer. Temperature was held at 25 ± 0.5 °C for all dissolution experiments. Rotation speed was 300 rpm for all studies. The concentration of active in the bulk solution was followed by UV spectrophotometry in real time using an immersed UV transmission probe (Ocean Optics). Spectra were collected every 2−10 s, depending on the speed of the dissolution. Dissolution rates were determined from the linear slope of the concentration−time profiles.

Powder X-ray diffraction data was collected on the compacts directly to assess solid form. Powder X-ray diffraction was performed using a Scintag X2 Advanced Diffraction System operating under Scintag DMS/NT 1.30a and Microsoft Windows NT 4.0 software. The system used a Copper X-ray source (45 kV and 40 mA) to provide Cu $K\alpha_1$ emission of 1.5406 Å and a solid-state Peltier cooled detector. The beam aperture was controlled using tube divergence and antiscatter slits of 2 and 4 mm and detector antiscatter and receiving slits of 0.5 and 0.2 mm width. Data were collected from 2 to 35° two-theta using a step scan of 0.03°/step with a one second per step counting time.

A diffusion layer based dissolution model[20,21] was used to calculate the diffusion layer pH in the dissolution experiments. There are a few key assumptions in the model, the major ones being that (1) a static diffusion layer is created, (2) a saturated solution is formed at the surface of the dissolving pellet and (3) the concentration of the drug in solution is assumed to be zero in the bulk fluid past the outer edge of the diffusion layer.

Diffusion layer modulated (DLM) solids are made by cocompressing one of the drug salt forms with an excipient designed to alter the diffusion layer properties (citric acid, sodium chloride, sodium bromide). The compound and the excipient are weighed out and are mixed in a mortar and pestle and the compacts are formed in the same manner as described above. When dissolution results are reported for DLM solids, they are normalized for the weight fraction of the active since all of the surface area of the compact is not available for dissolution. This allows for a direct visual comparison of the DLM and a neat API compact.

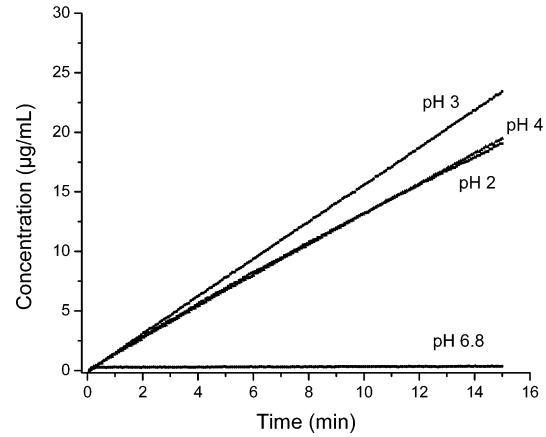

Figure 2. Rotating disk dissolution data at increasing pH values of 2, 3, 4, and 6.8 for sonepiperazole mesylate.

Results and Discussion

Sonepiperazole Mesylate. Figure 2 shows typical RDD results at nominal pH values for 2, 3, 4, and 6.8 for sonepiperazole mesylate. Linear concentration vs time data was acquired across the pH range from 2 to 4. This indicates that no solid form conversion occurred during the experiment and the salt dissolved throughout the time frame of the experiment. This observation was also corroborated with PXRD data on the remaining portion of the compacts after the dissolution experiments were completed which confirmed the same solid form as the starting material. Within the error of the experiment (±20%), all three of these dissolution profiles are equivalent. The average rotating disk dissolution flux for sonepiperazole mesylate under these conditions is about 67 $\mu g\ s^{-1}\ cm^{-2}$. This value is consistent with the relatively high solubility of the mesylate salt and again suggests that the free base is not precipitating, even at pH 4, where the free base is less soluble than the salt. However, when the solution pH is increased to 6.8, free base precipitation becomes prevalent and the dissolution rate is decreased sharply.

PNU-243672A (Hydrochloride Salt). Figure 3 shows typical RDD results for PNU-243672A at nominal pH values of 2, 3, and 4. In this case, we see much different behavior than was observed for sonepiperazole mesylate. All three curves are not equivalent. Nonlinear concentration vs time data was acquired for pH 3 and 4 conditions. Unlike sonepiperazole mesylate, when PXRD was run on the PNU-243672A compacts after the dissolution experiment was completed, the solid had converted to the crystalline free base form of PNU-243672 in the case of the pH 3 and pH 4 experiments (pH 2 post run PXRD analysis confirmed the original form of the salt). This PXRD data is shown in Figure 4 and is clear evidence of precipitation of the free base form occurring during the experiment. Since the concentration vs time curve does not increase to a maximum and then

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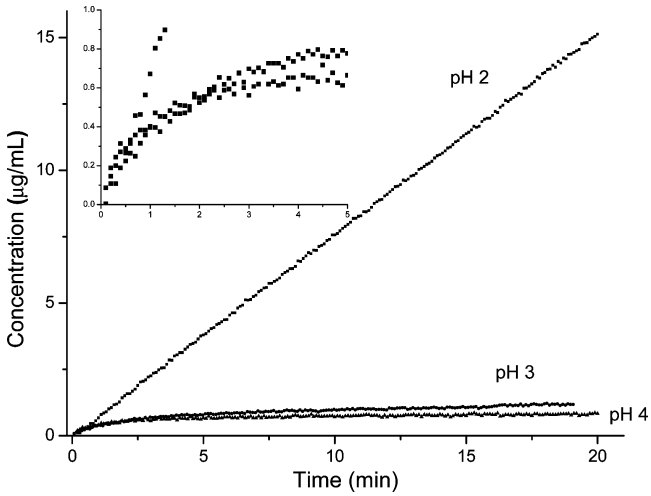

Figure 3. Rotating disk dissolution data for PNU-243672A as a function of pH. Inset shows the first five minutes of the experiments so that the curvature in the pH 3 and pH 4 profiles is visible.

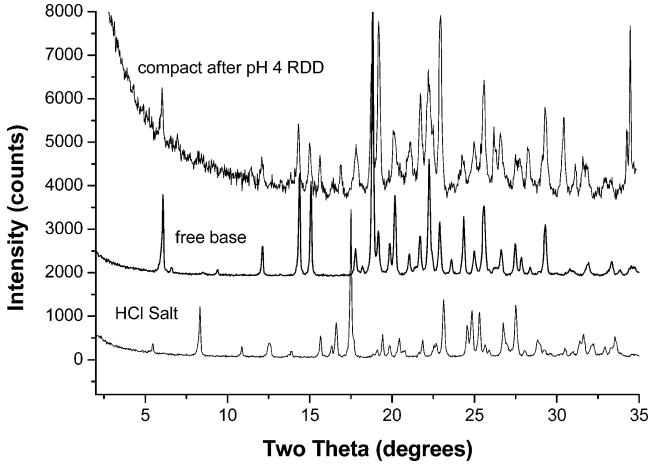

Figure 4. Powder X-ray diffraction data for PNU-243672A (HCl salt) after rotating disk dissolution experiments at pH 4 compared to free base and HCl salt standards. Conversion to free base form is evident. Diffraction patterns are offset for clarity.

decrease, it can be concluded that precipitation of PNU-243672 free base in these runs is occurring on the surface of the dissolving salt particles and not in the bulk fluid. As the inset graph shows, curvature of the dissolution profiles for the pH 3 and pH 4 cases occurs at very short times and the surface of the compact has fully converted to free base in about three minutes time. At pH 2, the salt dissolves as would be expected given its aqueous solubility (dissolution flux of 36 μg cm^{-2} s^{-1}). However, when the bulk pH is increased, precipitation of the free base (salt hydrolysis) occurs on the surface of the pellet and the dissolution rate is greatly decreased.

Delavirdine Mesylate. Delavirdine mesylate RDD behaves in a very similar manner to that of PNU-243672A. At pH 2, the material dissolves very rapidly (dissolution flux of 240 μg cm^{-2} s^{-1}), consistent with its high water solubility. The dissolution is so fast that the entire compact dissolves

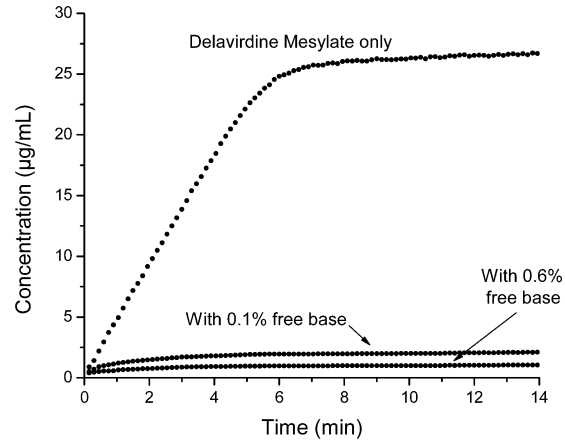

Figure 5. Rotating disk dissolution data for delavirdine mesylate at pH 2 spiked with 0%, 0.1% and 0.6% w/w of delavirdine free base.

in less than 10 min, so there is no PXRD analysis on the final compact. However, at higher bulk pH values of 3 and above, again, precipitation of the free base is observed both by a rapid decrease in the observed dissolution rate and by the orthogonal measurement of the powder X-ray diffraction patterns of the dissolution pellets after the experiments are completed. Much like the case of PNU-243672A, the dissolution profiles for delavirdine mesylate at pH 3 and 4 increase rapidly initially, but, in less than three minutes, conversion to another less soluble form occurs (delavirdine free base) on the surface of the mesylate salt. Then, the coating of delavirdine free base dissolves at a much slower rate than the underlying mesylate salt form. This results in curvature of the dissolution profiles for pH 3 and pH 4.

The dramatic impact that the free base has on the dissolution of salts such as delavirdine mesylate was demonstrated by comparing the dissolution of different delavirdine mesylate compacts at pH 2. A control compact was made from delavirdine mesylate only. The other compacts were made by spiking various amounts of delavirdine free base into the powder prior to making the compacts. These consisted of 0.1% and 0.6% w/w blends of delavirdine free base added to delavirdine mesylate. The results of the rotating disk dissolution study are shown in Figure 5. As previously noted, the dissolution for the mesylate salt was linear for the first 50% of the dissolution and dissolution went to completion. However, the compacts with small amount of free base showed surprisingly little dissolution due to rapid precipitation of free base on the surface of the salt. The spiking of the free base into the delavirdine mesylate compacts enhanced this event, which does not occur to a large extent at pH 2 without free base seeds. Conversion to the free base is thermodynamically favored at pH 2, and the presence of the free base seeds assists the process.

Dissolution Mechanism. The curving concentration vs time RDD profiles at pH 3 and pH 4 for PNU-243672A (Figure 3) are indicative of a surface precipitation mechanism. Similarly, the free base seeded delavirdine mesylate

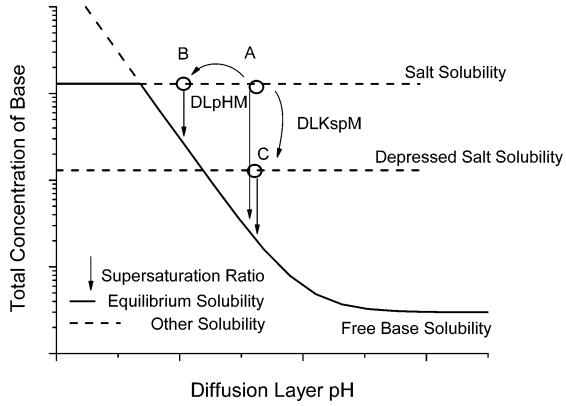

Figure 6. Schematic depiction of how a diffusion layer modulated solid can impact relative supersaturation ratios and therefore precipitation rates. Examples of pH modulation and Ksp modulation in the diffusion layer are described in the text.

dissolution experiments (Figure 5) also demonstrated surface precipitation within the diffusion layer of the dissolving salt (no precipitated particles are observed in the dissolution media).

The stagnant film model of drug dissolution assumes that an unstirred boundary layer exists at the dissolving solute surface in which only diffusion can occur.[22] Assuming sink conditions, then, the concentration of the drug outside of the boundary layer is zero. Therefore, the greatest concentration of a dissolving solute occurs directly at the surface of the dissolving pellet. In the case of a dissolving salt of a poorly water-soluble compound, the solubility of the free form of a basic drug compound can be exceeded by several orders of magnitude at the surface of the dissolving material (Figure 6). Given that precipitation is known to increase as the concentration above the saturation concentration increases, surface precipitation on the salt particle would be a thermodynamically possible event since that is where the supersaturation ratio is the highest in the system.

When the solubility of the free form is exceeded by this extent in the diffusion layer, precipitation of the poorly soluble free base is thermodynamically favored. During a USP type II dissolution experiment (or in vivo), the concentration of the compound in the bulk fluid is much less than the concentration in the diffusion layer. Since precipitation will be favored where the concentration is highest, significant free base precipitation, if possible, will tend to occur on the surface of the dissolving salt and not in the bulk dissolution medium where the concentration is much lower. If precipitation does occur on the surface of the salt, this will then lead to a large reduction in the dissolution rate as the free base form is less soluble than the salt.

The experimental observation of surface precipitation for compounds such as PNU-243672A and delavirdine mesylate leads to the following postulate:If the soluble salt converts to a poorly soluble free base in the diffusion layer via a surface precipitation mechanism, then the best way to improve the dissolution of the salt is to modify the diffusion layer directly by adding an acidic, solubilizing or supersaturation stabilizing excipient to the drug salt and then cocompressing the mixture to create a diffusion layer modulated (DLM) solid.

The diffusion layer of a DLM solid particle will have conditions which are less favorable to surface precipitation. Once the salt has dissolved and escapes from the high concentration environment of the diffusion layer, only the bulk precipitation mechanism can occur and the total dissolution may increase as shown in Figure 1, thereby increasing the in vivo availability of the drug. Another approach to eliminate surface precipitation would be to modify the bulk dissolution fluid, but in either a dissolution apparatus or an in vivo example, this would typically require large amounts of excipient which would be impossible to fit into a standard dosage form.

Perspectives on DLM Solid Design. A diffusion layer based dissolution model[20,21,23] can be used to calculate the surface pH in dissolution experiments. By calculating the pH at the surface of the dissolving salt, the supersaturation with respect to the free base can also be calculated. Then, the effect of the added excipients can be modeled to predict the impact that they would have on the diffusion layer conditions.

Figure 6 shows two approaches that could be used to modify the diffusion layer effectively using pH and solubility modification to enhance (or conceivably to retard) dissolution. In Figure 6, the case of a soluble salt of a poorly water-soluble base is illustrated. Similar arguments could be used for a soluble salt of a poorly soluble acid. Here, the solubility of the salt is determined by the Ksp and it crosses over the solubility curve for the free base at the pH_{max}. At pH values above this point (point A, for example), the salt is supersaturated with respect to the free base and the free base could possibly precipitate. In this case, supersaturation is defined as the ratio of the solubility of the salt to that of the free base. From classical nucleation and growth models, the rate of the conversion to the free base form will increase as the supersaturation level increases.[11] A DLM solid addresses this area of the solubility curves and alters the supersaturation in order to decrease the propensity for precipitation to occur on the surface of the salt particle during dissolution.

The simplest DLM solid that can be envisioned is one where, upon contact with water, the diffusion layer pH is modified by an excipient that is cocompressed with a soluble salt of a poorly soluble base. For every pH unit that the diffusion layer pH can be reduced, the ratio of the salt solubility to the free base is reduced by as much as ten times. This can have a huge impact on the dissolution profile. A

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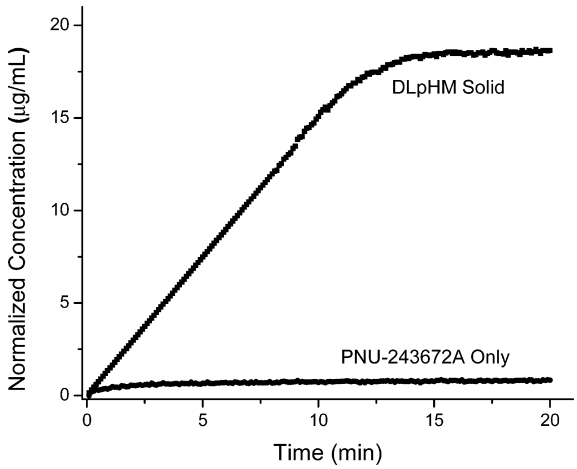

Figure 7. Rotating disk dissolution data at pH 4 for a PNU-243672A + citric acid diffusion layer pH modulated solid (DLpHM) with citric acid as compared to PNU-243672A alone.

pH modulated solid is shown in Figure 6 by starting at point A. If a pH modulating excipient is cocompressed with the salt, then the diffusion layer of the drug salt also contains a saturated solution of the modifying excipient. Assuming the modulating excipient decreases the pH by 1 unit to point B, then, the supersaturation with respect the free base form of the drug would be reduced by ten times. Since precipitation depends nonlinearly on the supersaturation ratio,[11] this could result in much greater than ten times the decrease in the precipitation rate and a large increase in dissolution rate of the drug and the amount of drug that could be maintained in solution.

The benefit of a DLM solid on dissolution can clearly be shown for the case of PNU-243672A. A pH modulated solid consisting of two parts PNU-243672A and one part citric acid by weight was cocompressed. Figure 7 shows the dissolution profile for a diffusion layer pH modulated solid at pH 4 as compared to the nondiffusion layer modulated solid. As shown in Figure 7, the dissolution at pH 4 for PNU-243672A is very slow and the material converts to free base during the dissolution experiment. The DLM solid of PNU-243672A and citric acid, however, dissolves completely, and no conversion to free base is observed under these dissolution conditions. This is a dramatic improvement in the dissolution of PNU-243672A as compared to that of neat PNU-243672A compacts at pH 4.

Using Mooney's model, the pH at the surface of the dissolving salt can be estimated.[20,21] In the case of no pH modifying excipient, at a bulk solution of pH 4, the surface pH can be estimated to be approximately 3.1, as the acidic salt of the base dissolves in the solution. This calculation is completed by using Mooney's approximations and assuming that the salt achieves its equilibrium solubility at the surface of the dissolving compact. However, with the citric acid included in the DLM solid, the pH of the diffusion layer drops significantly, to about 1.6 (the small amount of citric acid present in this experiment would have no impact on the bulk solution pH at pH 4). This estimate also assumes that the citric acid reaches its equilibrium solubility at the surface of the dissolving compact. Since this diffusion layer pH is now is less than it is when the bulk pH is 2, where the PNU-243672A dissolves without precipitation, the dissolution proceeds rapidly, without precipitation until complete (top curve in Figure 7). The DLM approach allows the compound to dissolve in a pH independent manner, showing no significant difference in dissolution rate from pH 2 to pH 4.

We have demonstrated the DLM phenomenon previously[24] and attributed the large increase in dissolution rate and the removal of the pH dependence of dissolution to the changing pH in the diffusion layer resulting from the modulation of the diffusion layer pH specifically. Li et al. have demonstrated that the diffusion layer conditions that a salt sees during dissolution significantly impact its dissolution rate.[25] These authors have also demonstrated the importance of solid form changes to dissolution rate.[26] Badawy and co-workers[27] have also shown a similar example of adding an acidic excipient to an HCl salt to reduce its propensity to precipitate through traditional USP type dissolution. Badawy also proposes that in their experiments they are altering the local pH environment, using what we would term a DLM approach. The rotating disk dissolution experiments presented in this paper confirm the pH modulation mechanism by strictly isolating the diffusion layer and separating it from other possible effects that can occur in standard USP type dissolution experiments.

A second example of successful pH modulation is delavirdine mesylate. In this case, citric acid was used to decrease the diffusion layer pH in order to prevent the precipitation of free base on the surface of the dissolving salt. Again, very similar and dramatic results were obtained. The DLM compacts were made using delavirdine mesylate and citric acid in a 2:1 weight ratio and then cocompressing the material into compacts. Figure 8 shows the dramatic enhancement in the dissolution provided by the diffusion layer approach. As can be seen from the dissolution profile, the diffusion layer modulated solid of delavirdine mesylate and citric acid dissolves completely, and no conversion to free base is observed under these dissolution conditions, even at pH 6. This is a huge increase in the dissolution performance when compared to the delavirdine mesylate bulk drug without

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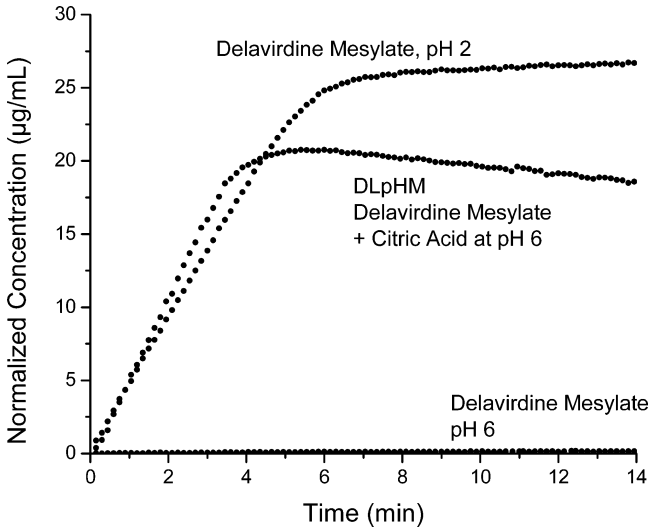

Figure 8. RDD profile at pH 6 for a delavirdine mesylate DLpHM solid prepared with citric acid as compared to the dissolution profiles of delavirdine mesylate alone at pH 2 and pH 6.

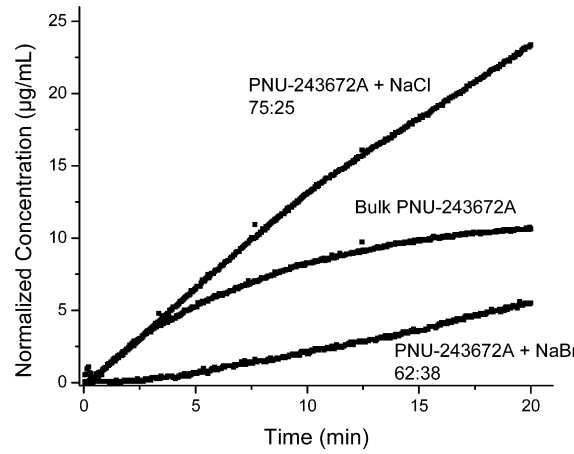

Figure 9. Rotating disk dissolution at pH 3 for diffusion layer modulated solids made from PNU-243672A and NaCl or NaBr as compared to that of neat PNU-243672A.

any diffusion layer modulation. The performance of the diffusion layer modulated solid provided pH independent dissolution. There was no significant impact of the bulk media pH on dissolution rate across the pH range from 2−6.

This finding was supported by a small ($n = 4$) rat oral bioavailability study[24] of a crushed delavirdine mesylate−citric acid compact (a diffusion layer pH modulated solid, DLpHM) with that of an equivalent amount of the crushed marketed delavirdine mesylate tablet (Rescriptor, Pfizer). The study showed that the resulting oral bioavailability of the DLpHM compact was higher than that of the marketed Rescriptor tablet ($p = 0.1$).

Another possibility for diffusion layer modulation is to use the Ksp of a salt to actually enhance the dissolution rate by depressing the solubility of the salt. Although this may appear to be counterintuitive, as Figure 6 shows, this approach would be expected to work. If we start at point A in Figure 6, a DLM solid could be imagined with an inactive salt of the counterion that is present in the active ingredient. On dissolution, in the diffusion layer, a solution is formed within the diffusion layer with the two salts. The presence of the extra counterion reduces the effective solubility of the drug salt (to point C) through the Ksp of the salt. This, in turn, can reduce the degree of supersaturation with respect to the free base. Although it would also decrease the initial dissolution rate, it will reduce the tendency to precipitate the free base, which could increase the amount of drug that could be dissolved in bulk solution.

The Ksp effect is clearly shown in the RDD profiles for PNU-243672A at pH 3 shown in Figure 9. In this case, the upper dissolution profile is from a compact consisting of a 3:1 w/w mixture of PNU-243672A and NaCl. As described above, the effective solubility of the PNU-243672A is reduced significantly by the presence of the NaCl, through the Ksp of the salt. This reduction in the solubility results in a decrease in the degree of supersaturation at the surface of the dissolving compact. This results in an increase in the dissolution rate for the diffusion layer Ksp modulated solid (DLKspM) solid compared to the bulk API alone. Finally, Figure 9 also shows the impact of a DLM solid of PNU-243672A + NaBr. In this case, since a significant common ion effect does not exist for PNU-243672A and NaBr, there is no observed increase in dissolution rate for the NaBr compact, despite the very large water solubility of the NaBr. This appears to be the first report of the use of the Ksp of a soluble salt of a poorly soluble basic drug to depress its solubility, yet increase its net dissolution rate by reducing its propensity to precipitate as the less soluble free base form. This DLKspM clearly shows how the mechanics of the dissolution process can be altered in order to influence the results.

The theoretical model shown in Figure 6 poses some alternate possibilities for improving dissolution. A simple approach which is not pictured would be to add a free base *solubilizing* agent to the diffusion layer thereby, giving a DLsM (diffusion layer solubilizing modulated powder). This would reduce the supersaturation ratio by increasing the effective solubility of the free base in the diffusion layer. This would reduce the propensity of the free base to precipitate and result in increased dissolution. An orthogonal approach would be to add a precipitation inhibitor to the solid, not changing the inherent thermodynamics of the system, but impacting the kinetics significantly. Whatever type of diffusion layer modulation is attempted, one must consider the possible chemical impact of adding possibly reactive excipients to the drug substance and chemical stability must be carefully monitored through the process.

A final important point about DLM solids is the need for proper cocompression of the excipients together to form a unified, uniform diffusion layer around dissolving particles that would be produced from a powder sample. Without this unified diffusion layer, the salt of the active compound will be exposed to nonideal conditions and precipitation could result. For example, the pH could go too high, increasing the precipitation rate significantly. A unified diffusion layer

is easy to achieve in the rotating disk experiment as the particles are well mixed and compressed together into the dissolution compact. In a real case of a formulation, however, it is important to consider how to accomplish this in the granular samples which result from a disintegrating tablet. Future publications on this topic will describe how to maintain the dissolution improvements that have been demonstrated in this paper in formulated tablets and take them beyond simple dissolution experiments to more relevant dissolution conditions. Additionally, how these differences in dissolution rate translate to improved performance in vivo will also be illustrated.

Conclusion

The dissolution mechanism of soluble salts of poorly soluble bases is complex. Both dissolution of the salt and precipitation of the free base can occur depending on the experimental conditions and properties of the molecule. In this paper, two distinct mechanisms for free base precipitation are proposed; these are surface free base growth via salt hydrolysis and bulk free base precipitation from solution. The propensity for these processes to occur must to be understood in order to optimize the dissolution of a soluble salt of a poorly soluble basic (or acidic) drug. The amount of drug that gets into solution is maximized by reducing the surface precipitation mechanism. Surface precipitation is the most damaging since it results in a coating of free base on the surface of the salt, reducing or eliminating its dissolution advantage over the free base form of the compound. Once the dissolved drug (poorly soluble basic or acidic compound) is away from the surface, its supersaturation is decreased and the propensity to precipitate is greatly reduced.

If the dissolution mechanism of a soluble salt of poorly soluble base is understood, formulations can be designed to alter the diffusion layer in order to increase the dissolution performance of the salt. In this paper, data for different DLM solids are presented. These DLMs act by using the pH, solubility or Ksp to modify the conditions at the surface of the dissolving salt in order to minimize the surface precipitation mechanism. The DLM technique can be broadened to include other approaches or combinations of approaches. Rotating disk dissolution data clearly shows how these formulated solids can act to improve the dissolution profile for these materials. The diffusion layer modulated solid technique holds great promise for improving the in vivo performance of many soluble salts of poorly soluble bases.

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