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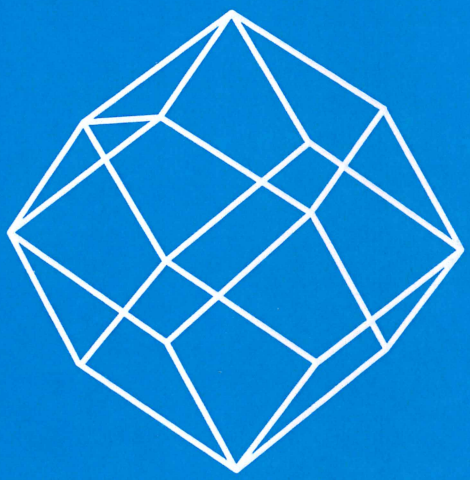

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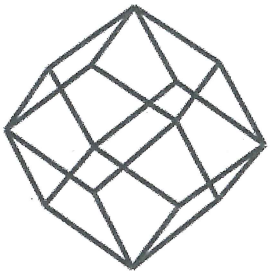

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Phase transformation of salts to their free bases: interplay of drug solubility and pH of excipients

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In the present work, the mechanism of the salt-to-free form drug transformation was explored by investigating the pH-solubility profiles of a model salt-free base system and the nucleation of the free base from the salt solution with increasing pH. The transformation of the salt to the free base during wet massing in the presence of excipients with different pHs was studied. It has been observed that the nucleation of the free base occurred when the pH of the salt solution reached a certain level $pH_{metastable}$, which was related to the free energy penalty associated with the creation of a new solid phase. The nucleation of the free base happened readily and thus the salt-to-free base transformation occurred rapidly during wet massing with the excipients with a pH above the $pH_{metastable}$. The results of the present work can support robust formulation design of solid dosage forms containing salts by optimal excipient selection.

1. Introduction

Salt formation is the most common approach for increasing solubility, dissolution rate and ultimately bioavailability of poorly water soluble drugs in solid dosage forms [1]. However, salts are sensitive to changes in the pH of the environment. When a given salt comes in contact with an aqueous medium, the relative concentration of the ionized and the neutral state of the dissolved drug molecules depends on the pH, and the free base or acid may precipitate out and lead to salt-to-free drug phase transformation. The phase transformation of the salt to the free form of the drug is extremely undesirable, since it will change the solubility and dissolution rate of the active substance and therefore alter the bioavailability of the final product [2-3]. Many of the commonly used excipients are acidic or basic in nature and thus can change the microenvironment pH of a system. In order to achieve effective control of the chemical and physical stability of a given salt form of the active pharmaceutical ingredient (API) during processing, a comprehensive understanding of the mechanism of the solid state transition between the solid forms of a salt and its free base or acid is required.

The salt-to-free form phase transformation during processing or storage is usually a solvent-mediated process, which either happens in solution or in the minimal amounts of water sorption from the environment. When a drug in salt form contacts with water, it disperses in water as anions and cations, and the dissociation

equilibrium between the ionized and the non-ionized species of the drug molecules is attained in the aqueous medium and the relative concentration of the ionized and the non-ionized species depends on the pKa of the drug and the pH of the surrounding medium. If the pH in the surrounding medium favors the formation of the non-ionized species, the concentration of the non-ionized species will increase and lead to supersaturation of the free drug in the system. However, whether or not the salt-to-free form phase transformation happens or how fast this transition occurs depends on the crystallization kinetics of the free form, where the nucleation of the new solid (the free drug) usually plays the most crucial role. This is because nucleation can happen only when the system overcomes the energy barrier for nucleation, which is related to the energy change for forming a new solid surface in the solution. In order to overcome the energy barrier, a certain level of supersaturation has to be reached, and therefore nucleation of the free drug is usually delayed when the concentration of the free drug exceeds the solubility. Furthermore, since the phase transformation process must involve the nucleation and crystal growth of the free drug, any system parameters that have an influence on the nucleation and growth kinetics of the free drug will affect the overall rate of the phase transformation. Those system parameters include the aqueous solubility of the salt and the free drug, the pH_{max} of the salt-free drug system, and other physical properties of the excipients [4]. However, in-depth investigation on the dependence of the salt-to-free drug phase transformation rate on the nucleation or the crystal growth kinetics of the free drug is limited. The underlying mechanism of the salt-to-free drug phase transformation process has not been fully understood.

The objective of the present work is to gain in-depth understanding of the mechanisms of the salt-to-free drug transformation during processing. A special emphasis is on investigating the interplay of the salt solubility and the pH of the excipients and subsequently how it affects the micro-environmental pH of the salt particles during processing. The nucleation behavior of the free base of a model salt was studied and the nucleation fundamentals was used to understand the salt-to-free base phase transition and to further predict the stability of the salt during processing.

2. Experimental Methods

2.1 Materials

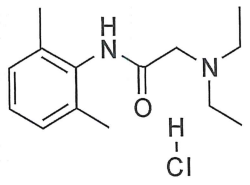

Fig. 1 Chemical structure of lidocaine hydrochloride

Lidocaine hydrochloride was used as the model compound in the present work. Lidocaine is a common local anesthetic and antiarrhythmic drug. It is typically used in the management of cardiac arrhythmias and compared with other local anesthetics it has intermediate potency, toxicity, onset and duration, which allows it to be used in any local anesthetic application [5]. The chemical structure of lidocaine hydrochloride is shown in Fig. 1. It has a molecular weight of 270.8 g/mol and a pKa of 7.9. Lidocaine free base is reported to be found in just one crystal form, whereas lidocaine hydrochloride may exist on its anhydrous and monohydrate form.

Lidocaine hydrochloride monohydrate was purchased from Sigma-Aldrich and was used as received. The excipents studied in this work includes: Calcium carbonate ($CaCO_3$), Calcium silicate ($CaSiO_3$), Magnesium oxide (MgO), and Magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$). The excipients were purchased from Sigma-Aldrich.

2.2 Methods

Solubility measurement

The aqueous solubility of lidocaine hydrochloride monohydrate (LDC MH) and the free base lidocaine was measured at room temperature (~ 22°C). Excess LDC MH solid was added to 5 ml pure water in a 25 ml container equipped with a magnetic stirrer. Samples were taken up through a 0.45 µm syringe filter at certain time intervals. The solution samples were analyzed with a Raman spectrometer. The concentration of the solution was predicted with a validated PLS calibration model. It has been observed that within 6 hours, the concentration of solution approaches a maximum and the solid-liquid equilibrium was obtained. Solubility of the free base was measured by keeping pH at 9-12 by adding NaOH solution and equilibrating the solid-liquid suspension for 12 hours. All measurements were repeated 3 times with minimal light exposure.

Nucleation of lidocaine (LD) free base from LDC MH aqueous solution

Nucleation of lidocaine free base from saturated solutions of LDC MH were studied. 10 ml saturated lidocaine hydrochloride (LDC) solution was mixed with a magnetic stirrer (mixing intensity 200 rpm). Saturated NaOH solution was drop wise added to the LDC solution. After addition of each drop of NaOH solution, the pH of the LDC solution started to increase and reached a stable value after 15 min, which implies that the equilibrium between the ionic and non-ionic species in the solution phase has been attained. The equilibrium pH of the solution was recorded and clear solution was sampled. The concentration of the solution samples was measured with the same method as used in solubility measurements.

Salt-to-free base transformation during wet massing with excipients

Wet massing of LDC MH and excipients was performed by mixing 2 g of LDC MH and 0.2 g of exicipient in a ceramic vial with a mortar. Small amount of water was added to the powder. The wet solid obtained was stored in a 25 ml screw-cap container to keep it in a wet condition for 24 hours. Solid samples were taken at certain time intervals to follow the

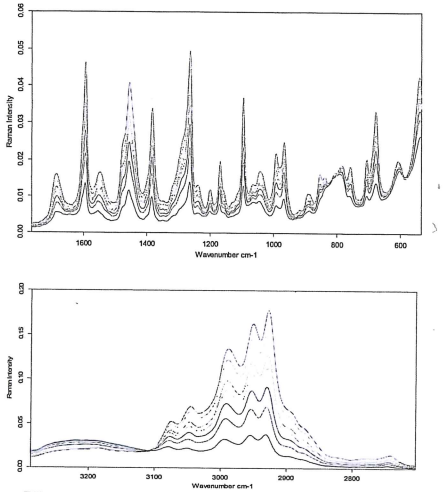

Fig. 2 Raman spectra of LDC solutions with different concentrations

phase transformation from the salt to the free base.

Raman spectroscopy for solution concentration prediction and salt-free base solid mixture quantification

A MultiRAM FT-Raman manufactured from Bruker Optics equipped with a 1064 nm wavelength laser and a liquid nitrogen cooled Ge detector was used in the present work to quantify the concentration of solutions and the solid mixtures of LDC MH and the free base. Fig. 2 shows the Raman spectra of the lidocaine solutions with different concentrations, it can be seen that the intensity of the Raman spectra reflects well the concentration of lidocaine in the solution. A PLS (partial least squares) model was generated based on the spectra taken from 8 standard lidocaine solutions with known concentrations, and was used to predict the concentration of the lidocaine solutions taken from the solubility measurements and the nucleation experiments. All spectra from the solutions were collected with a laser power of 500 MW and 120 scans per spectrum.

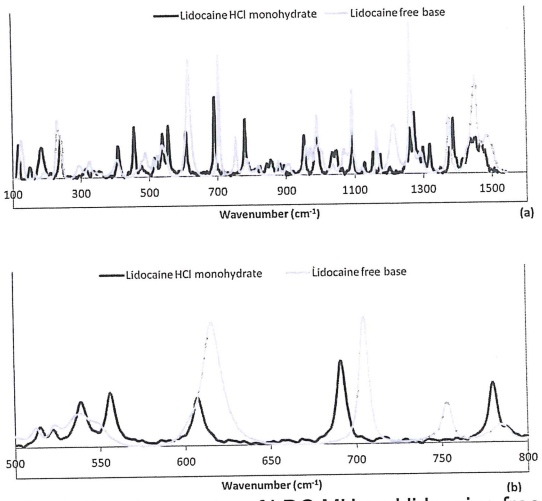

Fig. 3 Raman spectra of LDC MH and lidocaine free base

The Raman spectra taken from the crystals of LDC MH and lidocaine free base are shown in Fig. 3, where LDC MH and the free base have remarkable characteristic peaks in the whole wave number range shown in the figure. Raman spectra were collected from six salt-free base mixtures with different compositions, and a PLS model was built up. The solid samples taken from the wet massing experiments were firstly inspected qualitatively by looking at the characteristic peaks of LDC MH and lidocaine free base in the wave number range of 500-800 cm^{-1}, as shown in Fig. 3 (b). If the spectra indicated a phase change, the composition of the mixture was quantified with the PLS model. All spectra taken from the solid samples were collected using a laser power of 500 MW and 60 scans per spectrum.

3. Results and Discussion

3.1 pH-solubility profile of lidocaine salt-free base system

When the salt dissolves in water as anions (Cl^-) and cations (LDH^+), the dissociation equilibrium between the ionized (LDH^+) and the non-ionized (LD) species is developed in the solution. The dissociation constant can be written as:

$$K_a = \frac{[H^+][LD]}{[LDH^+]} \quad (1)$$

At high pH, the excess solid phase in equilibrium with the saturated solution is the free base, and the total solubility can be calculated as:

$$\text{At pH} > \text{pH}_{max},\ S_{Total} = [LDH^+] + [LD] = \left(1 + \frac{[H^+]}{K_a}\right) S_0 \quad (2)$$

Where S_0 is the intrinsic solubility of the free base lidocaine (LD).
At low pH, the excess solid phase in equilibrium with the saturated solution is the salt and in this case the total solubility can be calculated as:

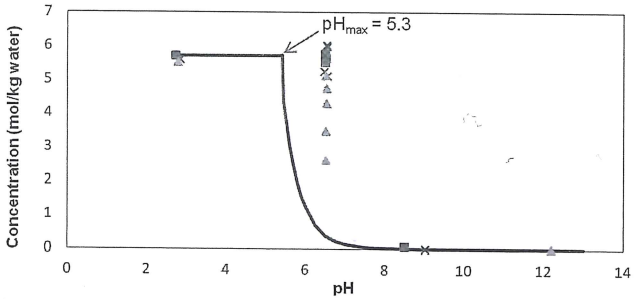

Fig. 4 Solubility profiles (–) of LDC MH salt-free base system; Concentration profiles of lidocaine during precipitation of the free base from saturated solutions of LDC MH, different symbols represent the measurement from different runs.

$$\text{At pH} < \text{pH}_{max},\ S_{Total} = \left(1 + \frac{K_a}{[H^+]}\right)\sqrt{K_{SP}} \quad (3)$$

Where K_{SP} is the solubility product of the salt: $K_{sp} = [LDH^+][Cl^-]$

The pH-solubility profile of LDC MH and its free base can be represented by the two independent solubility curves expressed by equation (3) and (4). The two curves intersect at pH_{max}, where both the salt and the free base are in equilibrium with the saturated solution [6].

$$\text{pH}_{max} = pK_a + \log\left(\frac{S_0}{\sqrt{K_{SP}}}\right) \quad (4)$$

The pH-solubility curve of the lidocaine salt-free base system can be calculated from the solubility product of the salt, the intrinsic solubility of the free base, and the pK_a of the system. The solubility curve is shown in Fig. 4, where the pH_{max} is also indicated in the figure.

3.2 Nucleation of the free base from saturated solutions of LDC MH

Nucleation of the free base lidocaine from saturate LDC solutions was studied by adding saturated NaOH solution to LDC solutions that is in equilibrium with LDC MH. The total concentrations of (LDH^+) and (LD) versus the pH of the solution are shown in Fig. 4.The salt LDC MH is very soluble in water, the saturated solution contains 5.7 mol drug/kg water, and with a pH of 2.7-2.8. When saturated NaOH solution was added to the solution, the pH increased and no nucleation of the free base was observed until the pH approached ~6.5, where the concentration of the non-ionized species (free base LD) was about 0.21 mol/kg water which is about 15 times of the intrinsic solubility of the free base (0.015 mol/kg water). The delayed nucleation of the free base is attributed to the free energy barrier for nucleation [7]. The classical nucleation theory has demonstrated that there is free energy penalty associated to the creation of a new interface in the system, and therefore spontaneous nucleation will not happen until the supersaturation level approaches a certain level where the size of the nucleus reaches a critical size so that the overall free energy change of the nucleation process becomes minus. It can be observed from figure 4 that there exists a maximum pH that can be attained before the onset of the free base nucleation, which is about 6.5. This maximum pH resembles the metastable zone limit in a cooling crystallization, and therefore is referred to as $\text{pH}_{metastable}$ in the present work.

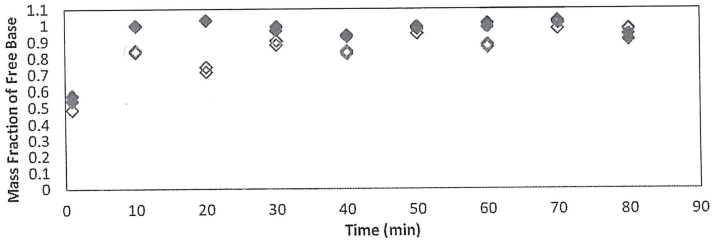

Fig. 5 Phase transformation profile of LDC MH to the free base in wet massing with MgO with repeated runs.

3.3 Transformation of LDC MH to the free base in wet massing with excipients

Wet massing experiments were performed by mixing 2 g of LDC MH and 0.2 g of four different excipients respectively. The excipients used in this study are all with a basic nature and with low solubility in water: Calcium carbonate ($CaCO_3$), Calcium silicate ($CaSiO_3$), Magnesium oxide (MgO), Magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$). It has been observed that the salt-to-free base transformation happened only in the wet massing with MgO, the phase transformation happened rapidly (shown in Fig. 5) and all LCD MH transformed to LD within 30-40 minutes. All the other three excipients didn't induce the salt-to-free base transformation even after 24 hours.

The four excipients studied in wet massing are all sparingly soluble in water and with a pH above the $\text{pH}_{metastable}$ obtained in the nucleation experiments. However, they exhibited very different effects on the salt-to free base transformation. In order to gain deeper understanding of the interplay of the salt solubility and the pH of the

excipients, suspensions of excipient-salt was prepared and the pH was monitored with time. As shown in Fig. 6, the pH at time=0 represents the pH of the excipient which has been measured in aqueous suspension of the excipient. The pH of all excipients is much higher than the $pH_{metastable}$. Then excess amount of LDC MH crystals were added to the excipient suspension, which caused significant decreasing of the pH. This is because of the dissociation of $LDCH^+$ ion in the solution led to increased concentration of H_3O^+. However, the pH of MgO-LDC suspension was about 6.6, slightly above the $pH_{metastable}$, whereas pH of the suspensions of $CaSiO_3$-LDC, $CaCO_3$-LDC, and $Mg(C_{18}H_{35}O_2)_2$-LDC was between 5 to 6.4, which was below the $pH_{metastable}$. This observation suggested that pH of the excipient-salt suspension, which was determined by the pH of the excipient and the aqueous solubility of the salt, was a very important factor that determined the occurrence and also the rate of the transformation. The nucleation of the free base was the most crucial step in the phase transformation. In the salt-to-free base transformations studied in the present work, the energy barrier for nucleation was reflected by the $pH_{metastable}$ at which the nucleation of the free base started. The $pH_{metastable}$ obtained from nucleation experiments can be used to predict the salt-to-free base transformation in wet massing with excipients. The LDC MH transformed rapidly to the free base during wet massing with MgO, in which the pH was above the $pH_{metastable}$. The transformation of LDC MH to the free base was significantly hindered during the wet massing with $CaCO_3$, $CaCO_3$, and $Mg(C_{18}H_{35}O_2)_2$, where the pH was below the $pH_{metastable}$. This observation also agrees with our previous study where the salt-to-free base phase transformation of different solid forms of amlodipine besylate in suspensions with different excipients has been investigated [8].

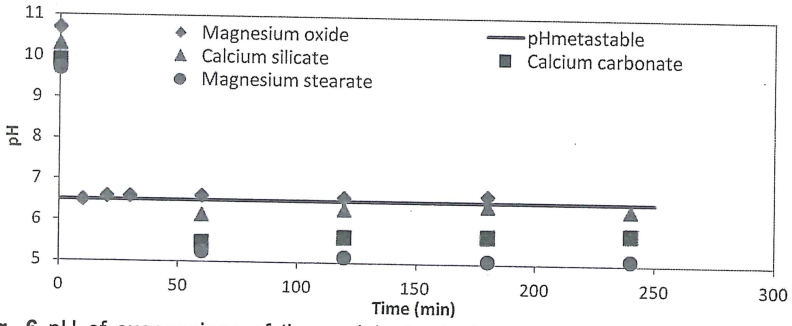

Fig. 6 pH of suspensions of the excipient-salt drug. $pH_{metastable}$ obtained from the nucleation experiments is shown with the lines.

4. Conclusions

Salts may contact with water and excipients with basic nature during processing, such as milling and wet granulation. Usually the local environment of the salt crystals during processing can be considered as that the salt crystals are surrounded by a thin layer of solution saturated with respect to the salt and the excipient. The pH of this micro-environment depends on both the aqueous solubility of the salt and the pH of the excipients. The salts with high aqueous solubility may show self-buffering

effects, so the pH of the local micro-environment might be much lower than the pH of the excipients. In a salt-free base system, a supersaturation with respect to the free base is generated when the micro-environmental pH is higher than the pH_{max}, however, the phase transformation could be retarded before the pH reaches a critical level $pH_{metastable}$. This is because the nucleation of the free base requires the system to overcome an energy barrier, which is related to the energy change for forming a new solid surface in the solution. The $pH_{metastable}$ can be assessed by performing nucleation experiments, and it can be used to predict the reactivity of the excipients with the salt. The excipients that create a micro-environmental pH higher than the $pH_{metastable}$ when mixed with the salt in aqueous medium have a great potential to induce the nucleation of the free base, and therefore cause the salt-to-free base transformation. The obtained results can provide guidance for selecting excipients for robust formulation design of solid dosage pharmaceuticals in salt forms.

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