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Protection of Deliquescence of Sodium Valproate by Hydrotalcite Using Different Synthetic Routes

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Abstract

Protection of deliquescence of sodium valproate from humidity was accomplished successfully by a solid-solid reaction with hydrotalcite. The level of protection was comparable to that obtained when the compound is synthesized by ion-exchange reaction in aqueous solution. The merit of the solid-solid reaction is enormous because the procedure consists of simply grinding the solid sodium valproate with hydrotalcite for 5 min.

Keywords: Sodium valproate; Deliquescence; Pharmaceuticals; Hygroscopicity

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Introduction

In recent years, many outstanding pharmaceuticals have been developed. These pharmaceuticals are sometimes very structurally complex with large molecular weights. Some also have low stability, e.g., they are damaged by light, oxygen, or heat. In order to overcome these deficiencies, various types of methods and materials have been applied.

Recently, we found that hydrotalcite, which is normally used as an antacid [1,2], can also be used to overcome some deficiencies of other drugs, and as a carrier for drug delivery systems (DDS) [3,4]. Sodium valproate (VPA) is an anti-epileptic drug, and is used widely under the commercial name of “Depakene”. However, it is very hygroscopic, and must be handled with care. In a recent communication, Nakayama et al. reported the complete elimination of the hygroscopicity by complexing sodium valproate with a hydrotalcite-like compound [5]. The complex was synthesized in aqueous solution using the ion-exchange property of the hydrotalcite-like compound. More recently, it was found that the complex could be synthesized using a solid-solid reaction by simply grinding the drug and the hydrotalcite-like compound together [6]. This method is similar to that used for drug preparation in pharmacies. Furthermore, it is simple, quick, economical, and solvent-free. In this communication, effective methods to reduce the hygroscopicity of sodium valproate using hydrotalcite-like compounds synthesized by different two methods, i.e., ion-exchange and solid-solid reactions will be compared.

Hydrotalcite as a commercial antacid is formulated as $Mg_2Al(OH)_2CO_3$ [LDH(CO_3)], and similar compounds with different compositions are called hydrotalcite-like compounds. Hydrotalcite-like compounds with the general formula of $M^{2+}_{1-x}M^{3+}_x(OH)_2(A^{n-})_{x/n}\cdot yH_2O$, where M^{2+} and M^{3+} are di- and tri-valent metals, respectively, and A^{n-} is an interlayer anion such as Cl^-, NO_3^-, or CO_3^{2-}, are called layered double hydroxides (LDHs). In this experiment, we chose $Mg_2Al(OH)_2NO_3$ [LDH(NO_3)] with a ratio of Mg: Al = 2:1, because naturally occurring hydrotalcite used as an antacid is a biocompatible Mg-Al type LDH. Furthermore, LDH(NO_3) with Mg: Al = 2:1 is the most reactive for the intercalation reaction. The composition of LDH(NO_3) used in the present study is $Mg_{0.66}Al_{0.33}(OH)_{2.02}(NO_3)_{0.27}(CO_3)_{0.02}\cdot 0.34H_2O$, and its ion-exchange capacity is 4.25 mmol/g.

Following the reported procedure, the complex was synthesized in aqueous solution using the ion-exchange method [5]. Half a gram of solid LDH(NO_3) was reacted in 30 mM of VPA aqueous solution for 1 day at room temperature. In the solid-solid reaction, 0.1 g of LDH(NO_3) was ground with 0.07 g of VPA for 5 min [6]. The obtained products are called LDH(NO_3)-VPA (i.e.) and LDH(NO_3)-VPA(s-s), respectively. **Figure 1** shows XRD patterns of (2) LDH(NO_3)-VPA (i.e.) and (3) LDH(NO_3)-VPA(s-s). For both compounds, the lower angle diffraction peaks appeared at similar 2θ angles, indicating that VPA is intercalated in the interlayer space of LDH(NO_3), and both compounds have almost the same structure **(Figure 2)**. No peaks due to the host LDH(NO_3) were observed, suggesting that

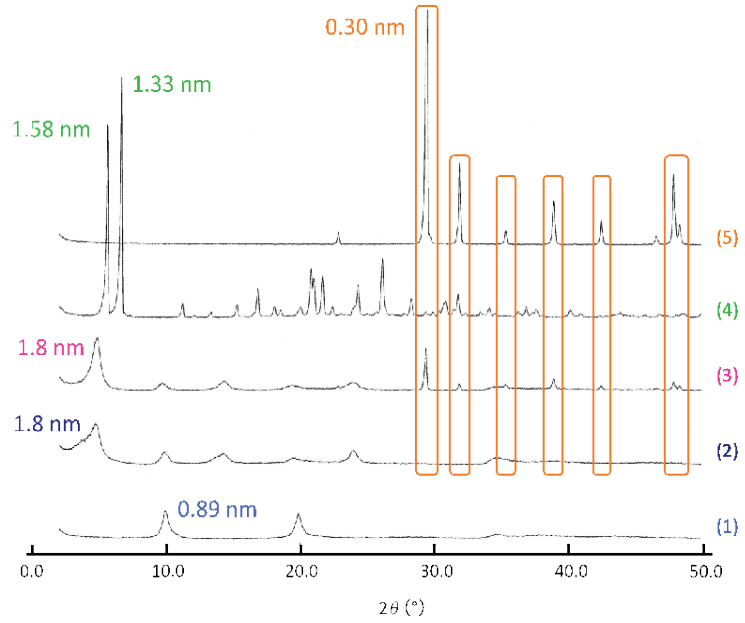

Figure 1 XRD patterns of (1) LDH(NO_3), (2) LDH(NO_3)-VPA (i.e.), (3) LDH(NO_3)-VPA(s-s), (4) sodium valproate, and (5) $NaNO_3$.

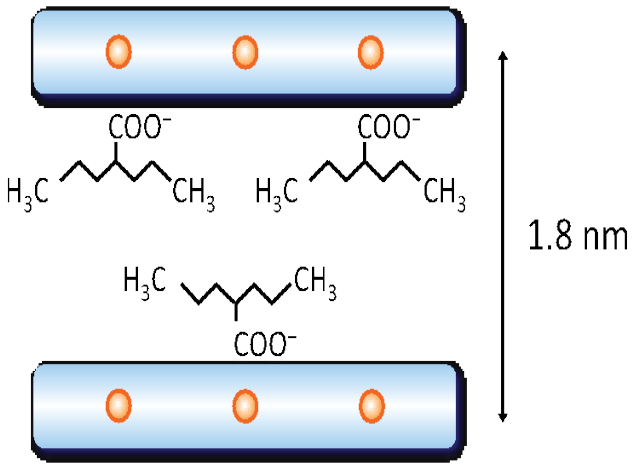

Figure 2 Schematic model of LDH(NO_3)-VPA (i.e.) and LDH(NO_3)-VPA(s-s).

valproate was intercalated completely in the interlayer space of LDH(NO_3). The intercalated valproate in the interlayer space of LDH(NO_3) was 3.8 mmol/g for LDH(NO_3)-VPA (i.e.) and 3.4 mmol/g for LDH(NO_3)-VPA(s-s). Almost complete exchange of valproate was attained for both compounds. Compared with LDH(NO_3)-VPA (i.e.), extra peaks appear at higher 2θ angles for LDH(NO_3)-VPA(s-s). These peaks are due to $NaNO_3$ produced by the reaction of Na^+ ion in VPA and NO_3^- in the interlayer space of LDH(NO_3) by grinding the solid. These peaks disappeared by washing with 200 µL H_2O, suggesting that $NaNO_3$ adheres to the outer surface of the product and is removed completely by washing.

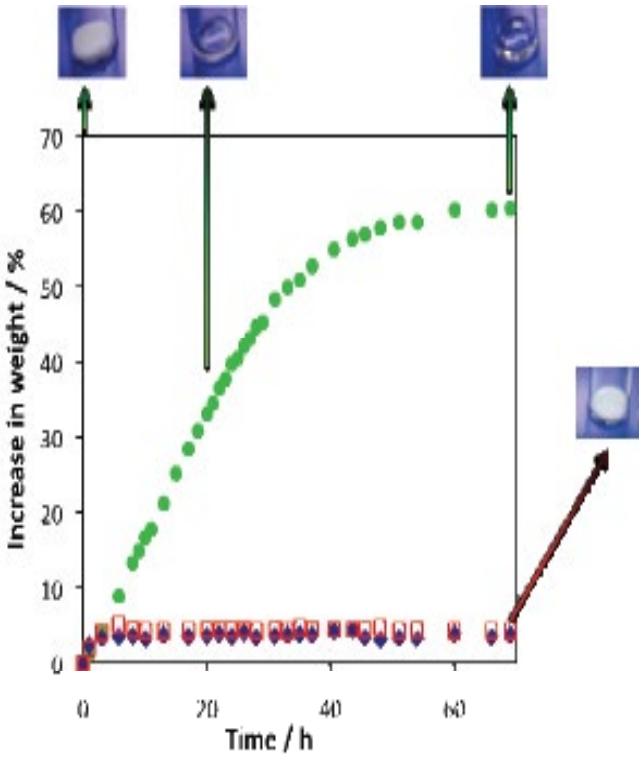

Figure 3 Exposed time dependence of increase in weight (%) of (1) sodium valproate (●), (2) LDH(NO_3)-VPA (i.e.) (◆), and (3) LDH(NO_3)-VPA(s-s) (▭) under relative humidity of 75%. Inserts are the photos of the solids at that time.

The hygroscopicity of valproate-intercalated LDH was examined under a relative humidity of 75%. For comparison purposes, solid sodium valproate was examined as well. **Figure 3** shows the increase in weight of (1) sodium valproate, (2) LDH(NO_3)-VPA (i.e.), and (3) LDH(NO_3)-VPA(s-s). The critical relative humidity of sodium valproate is 40% [7]. A considerable increase in weight due to adsorption of water vapor was observed for sodium valproate. For example, at 24 h, an increase in weight of 30% was observed

and deliquescence occurred. On the other hand, a less than 5% increase in weight was observed for both LDH(NO_3)-VPA (i.e.) and LDH(NO_3)-VPA(s-s) and no deliquescence was observed until 60 h. Therefore, complete protection from humidity was successfully attained for both compounds. Several phases of crystalline sodium valproate at various relative humidities have previously been reported [8]. In contrast, the powder XRD experiment showed no change in the profile of valproate-intercalated LDH after exposure to humidity. Therefore, valproate-intercalated LDH is stable even under severe humidity for over a month. Comparable performance was observed for LDH(NO_3)-VPA(s-s) and LDH(NO_3)-VPA (i.e.).

In conclusion, perfect protection of sodium valproate from humidity was attained by simply grinding sodium valproate and hydrotalcite for 5 min. This method is most likely applicable to other hygroscopic drugs and unstable compounds under humid conditions.

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