ADVANCED NANOHYBRID FORMULATION OF THE SPARINGLY SOLUBLE DRUG SULINDAC FOR CONTROLLED RELEASE STUDIES

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We offered an advanced nanohybrid formulation system of Sulindac (SUL) based on layered double hydroxide (LDH) nanoparticles. The formulated materials were characterized by X-rays, Infrared and SEM techniques to confirm the nanohybrid structure. The drug incorporation ratio was determined to be 45%. The drug solubility was improved after the LDH nanohybrid formation. The anion-exchange mechanism of LDH supported the dissolution process for the intercalated SUL.

Keywords: Nanohybrid; sulindac; LDH.

1. Introduction

Non-steroidal anti-inflammatory drug (NSAIDs) are drugs with analgesic and antipyretic effects. Sulindac (SUL) is a NSAID of acetic acid derivatives. It relieves the pain,

tenderness, inflammation and swelling^{1,2}. However SUL is a sparingly soluble drug and aqueous solubility is a major indicator for the drug activity in the intestinal fluids and the potential contribution to bioavailability issues. Therefore, the solubility and dissolution of SUL should be addressed and controlled carefully through an advanced formulation system. Furthermore, SUL has a carboxylic acid group that can impart local gastrointestinal irritation through the direct contact with mucous membrane³. To improve SUL dissolution properties, several approaches were reported for example solid dispersions with polyvinyl pyrrolidone⁴ and complexation with cyclodextrins⁵. However these formulations are using complicated and technically challenging processes. Thus, more advances formulations of SUL with controlled delivery doses are required. An innovative approach of oral drug delivery involves the use of layered double hydroxides (LDHs) nanoparticles as drug carriers. This new platform offers many potential advantages over the traditional oral drug delivery systems.

LDHs are a family of natural and synthetic compounds. LDH consists structurally of brucite-like sheet with hexagonal-shaped crystallite layers⁶. It can be prepared in laboratory by different techniques⁷⁻⁹. LDH possess excellent biomedical properties such as chemical inertness, null toxicity, biocompatibility, and antacidic and antipyretic properties¹⁰. Consequently, they can be used as drug matrixes, drug stabilizers during storage and drug delivery carriers.

Based on our knowledge, there is no report concerning the formulation of SUL in a form of nanohybrid. Here, we report the synthesis and characterization of a new formulation system of SUL-nanohybrid based on LDH materials. Subsequently, we study the solubility issue from the nanohybrid to evaluate the effect of LDH on SUL properties after the intercalation process.

2. Experimental work

2.1. Materials

Mg(NO₃)₂·6H₂O, Al(NO₃)₃·9H₂O (Wako Pure Chemical Industries, Ltd.) and SUL high grade (Sigma Chemical Co.,) were used as received. All solutions were prepared using deionized water (18.2 MΩ/cm, produced from Milli-Q Grandient ZMQG000kt).

2.2. Nanohybrid formulation of SUL-LDH

2.2.1. Synthesis of MgAl-NO₃ LDH

To a round flask containing 30 mL of 1.0 M NaNO₃ solution was added dropwise a 50 mL solution of 8.538 g (0.0333 M) of Mg(NO₃)₂·6H₂O and 6.249 g (0.01666 M) of Al(NO₃)₃·9H₂O ($Mg^{2+}/Al^{3+} = 2$) with constant stirring. During the metal ion addition, the pH of the suspension was kept constant at 8.0 by adding appropriate amounts of 2.0 M KOH solution. The final volume of the preparation medium was augmented to 100 mL by deionized water. The resultant suspension was stirred at 70 °C for 24 h under N₂ flow. At

the end of the reaction, the formed Mg-Al LDH material was collected by filtration, washed several times with deionized water, and finally freeze-dried.

2.2.2. Preparation of SUL nanohybrid

To a round flask, 1.0 g of SUL was dissolved in 60 mL deionized water by adjusting the solution pH to 8.0 using 2.0 M KOH solution. A 30 mL aqueous solution containing 8.538 g $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 6.249 g $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ was added dropwise with constant stirring to the drug solution. During the metal ion addition, the pH of the suspension was kept constant at 8.0 by adding appropriate amounts of 2.0 M KOH solution. The final volume of the preparation medium was augmented to 100 mL by deionized water. The resultant suspension was stirred at 70°C for 24 h under N_2 flow. At the end of the reaction, the formed SUL-LDH material was collected by filtration (0.45- μm Millipore membrane), washed several times by 0.1 M KOH solution and subsequently deionized water until a negative test was obtained for drug in the washing medium. A UV spectrophotometer (U-3210, Hitachi, Japan) was used to check for the presence of SUL in the washing medium at 254.0 nm. Finally, the collected SUL-LDH material was freeze-dried.

2.3. Characterization and measurements

X-ray powder diffraction patterns were recorded on a Rigaku X-ray diffractometer using $\text{CuK}\alpha$ radiation at $\lambda=1.5405 \text{ \AA}$. The measurement was performed in the 2θ range $1.5\text{--}70^\circ$ with a 2θ scanning step of 0.02° , a scanning step time of 5 s, a filament intensity of 40 mA, and a voltage of 150 kV. Infrared spectra (KBr disk method) were recorded on a Bio-Rad FTS 3000MX FT-IR spectrophotometer. The TGA was conducted with a Shimadzu thermogravimetric analyzer (TGA-50, TA-60WS) under a N_2 flow of 20 mL/min. The scanning electron micrographs (SEM) were captured by a Hitachi FE-SEMS-4700 microscope.

The incorporation ratio of SUL (the amount of drug intercalated per a unit weight of hybrid material) was determined as follows. The amount of SUL incorporated into LDH was calculated by using a UV quantitative method as follows. A known amount of the hybrid material was dissolved in 10.0 mL of 1.0 M HCl solution. The obtained solution was diluted using a phosphate buffer of pH 7.4. SUL concentration was determined from UV-absorption peak at 254.0 nm. SUL incorporation ratio was expressed by the percentage of SUL weight intercalated into a unit weight of hybrid. The UV method was also used to check the integrity of SUL after the intercalation process.

The solubility experiment was performed as follows: In a round-bottom flask, a sample of 100.0 mg of SUL or 200.0 mg of SUL-LDH nanohybrid was dispersed in 100 mL of buffer (a 100 mL solution mixture of 100.0 mM HCl and 100.0 mM KCl; a few drops of 10.0 mM HCl solution was used to adjust the solution pH at 2.0), which was maintained at $36.8 \pm 0.1^\circ\text{C}$ with constant agitation of 80 rpm. At appropriate time intervals, a 1.0 mL sample solution was withdrawn from the release medium and filtered

by using a 0.45 μm Millipore filter unit to remove the insoluble particles. Then, the filtrate was diluted and assayed for UV measurement. The removed aliquot was immediately replenished by the same volume of the used buffer, which was equilibrated at the same reaction temperature. The dissolution experiment of each sample was performed in duplicates.

3. Results and discussion

Successfully, the used synthetic technique showed SUL-LDH hybrids. The incorporation ratio was determined to be 45%. The elemental analysis showed a 10.83 % Mg, 5.65% Al by using titration, and 44.98% C and 4.77% H. Accordingly, the composite formula is $\text{Mg}_{0.66}\text{Al}_{0.34}(\text{OH})_2(\text{SUL})_{0.30}\cdot\text{XH}_2\text{O}$. The SEM was used to investigate the nanohybrid structure of the prepared materials. Figure 1 displays the SEM images of the synthesized NO_3 -LDH material and SUL-LDH hybrids. Image a shows uniform and regular hexagonal platelets characteristic for LDH particles. The regularity of the LDH particles confirmed the good crystallinity recorded by X-ray measurement (X-ray section). The LDH particles size was recorded in the nanoscale. In the case of SUL-LDH hybrid (images b), aggregates composed of small nanoparticles were observed. The aggregation process is probably due to a hydrophobic interaction of the LDH surface-adsorbed SUL.

Fig. 1. SEM images of NO_3 -LDH (a) and SUL-LDH (b) hybrids

Figure 2 shows the XRD patterns of LDH and SUL-LDH nanohybrid. The green Pattern indicated the formation of NO_3 form of LDH with sharp and symmetric ($00l$) reflections. Using Bragg's law, the $d003$ -spacing was calculated to be 8.9 $\text{\AA}$. As a result of intercalation of SUL (orange pattern), the basal spacing was expanded to 29.4 $\text{\AA}$. The SUL-LDH interlayer distance was calculated by subtracting the inorganic layer thickness (4.8 $\text{\AA}$)¹¹ from the basal spacing. The determined value was 24.6 $\text{\AA}$. The interlayer distance of SUL-LDH was larger than SUL molecular length (18.9 $\text{\AA}$). However LDH attaches its interlayer anions through an electrostatic interaction¹², we speculated that SUL molecules were stacked into LDH as a monolayer of interdigitated arrangement through the attachment of SUL carboxyl groups with the LDH positive layers. The X-ray pattern of the sample collected from the releasing medium indicated an anion exchange process of the intercalated drug. The 003 peak of CO_3 was detected at 2θ of 11.6.

FT-IR spectroscopy was used to verify the presence of the intercalated SUL and to gather information about the nanohybrids' molecular structure. In the case of NO_3 -LDH (Figure 3), the lattice vibration modes ($\nu_{\text{M-O-M}}$, $\nu_{\text{M-O}}$)¹³ at 550, 630, and 780 cm^{-1} and the

asymmetric stretching band of the interlayer nitrate (νNO_3) at 1360 cm^{-1} as well as the stretching vibration mode of the hydroxyl groups of LDH layers¹⁴ at 3440 cm^{-1} . The FT-IR spectrum of SUL showed complex features below 1500 cm^{-1} , which can be attributed to the bending and stretching of aromatic rings, carbon-carbon, and carbon-oxygen bonds. The stretching vibration band of COOH group was detected at 1610 cm^{-1} . The weak stretching vibration modes of SUL alkyl groups ($\nu_{\text{C-H}}$) were detected at 3000 cm^{-1} . As a result of intercalation of SUL into LDH, new bands are emerged such as symmetric and asymmetric modes of COO^- at 1560 and 1740 cm^{-1} , respectively¹⁵, besides the characteristic bands of SUL and LDH. In conclusion, the molecular structure information of SUL-LDH nanohybrid indicated that SUL molecules are intercalated into the gallery of LDH.

Chart 1. SUL molecular structure

Fig. 2. X-ray diffraction patterns

Fig. 3. Infrared spectra

The TGA study (figures are not displayed because of pages limit) showed significant changes in the thermal behavior of SUL before and after intercalation with LDH. After the intercalation, the amount of interlayer water was decreased, probably due to the hydrophobic nature of the intercalated SUL. The overall weight loss was increased from 51% to 69% in the final stage. The onset temperature of SUL decomposition shifted to a higher value (from 175°C to 225°C). Accordingly, the stability of SUL was promoted against thermal decomposition after the LDH nanohybrid formulation.

Figure 4 shows the solubility of SUL drug and SUL-LDH nanohybrid. The solubility of SUL before intercalation (blue pattern) was very small ($\sim 40\text{ mg/L}$) due to the acidic character of SUL, indicating the uncontrollable dissolution of SUL after administration. Figure 4 (red pattern) shows the release of SUL from LDH nanohybrid. SUL is a crystalline acidic drug. It has a small solubility in the acidic stomach due to the small dissociation of the crystalline molecules. Significant change in the amount of SUL dissolved with time progress was observed after the composite formation. More than

three times increase in the solubility of SUL was recorded in a controlled manner. The release of the intercalated SUL depended on both medium anionic species and LDH nanohybrid properties. The layered molecular structure of LDH limited the intercalation of SUL into two-dimensional directions. Such kind of stacking process prevented the crystallization of SUL into the gallery of LDH. As a consequence, SUL was released in an amorphous form suitable for dissolution.

Fig. 4. The dissolution of pure SUL and SUL-LDH nanohybrid

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