Intercalation of diclofenac in modified Zn/Al hydrotalcite-like preparation

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Abstract. The intercalation of a pharmaceutically active material diclofenac into modified Zn/Al Hydrotalcite-like (Zn/Al HTlc) preparation has been investigated by the coprecipitation and ion exchange method, respectively. The synthetic materials were characterized using X-Ray Diffraction (XRD); Fourier transforms infrared spectroscopy (FTIR); Scanning Electron Microscope (SEM); X-Ray Fluorescence (XRF) and surface area analyzer. The results show that the basal spacing of the product was expanded to 11.03 Å for direct synthesis and 10.68 Å for indirect synthesis, suggesting that diclofenac anion was intercalated into Zn/Al HTlc and arranged in a tilted bilayer fashion and the specific surface area of material increased after the intercalation of diclofenac.

1. Introduction

Recently, sustained release of drug for more effective delivery systems has received intense attention from the pharmaceutical industry due to the advantages they offer over conventional forms [1]. These materials can include colloids, gels, copolymers, porous media, and inorganic layered materials such as clays. These latter inorganic materials can exist in great variety and possess well-defined, ordered inter lamellae space potentially accessible by foreign species. This ability allows them to act as matrices or hosts for organic molecules, yielding interesting hybrid nanocomposite materials [2]. Among host–guest hybrid materials, synthetic hydrotalcite-like compounds (HTlcs) have emerged as promising delivery systems for efficient transport and release of pharmaceuticals [3]-[4]. There have been many studies focusing on the application of hydrotalcite-like (HTlcs) as a host for intercalation chemistry [5]-[8]. In addition, HTlc has demonstrated their suitability for different processes in the pharmaceutical and cosmetics industries, as they can absorb or host a large number of active species [9]-[10]. For instance, Carretero et al. [11] and Frunza et al. [12] have reported the intercalation of salicylate in ZnAl-hydrotalcite, and this matrix has been also used in the cosmetic field to prepare new sunscreen products [13]-[16]. Furthermore, MgAl hydrotalcite-like compounds have found application in medicinal chemistry as antacids [17]-[19], and as hosts for intercalation of molecular drug anions with the aim to study these intercalation compounds for storage, transport and ultimately controlled release of drugs [9]; [15]-[16]; [20]-[23]; [24]-[30].

Layered double hydroxides (LDHs), which are referred to as hydrotalcite-like compounds or as anionic clays, are an important class of lamellar ionic solids [31]. They can be described by the general formula: [M1-x2+ Mx3+ (OH)2]x+ (A-me-)x/m·nH2O, where MII are divalent cations, MIII are trivalent...
lations and \( A^{m-} \) is an exchangeable anion with charge \( (m^-) \). They have been widely investigated owing to their potential applications as ion exchangers, catalyst supports and so on [32]-[33]. Recently, LDHs have been investigated for storage and delivery of some drugs, such as NSAIDs (nonsteroidal anti-inflammatory drugs) widely used in rheumatism treatment. Similar to another NSAIDs, Diclofenac (DIK) use is associated with rare, but severe and sometimes fatal, gastrointestinal (GI) side effects, including ulceration, and hemorrhage, so it is an ideal candidate for incorporation in a controlled release device to diminish its adverse effects after oral administration.

Although there are a few studies on intercalated Diclofenac into Mg–Al–Cl–LDHs [21], Mg–Al–CO\(_3\)–LDHs [24], and Zn-Al-CO\(_3\)–LDHs by coprecipitation method [34], little is known in the literature on diclofenac- Zn/Al HTlc which is made by coprecipitation and anion exchange method. In this paper, we present and characterization of intercalation of diclofenac in modified Zn/Al hydrotalcite-like preparation.

2. Materials and methods

2.1. Materials
Zinc nitrate nonahydrate and aluminum nitrate tetrahydrate were purchased from Merck (Germany). The Diclofenac sodium salt (Na-DIK), was supplied by IFARS Company (Karanganyar, Indonesia).

2.2. Synthesis of Zn/Al Hydrotalcite-like (Zn/Al HTlc)
The Zn/Al HTlc precursor was synthesized by the coprecipitation method from a mixed metal nitrate salt solutions with Zn/Al ratio of 2:1 at pH 7. The solution was stirred for 30 min, heated 120 °C for 5 h in the oven. The resulting white slurry was filtered and washed with water (CO\(_2\) free). The product was dried at 80 °C and reserved for characterization.

2.3. Diclofenac intercalation to Zn/Al HTlc
**Direct synthetic by coprecipitation**
To distilled water (CO\(_2\) free) were added Zn(NO\(_3\))\(_2\).4H\(_2\)O and Al(NO\(_3\))\(_3\).9H\(_2\)O. The pH system was maintained at pH 7 by the addition of NaOH solution slowly and then added diclofenac sodium 0.1 M. The resulting system (HTlc-DIK) was stirred and was aged at 70 °C for 18 h. After aging, the particles were recovered by centrifuging (3000 rpm for 10min). The product was washed and dried at 70 °C for 5 h and reserved for characterization.

**Indirect synthetic by anion exchange**
In this method, 78 mL of a 50% v/v methanol solution (50% v/v) was transferred to a reaction flask containing Na-DIK. Intercalation reactions were performed after adding 1 g of Zn/Al hydrotalcite-like into the mixture at 60 °C for three days. After cooling, the mixture was centrifuged at 3000 rpm for 10 min. The residue was washed three times with carbon dioxide-free water and finally dried at room temperature and reserved for characterization.

2.4. Characterization
**Powder X-ray diffraction (PXRD) patterns** were obtained on a Bruker D8 Advance diffractometer, using CuK\(_\alpha\) radiation. The instrument was set at operating Voltage 35 KV and a current of 40 mA in 2\( \theta \) scale 2-70° range. Identification of the crystalline phases was made by comparison with JCPDS files and literature data. The Fourier-transform infrared (FT-IR) spectra were obtained using a Shimadzu IR Prestige-21 by the standard KBr disc method, in the 4000 to 400 cm\(^{-1}\) range. Elemental chemical analysis for Zn and Al were carried out in a Bruker X-Ray Fluorescence Bruker S2 Ranger. A Scanning Electron Microscope (SEM-EDX) FEI type Inspect S50 was used to study the surface morphology of the samples. The gas surface area analyzer was performed by Quantachrome Corporation NOVA Win 1200e.
3. Results and Discussion

3.1. XRD analysis

XRD patterns of the products demonstrate successful intercalation of diclofenac into both Zn/Al HTlc hosts by coprecipitation and anionic exchange (figure 1A, B, C respectively). They show the formation of, at least, a well crystallized hydrotalcite-like, with basal diffractions due to (00l) basal planes, thus confirming a lamellar structure. Before intercalation, the d- spacing of inorganic layer Zn/Al HTlc, is termed as initial basal spacing (8.81 Å at 2θ = 10.04). After intercalation, the basal spacing was expanded. An increase of the basal spacing leads to a shift of the diffraction peak at the lower angles. This expansion is reflected by the d-spacing values of the XRD patterns, which are 16.14; 11.63; 8.75 and 7.60 Å, respectively for intercalation diclofenac by coprecipitation method (HTlc-DIK-DS), and 12.35; 11.30; 10.21 and 8.84 Å, respectively for intercalation diclofenac by anion exchange method (HTlc-DIK-AE). As a result, a basal spacing value of 11.03 Å for HTlc-DIK-DS and 10.68 Å for HTlc-DIK-AE was obtained. In both products, the XRD patterns show some overlapping peaks. This result indicates the presence of some unreacted Zn/Al-NO$_3$-HTlc remains in the products. Previous studies have indicated that it is hard to exchange nitrate in HTlc with the incoming anions, due to the parallel orientation of nitrate ions with respect to the hydroxide layers. As a result, some nitrate anions remained after the intercalation process of diclofenac into Zn/Al HTlc, and this explained why some unreacted Zn/Al-NO$_3$-HTlc remained [35]. A slight discrepancy in the d$_{003}$ value between HTlc-DIK-DS and HTlc-DIK-AE is probably mainly due to the content of water in the interlayer galleries and the presence of nitrate ions in the interlayer region [36].

![Figure 1. Powder XRD patterns of (A) HTlc-DIK DS, (B) Zn/Al HTlc, (C) HTlc-DIK AE](image-url)
3.2. FTIR analysis
The FT-IR spectra of the drug-intercalated products are similar for all series. Figure 2 shows FTIR spectra of the Zn/Al HTlc, HTlc-DIK-DS, and HTlc-DIK-AE. The FTIR spectra show characteristic bands of diclofenac. The spectra show the absorption bands characteristic of the functional groups existing in the intercalated molecule. The spectra shows typical bands of the layered components, composed of absorption bands due to normal vibration modes corresponding to layer hydroxyl groups, water molecules, M–O and M–O–M′ stretching vibrations. The broadband around 3430 cm\(^{-1}\) is due to the stretching mode of the hydroxyl groups existing in the layers; broadening of this band is due to the formation of hydrogen bonds. The aromatic ring is responsible for the very weak C–H stretching mode bands just above 3000 cm\(^{-1}\). The aliphatic C–H groups give rise to the weak absorption at 2950 cm\(^{-1}\) [37]. It indicates that the diclofenac anions have been intercalated into the interlayer galleries of the Zn/Al HTlc. However, some of the bands are slightly shifted in position, due to the interaction between diclofenac anions and the inorganic HTlc host interlayers. Table 1 shows the FTIR assignments for HTlc-DIK-DS and HTlc-DIK-AE. An intense bands 1575-1578; 1504-1505; 1451-1452 and 1385-1400 cm\(^{-1}\) of the HTlc-DIK-DS and HTlc-DIK-AE are attributed to carboxylate stretching of the diclofenac anions, respectively. Peaks at 426-430 cm\(^{-1}\) are associated with M-O stretching modes in the Zn/Al HTlc; HTlc-DIK-DS and HTlc-DIK-AE [38].

**Figure 2.** FTIR spectra of Zn/Al HTlc (A); HTlc-DIK-AE (B); HTlc-DIK-DS (C) and Na-DIK (D)
## Table 1. The FTIR assignments of HTlc-DIK-AE and HTlc-DIK-DS

| Functional group   | Wavenumber (cm⁻¹) | Zn/Al HTlc | HTlc-DIK-AE | HTlc-DIK-DS | Na-DIK |
|--------------------|-------------------|------------|-------------|-------------|--------|
| OH stretching      | 3445.85           | 3426.31    | 3428.01     | 3386.09     | -      |
| NO₃                | 1382.40; 612-830  | 618.19     | 839.34      | -           | -      |
| Carboxylate        | 1451-1452; 1385-1400 | 1504-1505  | 1400-1451   | 1504-1577; 1400-1451 | -      |
| M-O stretching     | 426.74            | 427.31     | 430.54      | -           | -      |

### 3.3. Elemental Analysis

Elemental analysis was done for the inorganic composition of HTlc-DIK-DS and HTlc-DIK-AE, as shown in Table 2. As expected, the HTlc-DIK-DS and HTlc-DIK-AE contained inorganic constituents from diclofenac. Both elemental analysis and XRD study indicate that intercalation occurred in which diclofenac was intercalated into the HTlc inorganic interlayers.

### Table 2. An elemental analysis of the samples

| Samples                  | ZnO (%) | Cl (%) | Al₂O₃ (%) | Na₂O (%) | Trace Total (%) |
|--------------------------|---------|--------|-----------|----------|-----------------|
| Zn/Al HTlc               | 78.71   | 0.38   | 17.30     | -        | 3.28            |
| HTlc-DIK-DS              | 51.45   | 29.86  | 16.26     | -        | 2.33            |
| HTlc-DIK-AE              | 43.79   | 13.93  | 13.28     | 13.22    | 15.46           |

### 3.4. Specific Surface Area Analysis

The specific surface area of Zn/Al HTlc; HTlc-DIK-DS and HTlc-DIK-AE were also characterized. The calculated B.E.T. surface areas of this sample are shown in Table 3.

### Table 3. The surface area of samples

| Sample                  | S_{BET} (m².g⁻¹) | average (Å) | T_{total} (10⁻³.m³.g⁻¹) |
|-------------------------|------------------|-------------|-------------------------|
| Zn/Al HTlc              | 0.752            | 90.528      | 3.406                   |
| HTlc-DIK-DS             | 15.427           | 18.174      | 14.019                  |
| HTlc-DIK-AE             | 6.268            | 15.347      | 4.810                   |

Table 3 shows the comparison of the surface properties of the material Zn/Al HTlc, which are intercalated with both methods. Besides an intercalation of diclofenac into the area between the layers, it is possible there is also the mechanism of adsorption on metal hydroxide layers (brucite-like) Zn/Al hydrotalcite-like.

In addition, the diclofenac will enter into the pores, causing the inside of the pores was covered by diclofenac molecule. By the closing of the pores of the brucite-like due to a decrease in the average pore radius. It is demonstrated by the data of the average pore radius Zn/Al HTlc amounted to 90.528 Å while intercalation decreased to 18.174 Å on the direct synthesis method by coprecipitation and 15.347 Å on anion exchange methods.

Besides the effect on the decrease in the average pore radius, intercalation of diclofenac will increase the total pore volume. It is evidenced by the increase in value the total pore volume of 3.406 into 14.019 × 10⁻³ cm³.g⁻¹ on the direct synthesis method and 4.810 × 10⁻³ cm³.g⁻¹ anion exchange methods. In addition, increasing the value of the total pore volume will affect the brucite-like surface
area. The intercalation by directly synthesis method due to increased surface area of 0.752 m$^2$.g$^{-1}$ to 15.427 m$^2$.g$^{-1}$ while the intercalation with anion exchange methods increases to 6.268 m$^2$.g$^{-1}$. A greater increase of pore surface area in the direct synthesis method, suggesting that blending the diclofenac into the Zn/Al HTlc is preferred in this method rather than anion exchange methods.

3.5. Surface Characterization

The samples prepared have been also studied by SEM; some micrographs are included Zn/Al HTlc; HTlc-DIK-DS and HTlc-DIK-AE are shown in figure 3. A similar morphology is observed for both samples. Aggregated lamellar particles can be observed, although somewhat loose. All samples show non-uniform, irregular agglomerates of compact and non-porous plate-like structure. It is the usual morphology of hydrotalcite, described as a result of stacking of hexagonal layers.

![Figure 3. Scanning electron micrographs of Zn/Al HTlc (A); HTlc-DIK-DS (B) and HTlc-DIK-AE (C)](image)

4. Conclusions

Intercalation of diclofenac into modified Zn/Al hydrotalcite-like preparation using coprecipitation and anion exchange method to obtain HTlc-DIK-DS and HTlc-DIK-AE was accomplished well-crystallized solids, with basal spacings between 10 and 12Å. The XRD results confirmed the intercalation process in which diclofenac is arranged between the interlayers as tilted bilayers. Intercalation is further confirmed by FT-IR spectroscopy. FTIR study shows that the bands of the resulting product samples correspond to the characteristic functional groups of the diclofenac and HTlc structures, which support the intercalation process, although slightly shifted from their original positions due to the interactions between the layers.

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