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Hybrid systems based on "drug - in cyclodextrin - in nanoclays" for improving oxaprozin dissolution properties

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ABSTRACT

A combined approach based on drug complexation with cyclodextrins, and complex entrapment in nanoclays has been investigated, to join in a single delivery system the benefits of these carriers and potentiate their ability to improve the dissolution properties of oxaprozin (OXA), a poorly water-soluble anti-inflammatory drug. Based on previous studies, randomly methylated β -cyclodextrin (RAMEB) was chosen as the most effective cyclodextrin for OXA complexation. Adsorption equilibrium studies performed on three different clays (sepiolite, attapulgite, bentonite) allowed selection of sepiolite (SV) for its greater adsorption power towards OXA. DSC and XRPD studies indicated drug amorphization in both binary OXA-RAMEB coground and OXA-SV cofused products, due to its complexation or very fine dispersion in the clay structure, respectively. The drug amorphous state was maintained also in the ternary OXA-RAMEB-SV cofused system. Dissolution studies evidenced a clear synergistic effect of RAMEB complexation and clay nanoencapsulation in improving the OXA dissolution properties, with an almost 100% increase in percent dissolved and dissolution efficiency compared to the OXA-RAMEB coground system. Therefore, the proposed combined approach represents an interesting tool for improving the therapeutic effectiveness of poorly soluble drugs, and reducing the CD amount necessary for obtaining the desired drug solubility and dissolution rate increase.

Keywords: cyclodextrin complexation, nanoclays, oxaprozin, sepiolite, clay-cyclodextrin hybrid systems

1. Introduction

Oxaprozin (OXA) is a non-steroidal anti-inflammatory drug (NSAID), mainly used for the treatment of pain and inflammatory disorders, such as osteoarthritis and rheumatoid arthritis. However, its limited water solubility and poor stability may reduce its therapeutic effectiveness and increase the risk of appearance of adverse cardiovascular and/or gastro-intestinal events [1, 2]. In particular, despite its acidic nature and unlike most other acidic NSAIDs, it complies with the Biopharmaceutics Classification System low solubility criteria of Class II drugs over the entire pH range from 1.2 to 7.4 [3]. Therefore, an improvement of OXA solubility and dissolution properties is highly desirable, since it would allow to enhance its absorption rate and bioavailability, and, consequently, to reduce its dosage and the risk of dose-related adverse events.

Complexation with cyclodextrins (CDs) has been widely and successfully utilized to increase solubility, dissolution rate, chemical stability and bioavailability of a number of poorly soluble drugs, including different NSAIDs [4-6], obtaining some additional advantages such as masking of taste, lowering of dose, reduction of side effects [7-10]. Recent studies performed to investigate the ability of several natural and derivative CDs in improving OXA dissolution properties indicated the randomly-methylated β -CD (RAMEB) as the best carrier, and the equimolar OXA-RAMEB product obtained by co-grinding as the most effective in improving drug solubility and dissolution rate [11]. However, it is known that the amount of CDs that can be used in pharmaceutical dosage forms is limited by various problems, including, in particular for the methylated derivatives, their potential toxicity [12]. Therefore it would be advisable to find possible strategies able to potentiate the CD solubilizing effect, in order to reduce the amount to use and the associated drawbacks.

Among the different possible alternative approaches proposed over last years to improve the bioavailability of poorly soluble drugs, such as self-emulsifying delivery systems [13], solid dispersions [14], lipid-based formulations [15], the use of inorganic matrices appears of particular interest [16]. In particular, based on their high retention abilities, as well as their swelling and colloidal properties, nanoclays have attracted considerable attention as potential carriers for drug delivery [17,18]. These materials can provide spontaneous submicron dispersions in aqueous media, resulting in low cost

and biocompatible systems with large surface area and high inclusion capacity. Moreover, depending on the size and the surface chemistry of the pores, nanoclays can be used to sustain/target release of the loaded drugs and/or to improve their stability by protecting them from unfriendly environments [19-21], as well as to improve the drug dissolution properties [22,23].

Combined strategies exploiting at the same time both CD complexation, and encapsulation of the complexed drug into micro/nanocarriers, such as polymeric micro/nanoparticles [24,25], classic or ultradeformable liposomes [26,27], niosomes [28], micelles [29], solid lipid nanoparticles (SLN) [30], or nanostructured lipid carriers (NLC) [31] proved to be successful in improving the effectiveness of the two carriers, overcoming the related problems associated with their use. In particular, this approach was fruitfully applied by loading OXA as CD complex into PLGA nanoparticles, where the presence of CD showed to be useful not only to promote but also to regulate the drug release rate from the delivery system, depending on the type of CD used [32].

However, at the best of our knowledge, such kind of strategy was never applied to obtain delivery systems based on the joined use of CDs and nanoclays. Moreover, it has been reported that aluminum-magnesium-containing clays have antacid properties, and then their intercalation products could have also an action in lowering the gastro-lesivity of anti-inflammatory drugs [33, 34].

Therefore, taking into account all these considerations, in the present work we considered it worthy of interest to investigate the potential of a combined approach based on "OXA-in CD-in nanoclays", aimed to join, and possibly potentiate, the relative benefits of both carriers in a single drug delivery system. With this objective, we evaluated and compared the adsorption properties towards OXA of three different aluminum-magnesium containing clays, namely sepiolite, attapulgite and bentonite, in order to select the most effective one for preparing the ternary "drug- in CD - in clay" systems. On the other hand, based on the results of our previous studies [11], RAMEB was selected as the most effective CD for OXA complexation. The solid state characterization of binary (drug-CD and drug-clay), and ternary (drug-in CD-in clay) systems was carried out by differential scanning calorimetry, thermogravimetric analysis and powder X-ray diffractometry, while the dissolution properties of the different products were evaluated by the dispersed amount method.

2. Materials and Methods

2.1. Materials

Oxaprozin (4,5-diphenyl-2oxazole propionic acid) (OXA) was a gift from S.I.M.S. (Firenze, I). Amorphous randomly methylated β -cyclodextrin (RAMEB), average MS 1.8, was a gift from Wacker-Chemie GmbH (Munche, Germany). Sepiolite was from Vicalvaro (Spain) (SV); attapulgite (Pharmasorb colloidal[®], PHC) was from BASF, and bentonite (or smectite) (VeegumHS[®], VHS) was kindly gifted by Vanderbilt Minerals (USA). All the clays were sieved (90-125 μ m) before use. Other chemicals and solvents were of reagent grade and used without further purification.

2.2. Preparation of drug-RAMEB binary systems

OXA-RAMEB equimolar physical mixtures (PM), were obtained by 15 min tumble mixing weighed amounts of the respective simple components (75–150 μ m sieve granulometric fraction). Drug-RAMEB co-ground systems (GR) were obtained by ball-milling PM in a high-energy vibrational micro-mill (Mixer Mill MM 200, Retsch GmbH, Dusseldorf, Germany) at 24 Hz for 30 min [11].

2.3. Adsorption equilibrium studies

Adsorption studies were performed by the batch technique to obtain equilibrium isotherms. The experiments were carried out by adding a saturated aqueous solution of OXA with increasing volumes of a 2% w/w clay aqueous suspension (obtained by high-shear mixing, 15 min at 4000 rpm, with a Silverson LM5A), and leaving the dispersions to equilibrate 24 h under stirring in a thermostated bath at 37 °C. The suspensions were then centrifuged and filtered and the OXA concentration present in the supernatant was spectrometrically assayed at 285.5 nm (UV Perkin Elmer spectrophotometer Mod. Lambda 25). Each experiment was performed in triplicate.

The amount of OXA adsorbed onto the clay (q_e , mg/g), was calculated from the following equation:

$$q_e = (C_0 - C_e) \cdot V/W \quad (1)$$

where C_0 and C_e are the initial and the equilibrium concentrations of OXA in the

aqueous solution (mg/L), respectively, V the volume of the solution (L), and W the mass of the clay sample used (g).

The obtained data were used to plot the Langmuir adsorption isotherm:

$$C_e / q_e = (1 / q_m K_L) + (C_e / q_m) \quad (2)$$

where C_e is the equilibrium concentration of the adsorbate, q_e the adsorbed amount at equilibrium, q_m the maximum adsorption capacity and K_L the Langmuir adsorption constant.

The adimensional equilibrium parameter constant R_L was obtained by the following equation [35]:

$$R_L = 1 / (1 + C_e K_L)$$

2.4 Preparation of drug-clay and drug-RAMEB-clay systems

OXA-clay and (OXA-RAMEB GR)-clay interaction products at the selected drug:clay (w/w) ratio were prepared by heating 20 min at 200 °C the corresponding physical mixtures, and then let solidify overnight in a desiccator (cofused products, COF) [36]. Binary (OXA-clay) and ternary (OXA-RAMEB GR)-clay physical mixtures (PM) were also prepared for comparison purposes.

2.5. Solid state characterization of binary and ternary interaction products

2.5.1. Differential scanning calorimetry (DSC)

DSC analyses were performed with a Shimadzu mod. DSC50Q system, on 5-10 mg samples (Mettler AX26 Delta Range Microbalance) scanned in pierced Al pans at 10 °C/min between 40 and 200 °C under static air. The residual crystallinity of OXA in the different samples, expressed as relative degree of crystallinity (RDC%), was determined using the following equation:

$$RDC_{\%} = \frac{\Delta H_{\text{sample}}}{\Delta H_{\text{drug}}} \times 100$$

where ΔH_{sample} is the heat of fusion of the sample and ΔH_{drug} the heat of fusion of the pure crystalline OXA, normalized to the drug content in the sample. All the measurements were performed in triplicate. The relative standard deviation of crystallinity data was about $\pm 5\%$.

2.5.2. Thermogravimetric analysis (TGA)

TGA analyses were carried out on 10-20 mg samples using a Shimadzu mod. TGA-50H equipment working over the temperature range 25-250 °C at a heating rate of 10 °C/cm.

2.5.3. Powder X-ray diffractometry (XRPD)

XRPD patterns were taken at ambient temperature with a Philips PW1710 diffractometer (Lelyweg, The Netherlands) in the 5-40° 2θ exploration range, at a scan rate of 0.05 s⁻¹, using a CuKα radiation.

2.5.4. Scanning Electron Microscopy (SEM)

Micromorphology of the individual components and products was investigated on carbon coated samples by field emission scanning electron microscopy (FESEM) by using a GEMINI CARL ZEISS equipment, working at 3 KV.

2.5.5. Powder flowability

Bulk density, Carr Index and Hausner ratio, as indicators of the flowability and compressibility properties of the prepared powders, were assessed according to a modified pharmacopeial test [39]. An accurately weighed amount of powder (m) was poured into a 10 mL graduated glass cylinder and the bulk volume was measured (V_b); then it was tapped on a hard bench until to constant volume (tapped volume, V_t). For all formulations, measurements were performed in triplicate. The bulk density, Carr Index and Hausner ratio were calculated using the following equations:

$$\text{Bulk density} = \frac{g}{\text{cm}^3} = \frac{m}{V_b} ; \text{ Carr Index \%} = \frac{V_b - V_t}{V_b} \times 100 ; \quad \text{Hausner ratio:}$$
$$\frac{\text{tapped density}}{\text{bulk density}}$$

2.6. In vitro release studies

In vitro release studies were performed according to the dispersed amount method. Systems containing 50 mg of OXA were added in 75 mL of a pH 5.5 buffered

solution at 37 ± 0.5 °C, stirred at 100 rpm for 1 h. At given time intervals, samples (3 mL) were withdrawn, filtered (pore size 0.45 μm), replaced with an equal volume of fresh medium, and spectrometrically assayed for drug content as described above. The effect of the progressive dilution of the dissolution medium on the drug concentration was calculated according to the formula:

$$C_{i_{\text{corr}}} = C_i + \left(\frac{V_p}{V_0} \right) \sum C_i$$

where $C_{i_{\text{corr}}}$ is the corrected concentration, V_p the withdrawal volume and V_0 the total volume of the dissolution medium.

The amount of drug released was plotted versus time (mean of four determinations, coefficient of variation (C.V.) <3.5%). Dissolution efficiency (D.E.) was calculated from the area under the dissolution curve at time t and expressed as a % of the area of the rectangle described by 100 % dissolution in the same time.

The release data were statistically analysed by one-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls multiple comparison post test Graph Pad Prism vers. 3 software, San Diego, CA, USA). The differences were considered statistically significant when $P < 0.05$.

3. Results and Discussion

The first step of this project, aimed to the development of a "drug-in CD-in clay" delivery system, was devoted to the selection of the most suitable clay, for obtaining an efficient drug loading into the mineral matrix structure. With this purpose, we evaluated and compared the adsorption ability towards OXA of three different nanoclays, i.e. sepiolite (SV), attapulgite (Pharmasorb Colloidal, PHC) and bentonite (Veegum HS, VHS), which are hydrated magnesium or magnesium-aluminum silicates, with different structural and physicochemical properties. In particular, SV and PHC have typical fibrous habits, while VHS presents a typical lamellar stratified structure.

3.1. Adsorption equilibrium studies

Adsorption equilibrium studies were performed to calculate the maximum adsorption capacity of the three kinds of nanoclays towards OXA. The data obtained were fitted according to the Langmuir equation, assuming that the adsorption process

occurred at specific sites within the adsorbent, and that, at equilibrium, a saturation point was reached. As can be seen in Table 1, the best results were given by the system with SV. According to the Langmuir isotherm equation, calculated by the least square method (R^2 0.992), the maximum adsorption capacity value (q_m) of SV for OXA was 21.6 mg per g of clay, and the related Langmuir constant K_L was 231.5 mL/mg. Moreover, the adimensional equilibrium parameter constant (R_L) values were between 0.350 and 0.590, indicating that the adsorption behaviour of SV towards OXA was favourable [35]. On the contrary, the maximum adsorption capacity values for OXA obtained with PHC and VHS were both around 0.05 mg/g, indicating the low affinity of these clays for interacting with the drug, as confirmed by the low R_L values.

DSC studies performed on drug:clay mixtures at different w/w ratios (1:2, 1:4, 1:6) confirmed that SV was the best candidate for obtaining an effective solid-state interaction with OXA. In fact, as shown in Table 2, where the melting temperatures and the related ΔH values of OXA alone and in mixture with the different clays are reported, the complete disappearance of the OXA melting peak, indicative of its amorphous state and/or its almost molecular dispersion within the carrier matrix, was observed only in its combination with SV, as from the 1:4 w/w ratio. On the contrary, this effect was never achieved in the drug mixtures with PHC or VHS, also at higher clay contents (up to 1:6 w/w).

The more intense and effective drug-clay interactions observed in systems with SV could probably be attributed to the structural differences between the three nanoclays as visible in figure 1. The sepiolite (SV) and attapulgite (PHC) structures are similar, consisting in hollow nanotubes able to entrap drug molecules. However, the different dimensions of their channels (sepiolite 0.37x1.06 nm and attapulgite 0.37x0.64 nm) are coherent with the higher drug loading capacity observed for SV compared to PHC [37]. As regards to VHS, this nanoclay is a montmorillonite, with laminar structure and interlayer spaces able to retain drug molecules mainly by cation exchange with the hydrated cations present in the interlayers [17]. This process is clearly limited in our case, as OXA is an anionic drug.

Based on these results, SV was selected for the following studies and the 1:4 w/w drug:SV ratio was chosen for the preparation of binary (drug-clay) and ternary (drug-CD-clay) systems. Among the different procedures reported for obtaining drug-clay interaction products, the cofusion process, consisting in mixing together clay

and drug and heating up to the drug melting temperature, was selected, based on its reported effectiveness [38].

3.2. Solid state characterization of binary (OXA-RAMEB or OXA-SV) and ternary (OXA-RAMEB-SV) systems

Cofused ternary (OXA-RAMEB GR)-SV systems were then prepared and their solid state properties were investigated and compared with those of the corresponding binary systems (OXA-RAMEB GR and OXA-SV COF), as well as with the corresponding binary and ternary PM. In all these systems the drug:SV ratio was kept constant and equal to 1:4 (w/w), indicated by previous DSC studies as the optimal ratio for a complete drug-clay interaction.

3.2.1 Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TGA)

The thermal curves of raw materials and of the binary (OXA-RAMEB and OXA-SV) and ternary (OXA-RAMEB-SV) systems are shown in Figure 2 (a,b,c,d). The DSC trace of OXA was typical of a pure crystalline anhydrous substance, exhibiting a sharp melting peak at 162.79 °C (Fig. 2a). On the contrary the DSC curve of RAMEB indicated its amorphous hydrated nature, with a broad dehydration band peaked at about 77 °C. Also the thermal curve of SV was characterized by an intense dehydration band, with a peak around 115 °C. The drug melting peak was still clearly detectable in its binary PMs with RAMEB (Fig 1b; RDC=17.76%) and even more in its PM with SV (Fig. 1c; RDC 41.42%). On the contrary, it completely disappeared in both binary OXA-RAMEB GR and OXA-SV COF systems, indicating OXA amorphization in such samples (Fig. 2b,c). As expected, the amorphous state of the drug was observed also in the ternary COF system, as well as in the ternary PM obtained by mixing the OXA-RAMEB GR and the clay, and their respective DSC curves were practically identical.

TGA substantially confirmed the results of DSC studies (data not shown). No loss of weight of the pure OXA sample was observed between 25 and 250 °C, confirming its anhydrous nature and its thermal stability in this temperature range. An about 4 % and 11 % weight loss was instead observed for pure RAMEB and SV samples in the 50-110 and 60-150 °C range, respectively, due to their dehydration process. Similar values were also obtained for their respective binary and ternary

combinations with the drug. The absence of additional phenomena of weight loss, other than the dehydration one, confirmed the thermal stability of all the products.

3.2.2. Powder X-ray diffractometry (XRPD)

X-ray diffraction studies (Figure 3) were in agreement with the DSC results. As shown in Fig. 3a, the X-ray pattern of OXA was typical of a crystalline substance, exhibiting a series of sharp crystallinity peaks, with the most intense one at $9.6^\circ 2\theta$. In contrast, RAMEB showed a broad halo pattern, typical of an amorphous substance. The drug crystallinity peaks emerged from the amorphous patterns of the methylated CD in the OXA-RAMEB PM (Fig. 2b), whereas a complete OXA amorphization was achieved in the GR system. SV exhibited a crystalline pattern, with a very intense peak at $7.3^\circ 2\theta$ (Fig. 2a). The pattern of OXA-SV PM was the simple superimposition of those of the individual components, indicating the absence of solid state interactions between them; on the contrary, the disappearance of the typical drug diffraction peaks (included that at $9.6^\circ 2\theta$) was observed in the COF system, as a consequence of its intimate and almost molecular dispersion within the clay matrix (Fig. 2c). SV maintained instead almost unchanged its typical diffraction pattern after the cofusion process, indicating that the thermal treatment did not affect its crystalline structure. As expected, the completely amorphous state of OXA was maintained in both PM and COF (OXA-RAMEB GR)-SV ternary systems (Fig. 2d). Interestingly, a loss of SV crystallinity was observed in the ternary COF system, with respect to the corresponding ternary PM, probably as a consequence of the intimate interaction of the clay with the amorphous drug-CD complex during the cofusion process.

To clarify this possibility, textural analysis by field emission scanning electron microscope (FESEM Gemini, of Carl Zeiss SMT) was carried out to selected samples, revealing that the individual components, clearly separated in the physical mixture, became more closely amalgamated by co-fusion (Figure 4).

3.2.4. Powder flowability

Bulk density, Carr Index (CI) and Hausner Ratio (HR) of the prepared products were determined, as indicators of the powder flowability and compressibility properties,

which are key parameters for pharmaceutical manufacturing processes, in view of the future development of novel and more efficient drug formulations based on such products.

CI and HR are measures of the relative importance of interparticulate interactions and frictions, and then of the powder flow properties. CI values <10 or HR <1.11 are index of an 'excellent' flow; CI between 11–15 or HR between 1.12–1.18 of 'good' flow; CI between 16–20 or HR between 1.19–1.25 of 'fair' flow; CI between 21–25 or HR between 1.26–1.34 of passable flow; CI between 26–31 or HR between 1.35–1.45 of 'poor' flow; CI between 32–37 or HR between 1.46–1.59 of 'very poor' flow; CI>38 or HR>1.60 of 'very very poor' flow [40, 41].

The obtained data are presented in Table 3. The binary systems of OXA with SV, both as physical mixture or cofused systems, exhibited passable flow properties, similar to those of pure SV. On the other hand, the OXA-RAMEB binary physical mixture showed a CI value >38, index of a very very poor flow properties, and only a slight decrease of CI value, around 33, was observed for the corresponding coground product. Better flow properties were observed for the ternary (OXA-RAMEB GR)-SV physical mixture, even though it is still classified as a poorly-flowable powder. The best results in terms of powder flowability were found for the ternary cofused product, whose CI and HR values indicated good powder flow properties. Moreover, an appreciable increase of the bulk density was observed for such product with respect to the corresponding physical mixture. Both these results could be related to a change in the particle morphology as a consequence of the cofusion process which allowed the formation of more homogeneous system, with higher density and better flow properties at the same time.

3.2.3. Dissolution studies

The dissolution curves of OXA alone and from its binary systems with RAMEB or SV, and from its ternary (OXA-RAMEB GR)-SV systems are shown in Fig. 5, while the relative main dissolution parameters are presented in Table 4. Dissolution studies indicated that OXA complexation with RAMEB was significantly more effective ($P<0.05$) than entrapment in SV in improving its dissolution properties. In fact the OXA-SV COF system allowed only an about 2.5 and 2.0 times increase in P.D. 15 (% dissolved at 15 min), and D.E. 60 (Dissolution efficiency at 60 min),

respectively, with respect to drug alone, compared to the 8.8 and 6.6 times increase obtained with the OXA-RAMEB GR product. The simple OXA-RAMEB PM exhibited a better performance ($P < 0.05$) than the OXA-SV COF system, showing an about 4.4 and 3.4 times increase in P.D. 15 and D.E. 60 values, respectively. This result can be mainly attributable to the better wetting effect of RAMEB than SV towards OXA, as well as to a partial in situ complexation phenomenon during the dissolution process.

The ternary system obtained by physical mixing of the OXA-RAMEB GR system with SV showed a dissolution profile practically superimposable to that of the binary OXA-RAMEB GR system, without no appreciable effects ($P > 0.05$) due to the presence of the clay. By contrast, the corresponding ternary system prepared by cofusion evidenced a marked increase in drug solubility and dissolution rate, enabling a 17.0 and 13.3 times increase in P.D. 15 and D.E. 60 values with respect to the drug alone. In particular, the ternary COF system allowed a further 2 times increase in such values with respect to those given by the binary OXA-RAMEB GR system ($P < 0.05$). This finding indicated a synergistic effect between CD complexation and nano-entrapment in clay, in enhancing OXA dissolution behavior, thus proving the actual effectiveness of the combined use of both carriers. Evidently, the cofusion process gave rise to an effective interaction between the OXA-RAMEB GR complex and SV and enabled an efficient loading of the complex in the clay structure. It can be hypothesized that the adsorption of the drug-CD complex onto the finely divided clay surface markedly increased the effective surface area, and inhibited any possible aggregation phenomena, allowing at the same time its rapid and powerful release from the clay surface, when in contact with the dissolution medium, due to the weak bonds between them.

Conclusions

In this work we demonstrated that the joined use of CD complexation and loading of the complex in a hydrophilic clay mineral can be a successful strategy to strengthen the benefits of both these carriers with regard to their potential in enhancing the OXA solubility and dissolution rate, and, consequently, its therapeutic efficiency and safety.

RAMEB was selected for OXA complexation, since it was the most effective CD in enhancing the drug solubility and dissolution properties [11]. Among the different clays tested, SV was chosen for preparation of (OXA-RAMEB)-clay ternary systems in virtue of its greater ability to effectively adsorb the drug. DSC and XRPD studies indicated drug amorphization in both binary OXA-RAMEB GR and OXA-SV COF systems, as a consequence, respectively, of its complexation or its very fine dispersion in the clay structure. The amorphous state of the drug was maintained also in the ternary (OXA-RAMEB GR)-SV COF system, where a loss of SV crystallinity was also observed, as a consequence of the intimate interactions between SV and the amorphous complex, thus leading to reasonably hypothesize a drug - in CD - in clay nanoencapsulation. Dissolution studies evidenced a synergistic effect of CD complexation and clay nanoencapsulation in improving the drug dissolution properties, with an almost 100 % increase in terms of percent dissolved and dissolution efficiency with respect to the binary OXA-RAMEB GR system.

These results proved the high potential of the proposed combined approach in offering an interesting tool for improving the therapeutic effectiveness of poorly soluble drugs, and for reducing the amount of CD to use for obtaining the desired drug solubility and dissolution rate increase.

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Legend for Figures

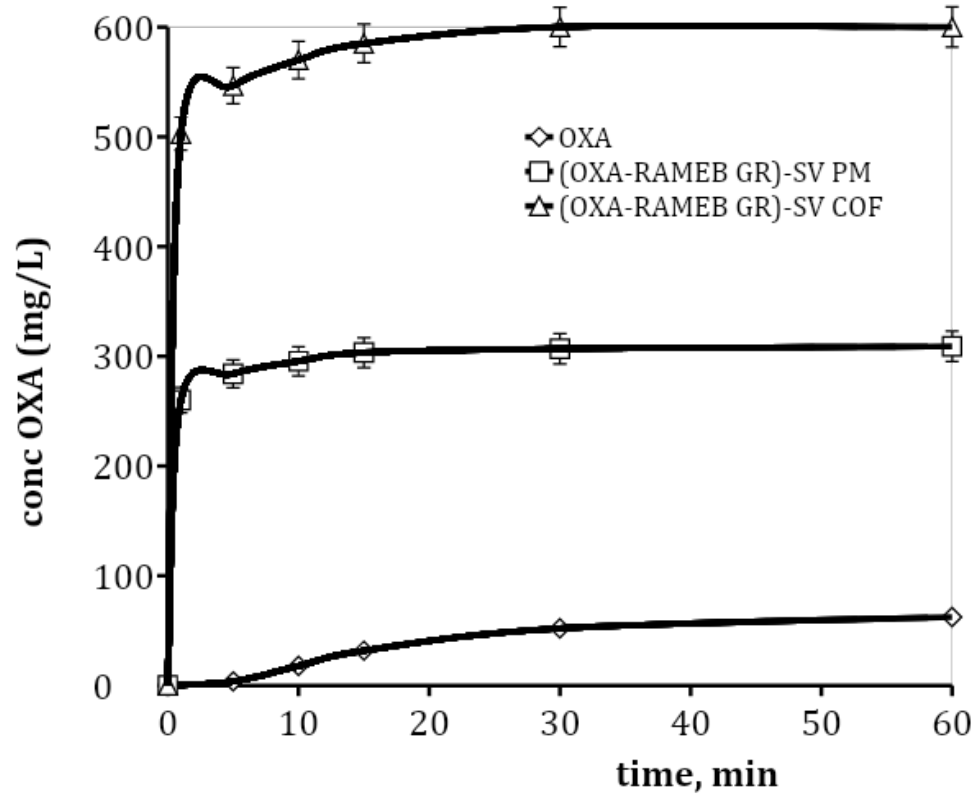
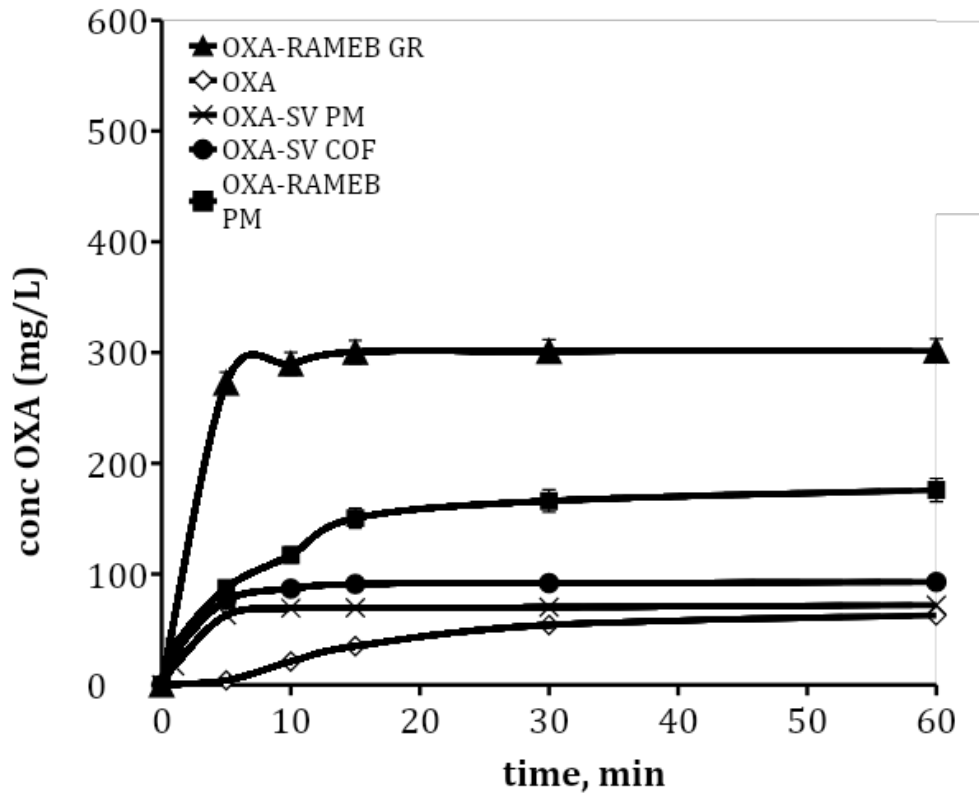
Figure 1 SEM micrographs nanoclays, sepiolite (SV), attapulgite (PHC) and bentonite (VHS)

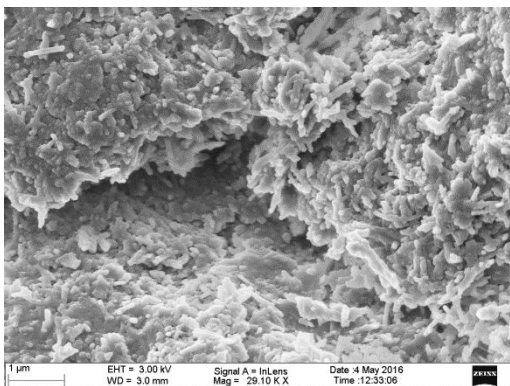
Figure 2 DSC curves of raw materials (a) and OXA-RAMEB (b), OXA-SV (c) and OXA-RAMEB-SV (d) physical mixtures (PM), coground (GR) or cofused (COF) systems.

Figure 3 Powder X-ray diffraction patterns of raw materials and OXA-RAMEB (A), OXA-SV (B) and OXA-RAMEB-SV (C) physical mixtures (PM), coground (GR) or cofused (COF) systems.

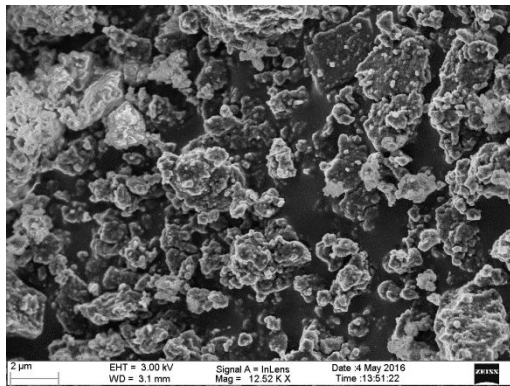
Figure 4 SEM micrographs of raw materials: sepiolite (A), oxaprozin (B) and RAMEB (C) and OXA-RAMEB-SV physical mixtures (D) and cofused systems (E).

Figure 5: Dissolution profiles of OXA from binary systems with RAMEB or SV (A), or from ternary (OXA-RAMEB)-SV systems (B).

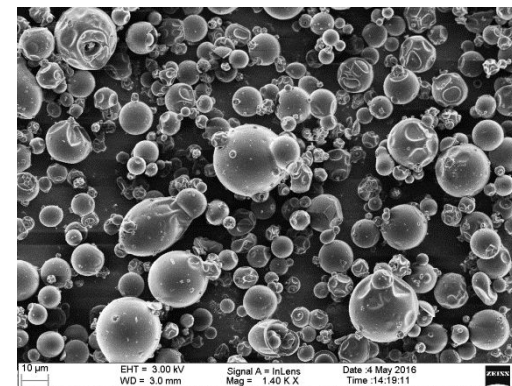
A**B**



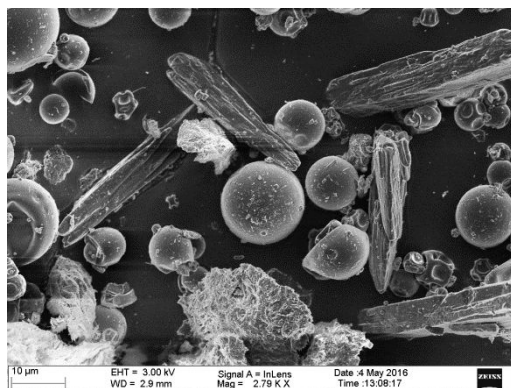
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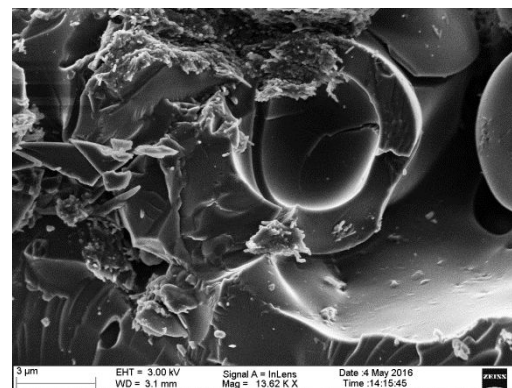
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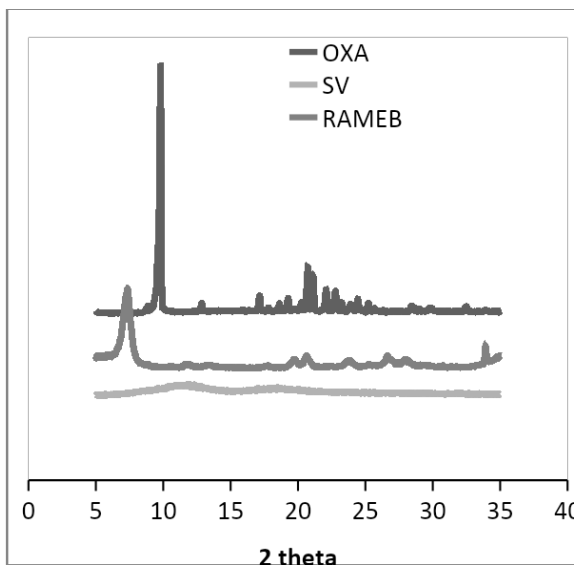
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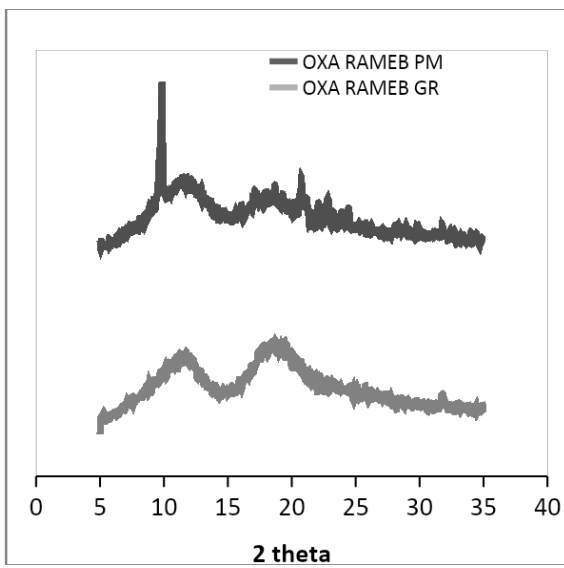
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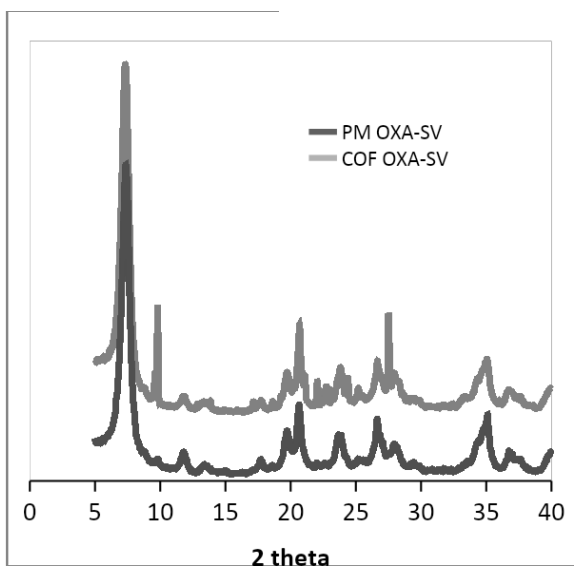
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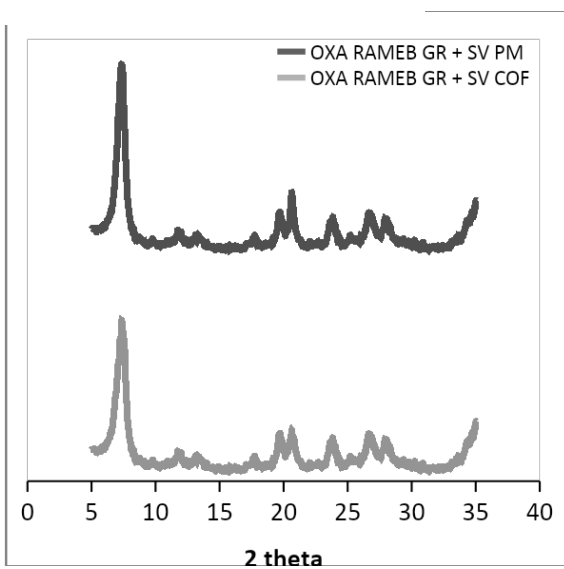
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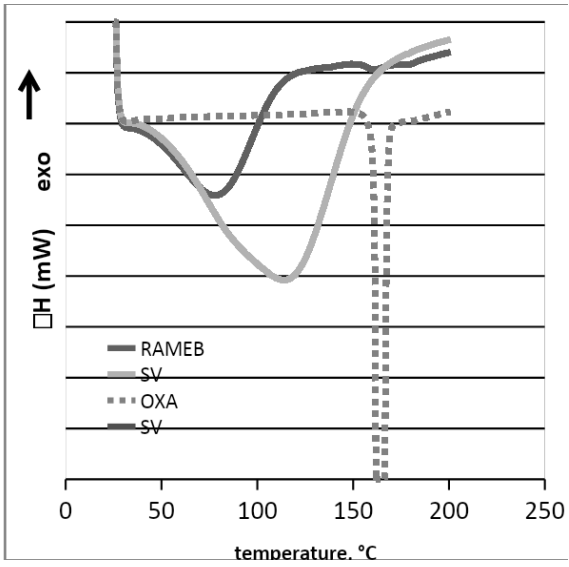
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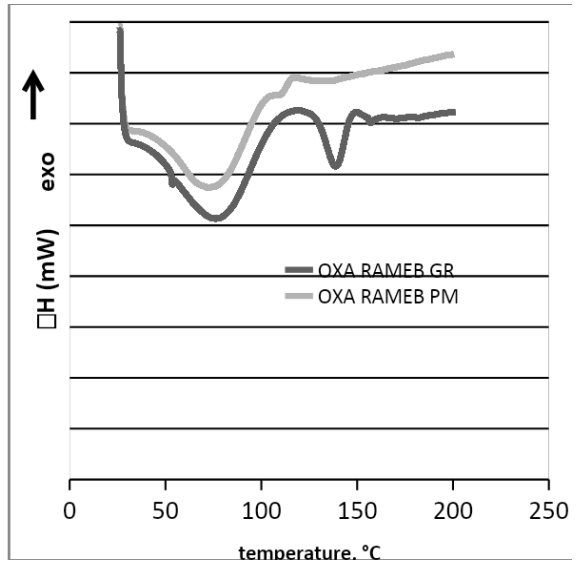
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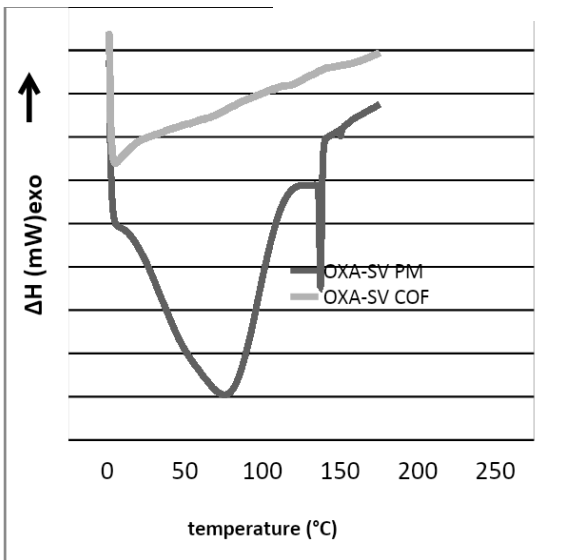
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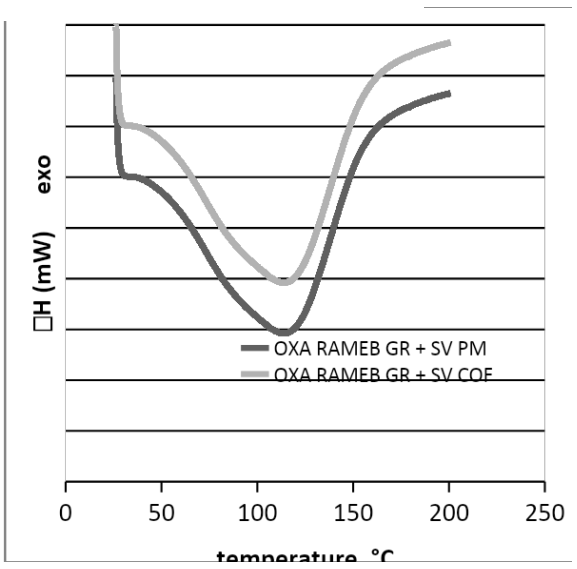
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b



c



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