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RESEARCH ARTICLE

New sol-gel derived aluminum oxide-ibuprofen nanocomposite as a controlled releasing medication

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ABSTRACT

Objective(s): In a new approach, following the development in metal oxide chemistry, the ibuprofen as low water soluble nonsteroidal anti-inflammatory drug diffused into synthetic sol-gel derived nano porous γ-alumina by an impregnation method in order to increase the solubility and control the drug release in physiological environment.

Methods: Sol-gel method was utilized for the fabrication of alumina by controlled hydrolysis of an aluminum alkoxide source. This vehicle favors high surface area, pore diameter and pore volume as well as hydroxyl rich surface which is needed for the drug formulation. Two different percent of the medication were loaded on the synthetic γ-alumina. The samples were characterized by X-ray diffraction (XRD), BET (Brunauer, Emmett and Teller), FT-IR and thermogravimetric analysis (TGA).

Results: The results showed that the drug molecules were well-distributed into the pores. 25 and 50% w/w of ibuprofen were prepared for drug release test which was studied by UV-Vis techniques. The release kinetic was obtained in simulated body fluid (SBF), simulated intestinal fluid (SIF) and simulated gastric fluid (SGF). The solubility of the drug reached to 90 and 84% for 25% (γ-Al-IBU25) and 50% (γ-Al-IBU50) drug loaded samples after 4 h of loading time, respectively. These results are comparable to reported commercial alumina with low amount of 25% release. The percent of the drug release is as follow for three environments: SBF > SIF > SGF.

Conclusions: It could be concluded that the new formulation led to enhancement solubility and controlled release of ibuprofen in the mentioned media.

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INTRODUCTION

Ibuprofen as non-steroidal anti-inflammatory (NSAIs) research chemical has been known for decades. It was mainly taken to reduce fever, inflammation and pain. It works by blocking the effect of prostaglandins hormones that causes inflammation. Ibuprofen is practically insoluble in water [1–5]. Dose controlling of the drug and modifying its physical properties has attracted many attentions. A number of different formulations have been introduced by using organic and inorganic carriers. Chitosan [6,7], sodium alginate [8,9], silica based MCM-41 and SBA-15 are the most important ones [10–12]. The last two supports were synthesized by using initial micellar phases with pores size in the range of 2-10 nm and surface area between 500 to1100 nm [13–24]. These materials can control the release because the drug is encapsulated into the nanoporous channels. Aluminum oxide (alumina) is a unique

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inorganic substance which has amphoteric property accompanied with high chemically and thermally stability [25]. Up to now, several methods such as calcination of aluminum polyhydroxo-polyvinyl alcohol, laser ablation of metal aluminum in the presence of oxygen [26], hydrolysis of aluminum alkoxides [27], thermal decomposition of aluminum sulfate [28], chemical vapor deposition of organometallic compounds with $Al(OH)_3$ have been employed to produce gamma-alumina [29]. Sol-gel synthesis of alumina makes the possibility to have variable products with different surface area, pore diameter, pore volume, surface acid-base property and hydroxyl density of the surface. Sol-gel preparation of nanoporous alumina leads to low density and highly porous alumina which is suitable for supporting a drug to modify its physical properties and further improve the release profile [30]. Controlled hydrolysis of an aluminum precursor firstly leads to the formation of boehmite (AlO(OH)). Boehmite needs a calcination process to give favorite phase of gamma-alumina as a support for the special drug. Boehmite should pass a variety of metastable structures Eta (η), theta (θ), kappa (κ), Zeta (χ) to reach the favorite gamma (γ) form which is porous and stable between 500-800 oC. Calcination of gamma phase more than 800 oC leads to a stable phase (δ) that is dense and nonporous. Synthesis of porous and hydroxyl rich γ-alumina offers advantages as a nanocarrier for medications in comparison to commercial alumina. Supported ibuprofen on commercial alumina lacks possessing the favorite surface area, pore diameter, density and amount of active hydroxyl groups [31,32]. Therefore, in this study, nanoporous alumina was synthesized via a sol-gel method and characterized by FT-IR, XRD, BET and TGA. Then it was utilized as a nanocarrier for ibuprofen to increase its solubility and keep a steady level of the drug in the blood stream. In vitro simulated fluids such as simulated gastric fluid (SGF), simulated body fluid (SBF) and simulated intestinal fluid (SIF) were used to exhibit the release profile (using UV-Vis instrument) and compare with other studies.

MATERIALS AND METHODS

All materials (2-butanol, aluminum-2-butoxide, disodium phosphate, potassium dihydrogen phosphate, sodium chloride, sodium bicarbonate, potassium chloride, sodium sulfate, calcium chloride, trisaminomethane) were prepared from Merck. The physic-chemical characteristic was established by FT-IR (Bruker(IFS-88)), XRD (Brucker D8 Advance), BET (Belsorp adsorption, BEL Japan Inc), TGA (Netzsch TG 209 F1 under air with the heating rate of 10 °C/min) and UV-Vis (Perkin Elmer UV-Vis Spectrophotometer Lambda35).

Sol–gel preparation of nanoporous alumina (γ-Al)

γ-alumina has been prepared according to our previous work [25]. In a typical synthesis, 11 mL of distilled water in 100 mL of 2-butanol was added to the solution of 730 ml aluminum-2-butoxide (0.25 M) at 75 °C. The prepared gel was stirred for 3 h and then aged for 100 h. Finally the product was calcined at 100 °C under air for 15 h to obtain the nanoporous γ-alumina. This alumina has the surface area of 219.99 m^2/g and pore diameter of 17.432 nm which are higher than commercial alumina [28]. In addition, synthetic sol-gel γ-alumina contains highly hydroxyl rich surface that is very important in drug delivery systems.

Impregnation of ibuprofen on nanoporous alumina (γ-Al-IBU25 and γ-Al-IBU50)

For preparing γ-Al-IBU25 loading of ibuprofen on γ-alumina, 0.03 g of γ-Al was added to 0.01 g solution of ibuprofen (25% w/w) in 2 mL ethanol. The impregnation was terminated after 24 h. Then the solvent was evaporated by rotary evaporator and dried in an oven for a night. The final sample of γ-Al-IBU25 was applied for in vitro experiments. The same procedure was used to prepare 50% of drug loading to obtain γ-Al-IBU50.

Drug loading could be calculated from the equation 1:

Loading Efficiency=((amount of drug loaded alumina)/(Total amount of drug used in preparation of drug loaded alumina))×100

In vitro release test of the nano drugs

Firstly, three types of the release solutions were prepared as follow: simulated intestinal fluid (SIF) was fabricated by dissolving of 5.928 g Na_2HPO_4 and 58.019 g of KH_2PO_4 in 1.0 liter de¬ionized water with pH of 7.4 [33]. Simulated gastric fluid (SGF) was prepared by making 0.1 M solution of HCl to reach pH 1.3 in deionized water. Simulated body fluid (SBF) was prepared by dissolving NaCl (7.996 g), $K_2HPO_4.3H_2O$ (0.228 g), $NaHCO_3$ (0.350 g), KCl (0.224 g), Na_2SO_4 (0.071 g), $MgCl_2.6H_2O$ (0.305 g), 1

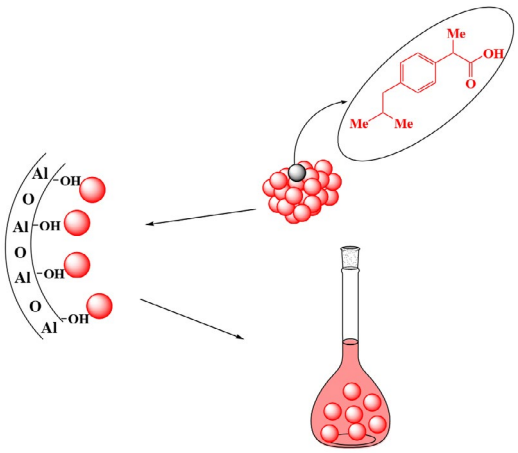

Fig.1. Preparation of the nano drug

N HCl (40 mL), $CaCl_2$ (0.278 g) and $NH_2C(CH_2OH)_3$ (6.057 g) in 1.0 L deionized water [34].

Kinetics of in vitro drug release was revealed by soaking 0.01 g of γ-Al-IBU25 and γ-Al-IBU50 nano drugs into 100 mL of SBF, SGF and SIF at 37 oC. Sampling carried out at time interval of 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, 360, 420 and 1440 min, and in each time 3 mL of the solution medium was withdrawn, filtered and then diluted before analysis. Finally, ibuprofen concentrations were determined by UV-Vis spectrophotometer at λmax of 265 nm.

RESULTS AND DISCUSSION

Characterization

Preparation of the nano drug and the release in simulated fluids is represented in Fig. 1. As the bulk ibuprofen is practically insoluble in water, sol-gel derived γ-alumina as a new carrier cause the increase in the solubility of the drug.

FT-IR spectra of γ-alumina (γ-Al), ibuprofen and γ-Al-IBU25 in the range of 400–4000 cm-1 are exhibited in Fig. 2. For γ-Al, the broad band at 578 and 846 cm^{-1} are related to νb,(AlO) and νs,(AlO) and the bands at 3750 and 1662 cm^{-1} are assigned to νs,(OH) and νb,(OH) respectively (Fig. 2a). The band at 2955 cm^{-1} is characteristic of νas,(Me) and the peaks at 1711 and 1231 cm^{-1} are belonged to νs,(C=O) and νs,(C-C) of the pure drug respectively. The band at 779 cm^{-1} represents the rocking vibration of CH_2 (Fig. 2c). Fig. 2b shows the vibrations for the nano drug γ-Al-IBU25. It is clear that the intensity of νs,(OH) of the pure alumina decreases significantly. It can prove the interaction of the drug with hydroxyl group of the surface via a hydrogen bonding. Hydrogen bond interaction cause that νs,(C=O) band shift from 1711 to 1720 cm^{-1}. It could be concluded that the hydrogen bond between OH of the surface and carboxyl group of the drug led to electron conjugation between carbonyl and other atoms [35].

Fig. 3 shows TG analysis of γ-alumina and 25% ibuprofen supported γ-alumina. γ-Al has totally about 7% weight loss up to 600 °C which is mainly related to missing of physical adsorbed water on the surface. TG curve of γ-Al-IBU25 nano drug indicated about 15% weight loss under 250 °C which is probably related to the evaporation of the adsorbed water molecules [36]. According to the literature, pure ibuprofen shows a thermogram

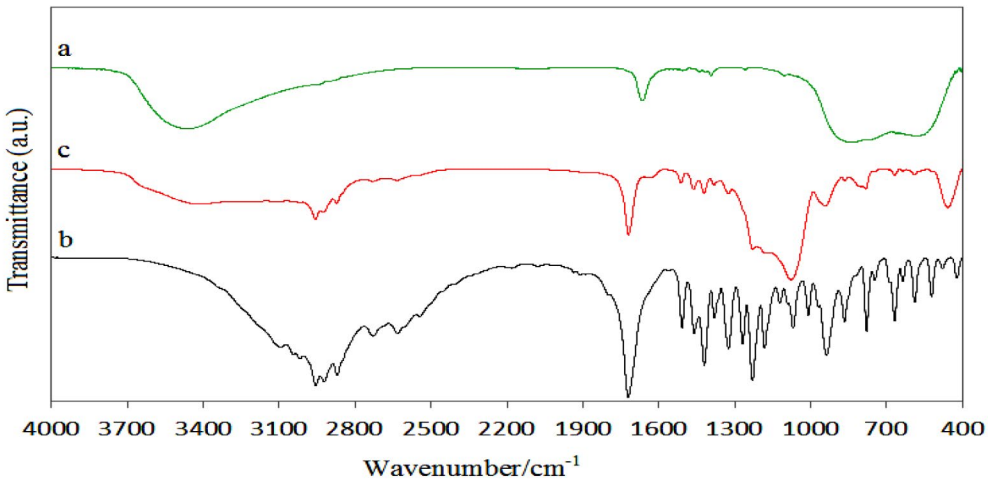

Fig. 2. FT-IR spectra of (a) γ-alumina (γ-Al), (b) ibuprofen (IBU) and (c) 25% ibuprofen supported γ-alumina (γ-Al-IBU25)

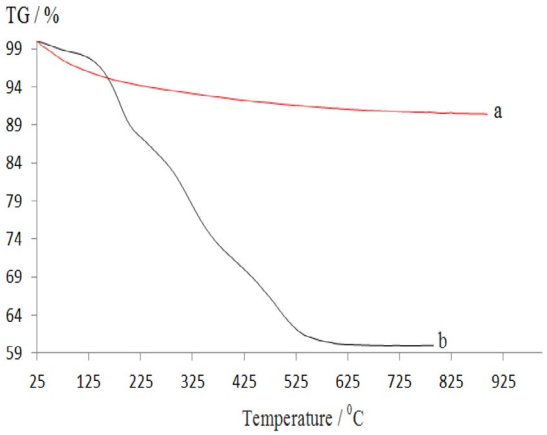

Fig. 3. TGA thermogram of (a) γ-alumina (γ-Al) and (b) 25% ibuprofen supported γ-alumina (γ-Al-IBU25)

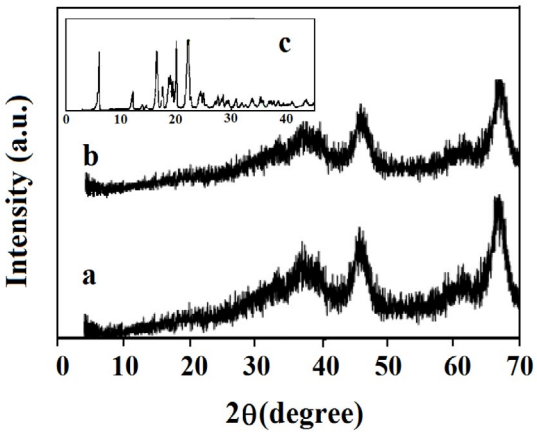

Fig. 4. XRD pattern (a) γ-alumina (γ-Al), (b) 25% ibuprofen supported γ-alumina (γ-Al-IBU25) and (c) ibuprofen

about 280 °C that is assigned to the evaporation of the drug. In this study, about 25% of weight loss between 250 to 600 °C could be observed. This result can prove that the drug has significant interaction with the support (Fig. 1 and 2). This weight loss is related to the combustion of the ibuprofen from the surface.

To verify that there is any bulk ibuprofen on the surface, it needs to take XRD of the γ-alumina and 25% ibuprofen supported γ-alumina on γ-alumina (with arbitrary unit for intensity) (Fig. 4). Pure γ-alumina (γ-Al) is almost amorphous with only background raised about 2θ = 38, 45 and 68° (Fig. 4a). By loading 25% of ibuprofen on γ-alumina no crystalline phase is observed on the alumina surface because the XRD pattern of γ-Al-IBU25 is unchanged. These results reveal again the fact that the bulk ibuprofen is disintegrated on the surface and has been distributed on the wall of the sol-gel derived alumina (Fig. 4b and c) [25].

In vitro tests

Pure ibuprofen has undesirable solubility in aqueous media [18]. Drug release profile was obtained during 72 h in the standard simulated fluids of SBF, SIF and SGF. Fig. 5a and 5b exhibits the release profile of 25 and 50% ibuprofen supported γ-alumina (γ-Al-IBU25 and γ-Al-IBU50) in SBF. Two mentioned nano drugs showed 80 and 74% of drug release after 15 min respectively. By reaching the soaking time up to 4 h, the release extent reaches to 90 and 86% respectively. The two samples firstly showed initial burst effect because ibuprofen has weak hydrogen interaction with the support. The release process occurs by ibuprofen diffusion from nano pores into the simulated solutions. As

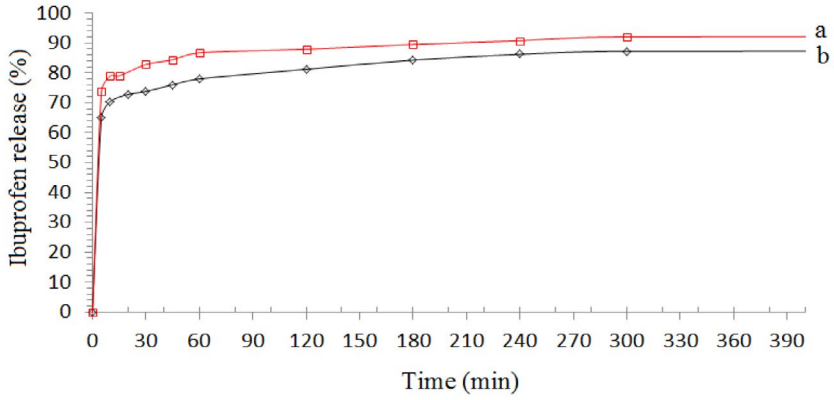

Fig. 5. Release profiles for 25 and 50% 25% ibuprofen supported γ-alumina in SBF (a) γ-Al-IBU25 and (b) γ-Al-IBU50

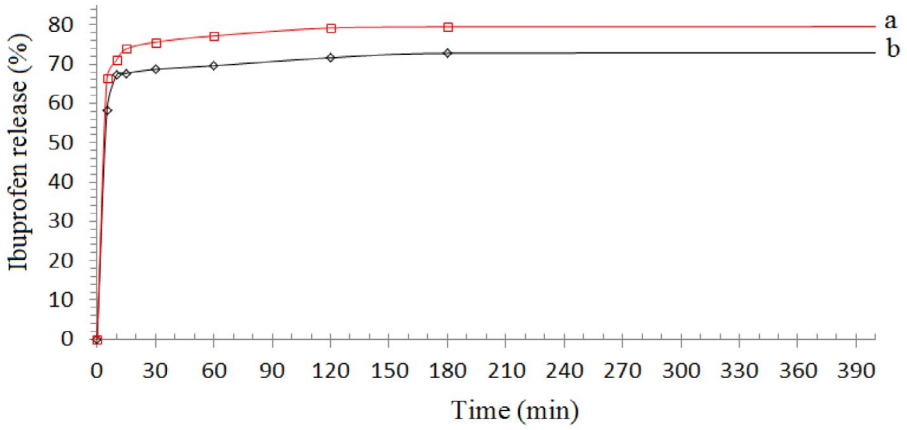

Fig. 6. Release profiles for 25 and 50% ibuprofen supported γ-alumina in SIF (a) γ-Al-IBU25 and (b) γ-Al-IBU50

can be seen, γ-Al-IBU25 revealed higher drug release percent compared to γ-Al-IBU50. Because, ibuprofen at lower loading (γ-Al-IBU25) has higher extent of interaction with γ-alumina (219.99 m^2/g surface area and 17.432 nm of pore diameter) compared to γ-Al-IBU50 sample. There are two interaction options for the drug molecules. One is intermolecular force between drug-drug molecules and another is the drug-support interactions. These two forces compete with each other when the amount of loading changes and further directly affect release profile. Evidently, 25% of ibuprofen loading has lower intermolecular interaction compared to the 50%, therefore, higher amount of the drug could be released into the simulated fluids.

The same process repeated for γ-Al-IBU25 and γ-Al-IBU50 in SIF (Fig. 6). Two distinct profiles could be observed in this figure. The two nano drugs showed 73 and 67% of drug release after 15 min of soaking time. By continuing the release process up to 4 h, the release percent reaches to 79 and 73% respectively. Fig. 7 indicates release curves of γ-Al-IBU25 and γ-Al-IBU50 in acidic SGF. In the first 15 min of the release time, γ-Al-IBU25 and γ-Al-IBU50 indicated 54 and 41% of release, and finally diffusion of ibuprofen into SGF reaches to 62 and 57% from the nano porous alumina after 4 h respectively. Low amount of release in SGF could be related to the acidic character of this simulated fluid and presence of the carboxylic group in the ibuprofen formula. It causes lowering the solubility. It seems that the new formulation could act as a pH responsive system.

Highly protonation of heteroatom on the ibuprofen molecule which is made by sol-gel alumina demonstrates that the mentioned alumina is a good candidate for the formulation of ibuprofen. On the other hand, commercial alumina

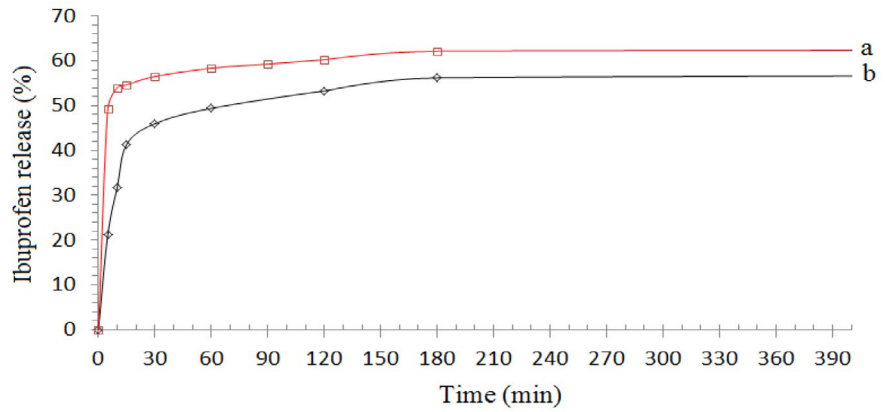

Fig. 7. Release profiles for 25 and 50% ibuprofen supported γ-alumina in SGF (a) γ-Al-IBU25 and (b) γ-Al-IBU50

has surface area of 190 m^2/g and pore diameter between 2 to 7 nm which is lower than synthetic alumina (220 m^2/g; 17 nm). Higher surface area of the sol-gel alumina causes dispersion of the drug on the surface and leads to higher interaction of the drug with the surface hydroxyl groups which results in an increase in disintegration between drug molecules and further enhancement on the solubility of ibuprofen. Higher pore diameter in sol-gel alumina diminishes the blockage of the channels and all of the capacity of the carrier could be utilized for hosting the drug molecules [37,38]. This effect, also, increases the probability of disintegration phenomena and increases the extent of the release. 90% of release of ibuprofen (after 4 h in SBF) from sol-gel alumina is affected substantially by the two mentioned parameters while the reported amount of release from commercial alumina is only 25% after the same release time [31,32]. It could be concluded that the results obtained in this study clearly show the importance of the synthetic nano carrier characteristics.

CONCLUSIONS

Formulation of ibuprofen, substantially affect the releasing profile. Although commercial and sol-gel derived alumina have the same formula, but the latter comprise higher pore volume, pore diameter, surface area, surface acid-base property and hydroxyl density than commercial alumina. In this study, low soluble ibuprofen was encapsulated into the nano porous sol-gel derived alumina. 25 and 50% of drug loading led to the γ-Al-IBU25 and γ-Al-IBU50 samples. After the characterization of the samples, they exhibited different release profile in SBF, SIF and SGF. 90% of release was obtained for γ-Al-IBU25 in SBF after 4 h. This result is superior than commercial alumina as a support (with lower surface area and pore diameter) only with 25% release in the same time.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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