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Ultrasonic Formation of Copper/Iron Graphene Oxide for Ketorolac Delivery

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New accessible sonochemical methods were developed for the functionalization of synthesized graphene oxide (GO) with copper/iron compounds and drug intercalation into their structure in aqueous solution at ambient conditions by using ultrasound (20 kHz) treatment. The sonochemical formation mechanism of a new nanomaterial was revealed through the structural analysis of three types of nanocomposites: (i) copper@graphene oxide, (ii) copper/iron@-graphene oxide and (iii) iron@graphene oxide. Unique copper/iron-modified graphene oxide nanocomposites can be used as nanocarriers for the anti-inflammatory drug (ketorolac) delivery in aqueous solution due to the reduced submicron size and enlarged surface area. Disintegration of the ultrasonically intercalated ketorolac followed the exponential decay curve fit at higher pH values of the aqueous solution with a higher decay constant observed in copper/iron-modified graphene oxide nanocomposites.

Keywords: Sonochemistry; graphene oxide; nanocomposite; NSAID; drug delivery.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications worldwide to treat the inflammation and pain, thereby reducing fever and inhibiting a thrombocyte aggregation. Among many NSAIDs, ketorolac is the most potent and effective analgesic to be used after surgery with efficacy comparable to opioids. However, when the drug is delivered to the human body through the gastro-intestinal system,

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the latter undergoes bleeding and develops gastritis after repeated doses of ketorolac over prolonged duration. Much research efforts are being put toward administration of ketorolac at a lower dose while maintaining its therapeutic efficacy.

The anti-inflammatory activity of NSAIDs can be enhanced through the formation of Cu(II) complexes with drugs functionalized with the carboxylate group acting as a bridging bidentate ligand involving Cu–O and Cu–Cu bonds in the complexes involving enzyme superoxide dismutase (SOD). The complexation of NSAIDs with Fe(II) among other materials leads to the scavenging of free radicals (including oxygen) and results in an enhanced gastric protection.

Graphene oxide (GO) in its pristine or modified form can be used as a successful drug molecular carrier due to its high surface area, biocompatibility and a very rich surface chemistry providing carbonyl, epoxide and carboxyl groups. GO as a molecular carrier can improve the bioavailability of drugs and decrease the dose of administration due to surface modification and reduction of the particle size.

There is a powerful technique in nanotechnology to modify GO with copper/iron compounds and transform this system into smart molecular carrier for healthier ketorolac administration. This method is based on sonochemistry that arises from acoustic cavitation: the formation, growth and implosive collapse of bubbles in liquid subjected to ultrasound treatment. The interfacial region of these bubbles has a temperature of $\sim 10^3$ K, pressure of $\sim 10^8$ Pa and very high gradients of shear forces that can be used for a particle size reduction, chemical reduction/oxidation of Cu or Fe on the GO surface and drug intercalation.

The present paper aims at (i) illuminating sonochemistry as a nanotechnology tool for functionalization of GO with copper, copper/iron and iron compounds; (ii) intercalating ketorolac into these unique nanocomposites by ultrasound treatment (20 kHz, 18 W/cm^2); (iii) finding out parameters of the ketorolac disintegration in the aqueous phase by using its prominent Raman peak at 1328 cm^{-1}.

2. Results and Discussion

2.1. *Sonochemical formation of copper/iron-modified graphene oxide nanocomposites*

Graphene oxide nanoflakes were synthesized from graphite by using an improved Hummers method[1] [Fig. 1(a)]. The synthesized nanoflakes with a smooth morphology and submicron size were sonochemically modified with copper[2] [Fig. 1(b)], copper/iron [Fig. 1(c)] and iron [Fig. 1(d)] compounds.

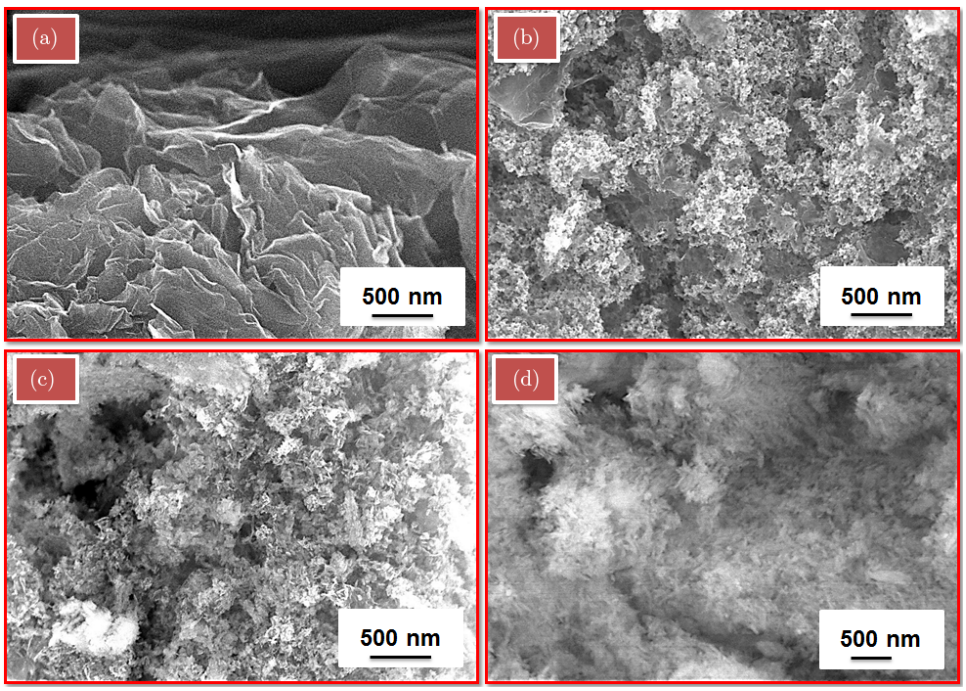

Fig. 1. Representative SEM images of (a) synthesized GO; and sonochemically prepared (b) copper-, (c) copper/iron- and (d) iron-modified@GO nanocomposites.

Copper@GO particles have an average diameter of ~ 600 nm [relative standard deviation (r.s.d.) $\approx$ 30%], copper/iron@GO particles acquire ~ 580 nm (r.s.d.$\approx$16%) and iron@GO particles obtain ~ 460 nm (r.s.d.$\approx$3%). Surface chemical composition and bonding of GO and its nanocomposites were investigated by XPS (Fig. 2).

Synthesized GO is composed of carbon- and oxygen-containing surface groups: carbonyl (R–C=O–R'), epoxide (R–C–O–C–R') and carboxyl (C(=O)OH) [Fig. 2(a)]. The surfaces of copper-@GO, copper/iron@GO and iron-@GO nanocomposites are enriched with carbon, oxygen and oxygen-containing compounds, indicating oxide phases on GO [Fig. 2(b)–2(d)].

The XPS analysis of Cu-2p lines reveals the main component peaks for the Cu^{+} [i.e., Cu(I)] in copper-@GO and copper/iron-@GO nanocomposites, attributing to $Cu^{2+}S^{2-}$, $Cu_2^{+}S^{2-}$, $Cu_2^{+}O^{2-}$ on the GO surface (curves B and C in Fig. 2). The presence of Cu^{2+} [i.e., Cu(II)] state demonstrates the formation of $Cu^{2+}S^{2-}$, $Cu^{2+}O^{2-}$ in the copper@GO nanocomposite (curves B in Fig. 2).

The XPS analysis of Fe-2p line in copper/iron@Go and iron@GO nanocomposites reveals a doublet implying the presence of hydrated iron oxide or ferric oxidation products (curves c and d in Fig. 2). This doublet may be indicative for $Fe^{2+}O^{2-}$, hematite α-Fe_2O_3, γ-Fe_2O_3 or hydroxyl-oxide FeO(OH) with an intermediate composition between goethite α-FeOOH and α-Fe_2O_3. Small satellite peaks (at ~ 719.8 eV and ~ 733.2 eV) appear only in copper/iron@GO nanocomposite, implying an existence of Fe^{3+} in FeO(OH) and Fe_2O_3.

2.2. *Sonochemical intercalation of ketorolac*

The anti-inflammatory drug ketorolac was intercalated in the GO and copper-, copper/iron- or iron-modified@GO nanocomposites by ultrasound treatment (3 min at 8 W/cm^2 and 20 kHz) in the

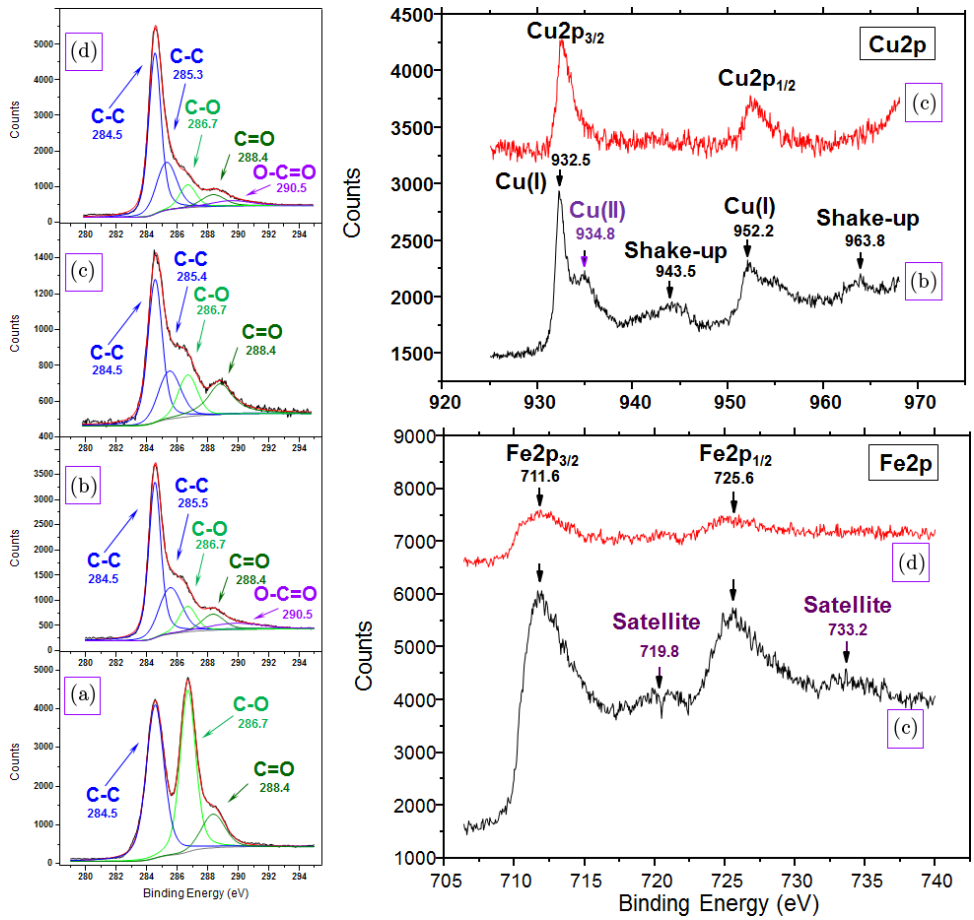

Fig. 2. XPS spectra of C-1s, Cu-2p and Fe-2p lines of (a) synthesized GO, (b) copper@GO, (c) copper/iron@GO and (d) iron@GO nanocomposites.

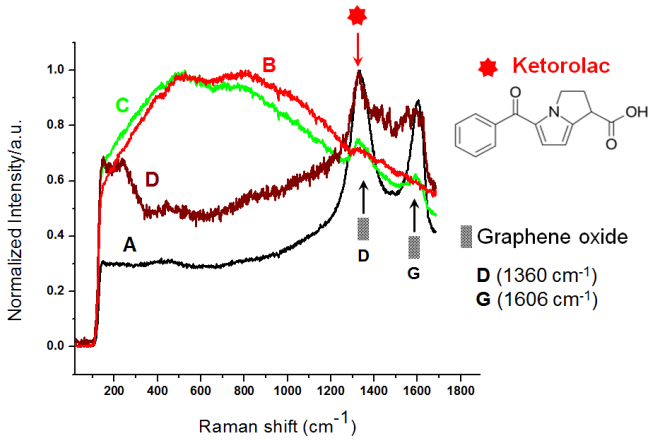

Fig. 3. Averaged representative Raman spectra of synthesized GO (A) and ketorolac powder (B) before sonication; and GO with ketorolac (C) and copper/iron@GO nanocomposite with ketorolac (D) after ultrasonic treatment in water. The arrows indicate the prominent Raman peak of ketorolac (1328 cm^{-1}) and the characteristic D and G Raman modes of GO (1360 cm^{-1} and 1606 cm^{-1}).

aqueous solution. The sonochemical intercalation of ketorolac was examined by Raman spectroscopy (Fig. 3).

Raman spectra reveal the most intense peak of ketorolac (1328 cm^{-1}) along with the two prominent D and G bands of GO in the copper/iron@GO nanocomposite after sonication. In contrast, these Raman peaks are weaker in GO after sonication with ketorolac, demonstrating higher intercalation efficiency in the copper/iron@GO nanocomposite.

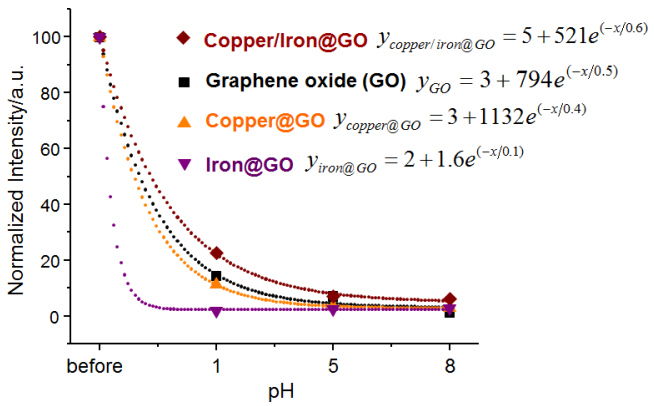

Fig. 4. Experimental data of normalized intensity at 1328 cm^{-1} in the aqueous solutions of GO, copper@GO, copper/iron@GO and iron@GO nanocomposites with intercalated ketorolac before and after incubation at pH = 1, 5 and 8. These data were fitted to exponential decay curves, revealing the decay constants to be 0.6 (copper/iron@GO), 0.5 (GO), 0.4 (copper@GO) and 0.1 (iron@GO), respectively.

2.3. *Ketorolac disintegration test*

We applied a disintegration test of ketorolac being sonochemically intercalated into GO, copper@GO, copper/iron@GO and iron@GO nanocomposites in aqueous solutions adjusted to the pH values of 1, 5 and 8. The drug disintegration was examined via the intensity decrease of the prominent Raman peak of ketorolac (1328 cm^{-1}) (Fig. 4).

Disintegration of the intercalated ketorolac occurred at higher pH values of aqueous solution and much faster from iron@GO nanocomposites.

3. Conclusion

New accessible sonochemical method was developed for the functionalization of graphene oxide with copper, copper/iron and iron compounds in aqueous solutions at ambient conditions. Unique nanocomposites can be sonochemically intercalated with the anti-inflammatory drug ketorolac. Among them copper/iron@GO can act as the most efficient nanocarrier due to effective intercalation of ketorolac into its structure and its much slower disintegration at high pH values of the solution.

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