Controlled Release of Alendronate from Nitrogen-Doped Mesoporous Carbon

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Abstract

We have synthesized a nitrogen doped mesoporous carbon with the BET surface area of 1066 m²/g, total pore volume 0.6 cm³/g and nitrogen content of 0.5 %. Total alendronate adsorption in this carbon was ~5%. The release experiments were designed in four different media with sequential pH values of 1.2, 4.5, 6.8 and 7.4 for 3, 1, 3 and 5 hours, respectively and at 37 °C to imitate the physiological conditions of stomach, duodenum, small intestine and colon, respectively. Release of the drug demonstrated a controlled fashion; only 20% of the drug was released in the media with pH=1.2, whereas 64% of the drug was released in pH=7.4. This is in contrary to pure alendronate that was completely dissolved within 30 minutes in the first release media (pH=1.2) only. The relatively larger uptake of alendronate in this carbon and its sustained fashion of release can be attributed to the hydrogen bonding between the drug and the nitrogen functionalities on carbon surface. Based on this result, it can be inferred that this formulation may lower the side effects of oral delivery of alendronate.

Keywords: Nitrogen doping, mesoporous carbon, alendronate, osteoporosis, controlled release

1. Introduction

Bisphosphonates are one type of synthetically produced drugs that are structurally similar to that of naturally occurring pyrophosphates. Alendronate and Zoledronate are two typical bisphosphonates, in which alendronate has the most common application in bone related problems. Alendronate is an aminobisphosphonate (figure 1) and it can suppress the activity of osteoclast cells thereby lowering the osteoclast-mediated bone resorption [1-5]. In addition to that, *in-vivo* and *in-vitro* studies proposed that bisphosphonates, like alendronate could possess osteo-stimulative properties [6,7] and mineralize nodules to help early osteoblastogenesis [8,9]. Recent studies demonstrated a possible relation between systematic usages of alendronate and avascular osteonecrosis of the jaw [10,11]. Alendronate has also shown a positive role in the treatment of intra-bony defects in patients with chronic periodontitis [12] or bone metastasis [13,14]. It is a well-prescribed medicine for osteoporosis, like post-menopausal osteoporosis, that causes bone weakening and easy fracturing of bones. Despite helpful effects in bone-related abnormalities, there are some severe side effects of this drug, especially for oral delivery. It causes severe burning in the esophagus followed by other gastro-intestinal problems [15]. It has been suggested that the patient should follow a strict regulation of staying upright for at least 30 minutes after taking this medication to minimize such effect. Besides that, it has very low bio-availability (~1 %) owing to poor absorption in the intestine [16,17] and rapid clearance from blood [18]. In order to enhance its total uptake, a higher dose is usually prescribed that cumulatively worsens the side effects.

Several passive formulations for alendronate delivery have been developed, but majority of them were focused in bio-ceramics for direct or local delivery towards rapid bone healing. Calcium phosphate or hydroxyapatite-based local delivery system for controlled release of alendronate has been reported successfully. The drug was directly loaded onto the bulk ceramic [19-21], functionalized with gelatin [22] or formulated with calcium phosphate and loaded into porous titanium [23]. Besides phosphates, silica based materials were quite popularly employed towards local delivery of alendronate. Ordered mesoporous silica [24,25] and aminopropyl [26] or phosphorous [27] doped silica were successfully developed for alendronate release. Different biocompatible polymeric materials were also developed for direct release of alendronate. Poly (lactic-co-glycolic acid) (PLGA) loaded hydroxyapatite microspheres were developed for control

release of alendronate for bone repair [28]; pure PLGA/alendronate formulations were also employed for dental applications [29]. Polyethylene glycol (PEG)-dendrimer and H₂N-PEG-dendrimer-(COOH)₄ based polymeric systems were successfully reported as combined carriers of alendronate and paclitaxel [30]. Different types of bisphosphonate carriers are discussed in the review [31]. In order to enhance the oral bioavailability of alendronate, Han et al. [32] employed chitosan-coated liposomes with 200 nm size that enhanced the cellular uptake of the drug in Caco-2 cells. These drug carriers increased the oral bioavailability by 2.6 times compared to free drug in rat-based animal model study.

In today's perspective, carbon-based drug carriers have gained lot of interests in biomedical platforms. Traditionally, activated carbon material was employed as a remedy for drug overdose or poison arrester upon accidental indigestion. Different carbon materials that have already demonstrated their potential role in controlled drug delivery are carbon nanotube, carbon dots or mesoporous carbons. Especially, mesoporous carbons have demonstrated a successful role in both bulk and nano forms [33,34]. Different research groups, including ours reported the control release of multitude of drugs from mesoporous carbon-based materials, including captopril [35,36], furosemide [36], ranitidine hydrochloride [37], ibuprofen [37], antipyrine [38,39] indomethacin [39] and others. Our recent study confirmed the biocompatibility of mesoporous carbon materials in terms of cytotoxicity with HeLa cell, cell viability with fibroblast cells, hemolysis, and protein adsorption results [40]. Our recent study also confirmed the benign nature of mesoporous carbons compared to nano-carbons through the measurement of reactive oxygen generation, Adenosine Triphosphate (ATP) depletion and cellular uptake through TEM visualization [41]. Motivated by the potential role of mesoporous carbons in controlled drug delivery, we have employed nitrogen doped mesoporous carbon in the controlled release of alendronate towards oral delivery.

2. Experimental

2.1 Synthesis of nitrogen doped mesoporous carbon

Nitrogen doped mesoporous carbons were synthesized from the modified procedures reported by Wei et al. [42] Typically, 5 g resorcinol and 5 g Pluronic F127 were dissolved in 30 cm³ solvent composed of 1:1 volumetric ratio of water and ethanol along with 0.6 cm³ 36% HCl. Upon mixing, 5 cm³ 37% formaldehyde solution was added as cross-linking agent and stirred for

3 hours. After that, 5 g dicyandiamide was added to the mixture and stirred for 48 hours. Then the mixture was separated from the solvent and cured at 200 °C for two hours in air and then put to carbonization in a porcelain boat in a tube furnace. In the course of carbonization, it was heated to 400 °C in 1 °C/min followed by 1000 °C at 2 °C/min and then cooled down to ambient temperature. In order to further activate the carbonized material, it is mixed solid KOH in 1:3 ratio and heated in nitrogen atmosphere up to 1000 °C in 5 °C/min and then cooled down to ambient temperature. All the heating and cooling operations are performed in nitrogen atmosphere. The activated carbon material was washed with DI water several times and then filtered and dried before any characterization.

2.2 Materials characterization

The mesoporous carbon was characterized with pore size distribution by N₂ adsorption-desorption at liquid nitrogen temperature (77 K) and CO₂ adsorption at 273 K, electron microscopy by TEM and SEM-EDX and thermal stability by thermogravimetric analysis (TGA). The N₂ and CO₂ adsorption-desorption measurements were performed in Quantachrome's Autosorb-iQ instrument. To maintain 273 K for CO₂ adsorption, a Julabo® temperature controller was employed with 1:1 mixture of water and propylene glycol as chilling fluid. N₂ adsorption at 77 K was employed to calculate Brunauer-Emmett-Teller (BET) surface area, whereas both N₂ and CO₂ adsorption were used to calculate pore size distribution by non-local density function theory (NLDFT) in instrument's built-in software. Thermogravimetric Analysis (TGA) was performed in TA instruments' SDT Q600 instrument. TEM images were captured in Carl Zeiss Libra 120 TEM operating at 120 kV. The scanning electron microscopy (SEM) imaging was performed in a Carl Zeiss Merlin SEM equipped with EDX facility.

2.3 Alendronate loading and release

In order to load (adsorb) alendronate onto nitrogen doped mesoporous carbon, 0.1 g of pure alendronate is dissolved onto 10 cm³ DI water adjusted with pH of 1.2 by HCl and then, 0.5 g of pure mesoporous carbon was added and stirred overnight. After that, the carbon is separated from the solution by filtration and quickly washed with DI water to remove alendronate that might have accumulated outside from the solution. The carbon was dried in oven at 100 °C overnight and used thereafter. The drug-loading amount was determined by comparing

thermogravimetric analysis (TGA) data of pure drug, pure carbon and drug-loaded carbons. During TGA study, all the materials were heated upto 105 °C for 3 minutes to eliminate effect of pre-loaded moisture or HCl.

In order to investigate the controlled release of alendronate from mesoporous carbons, all the release experiments were conducted for 0.1 g of alendronate loaded carbon in 50 mL release media at 37 °C. The pH and exposure time of the release media were sequentially set to 1.2, 4.5, 6.8 and 7.4 for 3, 1, 3, and 5 hours, respectively to mimic the physiological conditions of stomach, duodenum, small intestine and colon, respectively [39]. The medium with pH=1.2 (simulated gastric fluid, SGF) was composed of HCl and 1% NaCl without any enzyme. Rest of the pH was set by HCl adjustment only. At the specific time intervals, 2.5 cm³ of the release medium was withdrawn and replenished immediately with fresh release media. The collected sample was preserved for further analysis. After completing release medium of one pH, the carbon is separated, dried and inserted onto the next medium with corrected weight. All the runs were repeated thrice and the average values were reported with standard deviation.

Since alendronate is not UV active, it was derivatized for UV active component with ninhydrin according to a modified procedure reported by Sultana et al. [43] Typically, a reagent mixture was prepared by mixing 0.13 g ninhydrin and 0.085 g NaHCO₃ in 50 cm³ methanol and 10 cm³ DI water. 2.5 cm³ alendronate solution was mixed with 60 microliters of 10 M NaOH solution and then added with 3 cm³ reagent mixture followed by heating at 100 °C for 30 minutes. After that, the mixture was cooled, mixed with DI water to make the total volume upto 7.5 cm³ and analyzed in UV spectroscope. To study the release alendronate, a tablet of pure alendronate (0.1 g) was prepared in a machine press and the release experiments were performed in the same fashion. To collect the samples for pure alendronate, 13 microliters of release medium was mixed with 2.5 cm³ of stock solution and rest of the analysis protocols were same as that alendronate loaded carbons. For UV spectroscopic measurements, a calibration plot was made with the alendronate concentrations of 60, 50, 40, 30, 20, and 10 ppm with their corresponding absorbance values at the wavelength of 420 nm. The proposed reaction mechanism between alendronate and ninhydrin was similar to that of primary amine detection by ninhydrin and is given by

3. Results and Discussions

3.1 Materials characteristics

Nitrogen adsorption-desorption plot at 77 K of the carbon is shown in the inset of [figure 2](#). It is of type IV according to IUPAC classifications. The hysteresis loops is originated due to the condensation of the nitrogen in the mesopores. Brunauer-Emmett-Teller (BET) surface area of this carbon is 1066 m²/g. [Figure 2](#) represents the combined pore size distribution calculated by NLDFT theory from the nitrogen and carbon dioxide adsorption plots. In the narrow micropore region, it has the pore width in the range of 3.5, 5 and 7.85 Å. It has a distributed mesoporosity within the range of 20 to 90 Å. Despite similar protocol of synthesizing pure mesoporous carbons demonstrated a clear mesopore peak within the range of 50 to 60 Å in our past studies, such distorted mesoporosity might have been caused by the presence of dicyandiamide in the reaction mixture. The total pore volume of the carbons is 0.6 cm³/g. Thermogravimetric analysis (TGA) of this material ([figure S1](#), supporting information) demonstrated about 8% mass loss when heated in nitrogen atmosphere upto 1000 °C, which might have been caused by the dissociation of the oxygen and nitrogen containing functional groups from the carbon surface. SEM and TEM images ([figure 3](#)) reveal that the particles are irregular in shape and have a wide size distribution. Smaller particles are in the range of 1 to 1.5 μm, whereas the larger particles are within 200 μm. They have a rough surface topography and no ordered porosity is observed in high magnification SEM or TEM images. [Figure 3\(e\)](#) and [\(f\)](#) show the Energy Dispersive X-ray (EDX) image of the carbon; magenta and green dots show the presence of carbon and nitrogen atoms, respectively. A separate study on X-ray photoelectron spectroscopy (XPS) ([figure S2](#), supporting information) revealed that this mesoporous carbon has about 0.5 % nitrogen.

3.2 Alendronate loading and release

Alendronate loading amount was ~5 % as suggested by thermogravimetric analysis (TGA) and it was calculated by the comparing the char yield from pure carbon, pure alendronate and alendronate loaded carbon at the same temperature and in N₂ atmosphere. Alendronate release profile in four different release media is shown in [figure 4](#). Pure alendronate was completely dissolved in less than 30 minutes in the release media of pH=1.2 and hence could not be used for the rest of the media. On the contrary, alendronate from the mesoporous carbons exhibited a controlled release profile and it continued to release after 11 hours of starting the experiment in the pH of 7.4. In pH=1.2, the mesoporous carbon released only 20% of total release, followed by about 8-9% in pH=4.5 and 6.8. Largest release of about 64% took place in pH=7.4.

High loading of alendronate in this nitrogen doped mesoporous carbon as well as the largest release of this drug in the medium with highest pH may be attributed to the hydrogen bonding between alendronate and nitrogen functionalities on the carbon surface. As reported in the previous literature [24], it has been suggested that such hydrogen bonding may form between –OH or O⁻ groups of alendronate and N atoms or NH⁺ species present in the carbon surface. ([Scheme 1](#)). It can also be hypothesized that normal dispersive forces required for the physisorption of alendronate within the carbon materials may not be strong enough for the significant adsorption of drug and therefore, adsorption was not more than 1-2% in the relatively higher surface area carbons (not shown in this communication). On the contrary, nitrogen functionalities present in our material enhanced the adsorption more than double that of other carbons. The hypothesis on the hydrogen bonding may also be confirmed from the release pattern of drug. In lower pH, the hydrogen bonding was strong enough to hold the majority of alendronate molecules within the pore surface. At higher pH, such bonding turned weak or almost non-existing and hence majority of the drug molecules was released. The burst release or relatively higher release of alendronate in pH=1.2 (~20%) compared to two other pH (4.5 and 6.8) may be attributed to those alendronate molecules that were present near the pore mouth or not within the influence of hydrogen bonding. Although we did not perform an optimization study on nitrogen content that relates to the trade-off between higher alendronate loading versus controlled release profile, it is clear that very high nitrogen functionalities might have delayed

the release beyond the actual residence time of the carbon within the gastro-intestinal (GI) tract. As mentioned earlier, side effect of release of alendronate in stomach is quite severe; it causes severe burn and damage in the esophagus and the patients need to follow strict protocol upon taking this medication. As the release amount of alendronate from mesoporous carbon in pH=1.2 (stomach) is quite small compared to rest of the media (pH equivalent to that of intestine or colon), it can be argued that such formulation will cause less side effect for oral delivery compared to that of pure drug.

Higuchi kinetics [44] is one of the most common pharmacokinetics equations to model drug release rates and it is given by $a = kt^{\frac{1}{2}}$, where a is drug release amount, k is Higuchi rate constant and t is the release time. Rate constant k can be calculated by linear regression of a versus $t^{1/2}$. For alendronate release from mesoporous carbon, the Higuchi rate constant values were calculated as 0.0267, 0.0148, 0.0068, and 0.0488 (mg/g)($1/s^{1/2}$) for pH=1.2, 4.5, 6.8 and 7.4, respectively.

4. Conclusions

In this phase of research, we have synthesized nitrogen doped mesoporous carbons from resorcinol as carbon precursor, Pluronic F127 as structure dictating agent and dicyandiamide as nitrogen source. The resultant mesoporous carbon has BET surface area 1066 m²/g and total pore volume of 0.6 cm³/g. It has nitrogen content of 0.5 %. The particles are of irregular shape and the size varied within 1-200 μm. The alendronate loading amount in this carbon is 5 %, which is higher than other porous carbon materials with higher surface area. In a release experiment with four different pH values of 1.2, 4.5, 6.8 and 7.4, representing stomach, duodenum, small intestine and colon, respectively, it exhibited a much sustained release pattern compared to pure alendronate. Unlike pure alendronate that was completely dissolved in less than 30 minutes in pH=1.2, the mesoporous carbon released only 20% of the drug in this pH and maximum of amount of drug (64%) was released in pH=7.4. The higher uptake of alendronate in this nitrogen-doped mesoporous carbon and its delayed release may be attributed to the hydrogen bonding between the drug and nitrogen functionalities on the carbon surface. Based on the results, it can be hypothesized that such delayed release may decrease the side effects and strict protocol of

alendronate use in patients, although that requires much more rigorous studies with human subjects in future.

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6. References

- [1] G.A. Rodan, T.J. Martin, *Science* 289 (2000) 1508.
- [2] S. Colucci, V. Minielli, G. Zambonin, N. Cirulli, G. Mori, M. Serra, V. Patella, A. Zambonin Zallone, M. Grano, *Calcif. Tissue Int.* 63 (1998) 230.
- [3] H. Fleisch, *Drugs* 42 (1991) 919-944.
- [4] E.R. Van Beek, L.H. Cohen, I.M. Leroy, F.H. Ebetino, C.W.G.M. Löwik, S.E. Papapoulos, *Bone* 33 (2003) 805.
- [5] P.D. Miller, *Clin. Ther.* 27 (2005) 361
- [6] A. Goziotis, B. Sukhu, M. Torontali, M. Dowhaniuk, H. C. Tenenbaum. *Bone* 16 (1995) 317S-327S.
- [7] H. C. Tenenbaum, M. Torontali, B. Sukhu. *Bone* 13 (1992) 249-255.
- [8] C. Vitte, H. Fleisch, H. L. Guenther, *Endocrinology* 137 (1996) 2324-2333.
- [9] N. Giuliani, M. Pedrazzoni, G. Negri, G. Passeri, M. Impicciatore, G. Girasole, *Bone* 22 (1998) 455-461.
- [10] K. M. Soileau, *J Periodontol.* 77 (2006) 738-743.
- [11] H. L. Wang, D. Weber, L. K. McCauley, *J Periodontal* 78 (2007) 584-594.
- [12] A. Sharma, A.R. Pradeep, *J. periodontology* 83 (2012) 11-18.
- [13] E. Siris, R.S. Weinstein, R. Altman, J.M. Conte, M. Favus, A. Lombardi, K. Lyles, H. McIlwain, W.A. Murphy Jr., C. Reda, R. Rude, M. Seton, R. Tiegs, D. Thomson, J.R. Tucci, A.J. Yates, M. Zimering, *J. Clin. Endocrinol. Meta.* 81 (1996) 961.
- [14] P.P. Major, A. Lipton, J. Berenson, G. Hortobagyi, *Cancer* 88 (2000) 6.

- [15] F. Lanza, B. Sahba, H. Schwartz, S. Winograd, J. Torosis, H. Quan, R. Reyes, T. Musliner, A. Daifotis, A. Leung, *Am. J. Gastroen.* 97 (2002) 58.
- [16] R.G.G. Russell, M. J Rogers, *Bone* 25 (1999) 97.
- [17] A. Erza, G. Golomb, *Adv. Drug Deliver. Rev.* 42 (2000) 175.
- [18] F. Lanza, B. Sahba, H. Schwartz, S. Winograd, J. Torosis, H. Quan, R. Reyes, T. Musliner, A. Daifotis, A. Leung, *Am. J. Gastroen.* 97 (2002) 58.
- [19] C. W. Kim, Y. P. Yun, H. J. Lee, Y. S. Hwang, I. K. Kwon, S. C. Lee, *J. Controlled Release* 147 (2010) 45–53.
- [20] Z. Jindong, T. Hai, G. Junchao, W. Bo, B. Li, W. B. Qiang, *Orthopedics* 33 (2010).
- [21] H. Seshima, M. Yoshinari, S. Takemoto, M. Hattori, E. Kawada, T. Inoue, Y. Oda, *J Biomed. Mater. Res. B. Appl. Biomater.* 78 (2006) 215-221
- [22] S. Panzavolta, P. Torricelli, B. Braccia, M. Finib, A. Bigia, *J. Inorganic Biochemistry* 104 (2010) 1099- 1106
- [23] D. S. Garbuz, Y. Hu, W. Y. Kim, K. Duan, B. A. Masri, T. R. Oxland, H. Burt, R. Wang, C. P. Duncan, *J. Bone Joint Surg. Am.* 90 (2008) 1090-1100
- [24] F. Balas , M. Manzano , P. Horcajada , M. Vallet-Regí, *J. Am. Chem. Soc.* 128 (2006) 8116-8117
- [25] M. Vallet-Regí, M. Colilla, and I. Izquierdo-Barba, *J. Biomed. Nanotechnol.* 4 (2008) 1-15
- [26] A. Nieto, F. Balas, M. Colilla, M. Manzano, M. Vallet-Regí, *Microporous and Mesoporous Materials* 116 (2008) 4–13
- [27] M. Colilla, I. Izquierdo-Barba, M. Vallet-Regí, *Microporous and Mesoporous Materials* 135 (2010) 51–59
- [28] X. Shi, Y. Wang, L. Ren, Y. Gong, D. A. Wang, *Pharmaceutical Research* 26 (2009) 422-430
- [29] E. H. Nafea, M. A. El-Massik, L. K. El-Khordagui, M. A. Marei, N. M. Khalafallah, *J. Microencapsul.* 24 (2007) 525–538.
- [30] C. Clementi, K. Miller, A. Mero, R. Satchi-Fainaro, G. Pasut, *Mol. Pharmaceutics* 8 (2011) 1063–1072
- [31] A. Ezra, G. Golomb, *Adv. Drug Deliv.* 42 (2000) 175–195
- [32] H. K. Han, H. J. Shin, D. H. Ha, *European Journal of Pharmaceutical Sciences* 46 (2012) 500–507
- [33] X. Zhang, T. Zhang, Y. Ye, H. Chen, H. Sun, X. Zhou, Z. Ma, B. Wu, *European Journal of Pharmaceutics and Biopharmaceutics* 94 (2015) 30–41
- [34] J. Zhu, L. Liao, X. Bian, J. Kong, P. Yang, B. Liu, *Small* 8 (2012) 2715–2720.
- [35] D. Saha, E. A. Payzant, A. S. Kumbhar, A. K. Naskar, *ACS Appl. Mater. Interfaces* 5 (2013) 5868–5874.
- [36] D. Saha, K. E. Warren, A. K. Naskar, *Carbon* 71 (2014) 47–57.
- [37] X. Wang, P. Liu, Y. Tian, L. Zang, *Microporous Mesoporous Mater* 145 (2011) 98–103.
- [38] D. Saha, K. E. Warren, A. K. Naskar, *Microporous Mesoporous Mater* 196, (2014) 327–334.

- [39] D. Saha, T. Moken, J. Chen, D. K. Hensley, K. Delaney, M. A. Hunt, K. Nelson, A. Spurri, L. Benham, R. Brice, M. Azoro, RSC Adv. 5 (2015) 23699
- [40] M. F. Gencoglu, A. Spurri, M. Franko, J. Chen, D. K. Hensley, C. L. Heldt, D. Saha, ACS Appl. Mater. Interfaces 6 (2014) 15068.
- [41] D. Saha, C.L. Heldt, M. F. Gencoglu, K. S. Vijayaragavan, Jihua Chen, A. Saksule, Toxicology (under review)
- [42] J. Wei, D. Zhou, Z. Sun, Y. Deng, Y. Xia, D. Zhao, Adv. Funct. Mater. 23 (2013) 2322
- [43] S. Sultana, S. Talegaonkar, G. Mittal, A. Bhatnagar, F. J. Ahmad, Chromatographia 72 (2010) 321-326.
- [44] J. Siepmann, N.A. Peppas, Intl J. Pharmaceutics 418 (2011) 6-12.
- [45] <https://www.wavefun.com/products/spartan.html> (accessed March 2016)

Figure 1. Molecular structure of alendronate, stabilized ball and stick configuration by Spartan software [45], grey: carbon, white: hydrogen, blue: nitrogen, orange: phosphorous, red: oxygen (top), molecular formula (bottom). Colored picture is available in online version only.

Figure 2. Pore size distribution obtained from N_2 and CO_2 adsorption plot by non-local density function theory (NLDFT), Nitrogen adsorption-desorption on mesoporous carbons on carbons at 77 K (*inset*)

(a)

(b)

(c)

(d)

(e)

(f)

Figure 3. SEM images in low and high magnification (a and b), TEM images in low and high magnification (c and d), Energy dispersive results in x-ray (EDX) results for carbon (e) and nitrogen (f) in the mesoporous carbon. Colored picture is available in online version only.

Figure 4. Results of release experiments of alendronate from nitrogen-doped micro-mesoporous carbon in four different pH media to simulate gastro-intestinal conditions (red). Results were compared with pure alendronate (blue).

Scheme 1. Hypothetical scheme of adsorbed alendronate within the pore surface of carbon, stabilized by hydrogen bonding with the nitrogen species present on carbon surface

Graphical Abstract