

RSC Advances



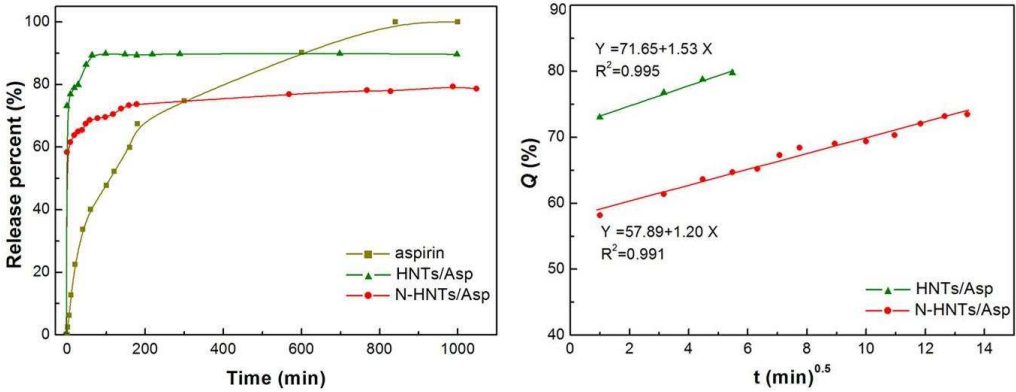
This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Graphical Abstract



Natural halloysite nanotubes modified as aspirin carrier

Huilin Lun, Jing Ouyang, Huaming Yang *

Department of Inorganic Materials, School of Minerals Processing and Bioengineering, Central South University, Changsha 410083, China

** Corresponding author. E-mail: hmyang@csu.edu.cn, Tel.: +86-731-88830549, Fax: +86-731-88710804.*

Abstract

Natural halloysite nanotubes (HNTs) modified with 3-aminopropyltriethoxysilane were performed as the aspirin carrier. The structure, drug loading and release profiles of samples were characterized by X-ray diffraction (XRD), thermogravimetry-differential scanning calorimetry (TG-DSC), transmission electron microscope (TEM), Fourier transform infrared spectroscopy (FTIR) and UV-spectrophotometer. Higuchi model $Q=kt^{0.5}$ was employed to analyze the dissolution data in details. The results indicated that the modification of HNTs could improve the amount of aspirin from 3.84 to 11.98 wt%. The physical state of aspirin was nanocrystal and amorphous affected by the confined space of HNTs, which significantly enhanced the dissolution rate created by a burst release within first hour. The linearity of Higuchi equation indicated that the aspirin release mechanism for modified HNTs was fitted to be Fick's diffusion and the dissolution rate was slower than that of natural HNTs. The as-synthesized N-HNTs could have interesting potential application in the drug carrier systems.

Keywords: Halloysite nanotubes (HNTs); Aspirin; Carrier; Nanocrystal; Dissolution

Introduction

Aspirin, one kind of slightly water-soluble drug, is widely used for the treatment of cardiovascular diseases and as a nonsteroidal anti-inflammatory drug.¹ The low rate of dissolution is the limiting factor for the drug absorption rate and it is not convenient to maintain effective concentration in the body. Alternative methods are used to achieve a higher solubility of these drugs, such as emulsification, solid dispersion approach, micronization, amorphous form and micro/nanoparticles of drugs.² With the amorphous or micro/nanoparticle formulation of these drugs, the rapid dissolution of drugs from synthetic mesoporous silica^{3,4} and amorphous microporous silica^{5,6} has attracted interest in controlled release applications. However, the preparation costs of these mesoporous materials are high, which severely limits their actual applications in the pharmaceutical industry.

Halloysite, a hydrated layered aluminosilicate of the kaolinite group, has a molecular formula of $\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4 \cdot 2\text{H}_2\text{O}$ and possesses hollow cylinders formed by multiple-rolled layers containing gibbsite octahedral sheet (Al-OH) groups on the internal surface and siloxane groups (Si-O-Si) on the external surface. Generally, tubular halloysite is approximately 0.02-30 μm long and has an inner lumen diameter of 10-100 nm⁷. Halloysite nanotubes (HNTs) recently have garnered interest in medicine and have been used in the drug delivery system of ibuprofen,⁸ vinyl alcohol,⁹ opioid fentanyl,¹⁰ chitosan,¹¹ and polypropylene amine,¹² due to its natural nanosized tubular structure, capability for drugs sustained release from its lumen, nontoxic,¹² biocompatible, less expensive and freely available. However, a drawback of using HNTs as drug carriers is relatively low loading capacity and the modification with specific functional groups is viable for

overcoming this drawback.^{8,13}

In this paper, the performance of HNTs modified by 3-aminopropyltriethoxysilane (APTES) as a carrier for aspirin was investigated. The effect of surface modification of HNTs on aspirin loading was studied, and the physical phase change and the dissolution properties of aspirin after loading onto modified HNTs were emphasized.

Experimental

Natural HNTs, obtained from Hunan, China, were washed with deionized water and dried at 60°C for 12h. The acetylsalicylic acid (aspirin, Aladdin) and 3-aminopropyltriethoxysilane (APTES) were A.R. grade. Deionized water was used throughout the experiment. HNTs modified by APTES (N-HNTs) were performed as follows: 4 mL of APTES was dissolved in 200 mL of dry toluene and then 5 g of HNTs was added with constant ultrasonic dispersion for 30 min. Evacuation pretreatment had to be carried out at this stage. The suspension was refluxed at 120°C for 20 h under constant stirring. In the refluxing system, a calcium chloride drying tube was attached to the end to ensure a dry environment. The solid phase in the resultant mixture was filtered and washed with toluene to remove the excess APTES and dried overnight at 120°C for further curing.

Aspirin-loaded HNTs composites were prepared as follows: 3 g of aspirin was dissolved in 100 mL of ethanol, and 2 g of HNTs (modified or natural) powders were then added with constant stirring for 12 h at room temperature. The solid part of the dispersion was separated by centrifugation, washed with ethanol to remove the excess aspirin and dried overnight at 60°C.

The aspirin-loaded modified sample was labeled as N-HNTs/Asp, while the aspirin-loaded natural HNTs sample was HNTs/Asp. The amount of aspirin loaded was measured using elemental analysis (Leco TCH-600 N/H/O and NCS CS-3000 analyzer). A mechanical mixture of N-HNTs and aspirin (85:15, w/w) was labeled as N-HNTs/Asp_{mix}.

The morphology of the samples was observed by a transmission electron microscope (TEM, JEOL IEM-200CX). X-ray diffraction (XRD) patterns were obtained by an X-ray diffraction apparatus (DX-2700) with an acceleration voltage of 40 kV and an emission current of 40 mA. Thermogravimetry-differential scanning calorimetry (TG-DSC) was performed in air using a NETZSCH STA449C thermal analyzer at a heating rate of 10 °C/min. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 5700 spectrophotometer using KBr pellets for samples. The element contents of the samples were analyzed by Leco TCH-600 N/H/O and NCS CS-3000 analyzer. The aspirin content (M_{Asp} , g Asp g⁻¹ halloysite) was calculated as $M_{\text{Asp}} = W_C/K$, where K is the content of C in aspirin, and W_C is the mass percentage of C in aspirin determined from the elemental analysis. Nitrogen adsorption-desorption isotherms were obtained at -196 °C, using a Micromeritics ASAP 2020. All the samples were vacuum-dried at 80 °C for 10 h prior to the measurements. The specific surface area was determined by the Brunauer-Emmett-Teller (BET) method and the total pore volume was obtained from the maximum amount of nitrogen gas adsorbed at a partial pressure, P/P_0 , above 0.99. The pore size distribution was calculated by the Barrett-Joyner-Halenda (BJH) method, using the nitrogen adsorption branch of the isotherm. The release profiles of aspirin were analyzed for aspirin with UV-vis spectroscopy (Unico UV-2600). Typically, 100 mg of known aspirin amount samples and pure aspirin crystal were

respectively placed in a 100 mL simulated intestinal fluid with pH = 6.8 and 37 °C in a beaker. The simulated intestinal fluid was phosphate buffer solution prepared by the mixture of 250 mL KH_2PO_4 (0.2M) with 118 mL of NaOH (0.2M). The contents were stirred at 200 rpm, and 4 mL aliquots were removed at intervals of time. The transparent supernatants were analyzed at wavelength 296 nm. After each measurement, the aliquots were conveyed back to the beaker.

Results and discussion

For XRD patterns of HNTs (Fig. 1), all of the observed diffraction peaks are indexed to the characteristic of halloysite (JCPDS 29-1487). After modification with APTES, the reflections of HNTs remain unchanged, indicating that the modification with APTES doesn't affect the structure of HNTs, which is in accordance with the observation that APTES is only grafted onto the surface hydroxyl groups of the internal surfaces, edges, and external surfaces of tubular halloysite.¹³ Obvious diffraction peaks of aspirin are detected at $2\theta = 7.8, 15.6, 16.8, 17.9, 22.6, 27.1, 31.4$ and 32.6 ¹⁴ in N-HNTs/Asp_{mix}. Three new peaks are observed at $2\theta = 16.5, 17.9$ and 22.6 in HNTs/Asp and N-HNTs/Asp belonging to the aspirin characteristic diffraction peaks, indicating the existence of aspirin in resultant substance. However, the intensity of reflections of aspirin in N-HNTs/Asp is lower than that of the N-HNTs/Asp_{mix}. The aspirin stored in the HNTs is supposed to be amorphous or nanocrystal according to the previous report on amorphous and nanocrystal state formation about ibuprofen in mesoporous silica.¹⁵

Through the DSC analysis of HNTs (Fig. 2), a weak endothermic valley at about 69°C is attributed to the evaporation of adsorbed water.¹⁶ The crystal aspirin exhibits a clear endothermic

peak at 141 °C, which is characteristic of the melting of the bulk phase of aspirin.¹⁷ A small endothermic peak at 127°C of N-HNTs/Asp shows a reduction in the enthalpy of fusion. After the calculation for enthalpy change (ΔH) according to the DSC thermal analysis,¹⁸ the ΔH of pure aspirin is 2.50 J/g, while the ΔH of aspirin in N-HNTs/Asp is 0.31 J/g, which indicates the decrease in crystallinity of the drug and also suggests partial amorphous formation.¹⁵ The endothermic peak of N-HNTs/Asp shifts to a lower temperature due to the Gibbs-Thomson effect in a confined environment. Similar results are obtained for vaporization of a liquid confined into the HNT cavity.¹⁹

N content (wt %) of N-HNTs is around 0.22 after modified with APTES (Table 1) and the C/N molar ratio is around 3.71, which is almost consistent with that of 3-aminopropyl groups (the C/N molar ratio is 3.00). Meanwhile, after aspirin loading, the C content (wt %) of N-HNTs/Asp obviously increases from 2.30 (before loading) to 7.89 and this proves the successful loading of aspirin molecules. The aspirin content of HNTs/Asp and N-HNTs/Asp is 3.84 and 11.98, respectively, which indicates that the modification of HNTs by APTES could promote the loading of aspirin.

N₂ adsorption-desorption isotherms of samples (Fig. 3) exhibit type II with distinct type *H3* hysteresis loop in the relative pressure (P/P_0) and this type of isotherm is a typical characteristic of mesoporous and macropores structures.²⁰ After modification with APTES, the BET specific surface area and pore volume of HNTs decrease from 59.12 m²/g and 0.24 cm³/g to 42.44 m²/g and 0.17 cm³/g (Table 2), respectively, suggesting the presence of aminopropyl groups on the surface of pore channels. After loading of aspirin, HNTs/Asp and N-HNTs/Asp show lower

values of BET specific surface area and pore volume ($56.85 \text{ m}^2/\text{g}$ and $0.17 \text{ cm}^3/\text{g}$ for N-HNTs, and $27.29 \text{ m}^2/\text{g}$ and $0.13 \text{ cm}^3/\text{g}$ for N-HNTs/Asp, respectively). These results are further confirmed by the observation from their pore size distribution (inserted in Fig. 3). The pores of HNTs are center at about 3 and 18 nm. The 3 nm can be ascribed to mesopores that are newly formed during dehydration of HNTs⁸ and the 18 nm are identified as the lumen pores of HNTs. The intensity of these pore sizes is weaker after loading of aspirin, indicating loading of aspirin molecules in the pore channels.

The TEM images (Fig. 4a and b) show the tubular structure of HNTs with lumens ranging from about 10 to 20 nm. After modification with APTES, the tubular structure of HNTs has not changed (Fig. 4c). Fig. 4d shows the lumens of N-HNTs are blocked by aspirin particles. Aspirin can be anchored on N-HNTs by electrostatic attraction between the carboxylate of aspirin and the aminopropyl groups.⁸ The discontinuous loading of aspirin in the lumen may be due to the incomplete removal of air from the lumen (Fig. 4d). The filling of aspirin in the lumen of halloysite is driven by capillary forces as reported.²¹ The aspirin-ethanol solution is probably driven into the lumen by these powerful capillary forces and form aggregates in the lumen. The TEM observations also indicate some aspirin crystals load onto the external surface of N-HNTs (denoted by the arrow in Fig. 4d). Aspirin crystallites of this type are deposited at the surface of HNTs through hydrogen bonding or van der Waals force between the surface hydroxyl group or the siloxane group of HNTs and the carboxyl group of the aspirin.²² The state of the aspirin crystallites in the lumen of HNTs could be evaluated on the basis of the study by Sliwiska-Barttkowiak et al.²³ Based on this study, considering the molecular size of aspirin (0.8

nm $\times$ 0.6 nm¹⁷) and the lumen diameter of HNTs (10 to 20 nm), it could be anticipated that the aspirin in the lumen of HNTs coexisted in nanocrystal and amorphous states.

HNTs possess some obvious signals, such as deformation vibrations of Si-O-Si and Al-O-Si at 468 and 560 cm⁻¹, and inner Si-O stretching vibration at 1039 cm⁻¹ (Fig. 5). The intensity of O-H deformation vibration of the inner hydroxyl groups is at 911 cm⁻¹.²⁴ The weak band at 1635 cm⁻¹ is attributed to O-H deformation vibration of the adsorbed water. HNTs also exhibit the O-H stretching vibration of inner-surface Al-OH groups and inner Al-OH groups at 3696 and 3626 cm⁻¹, respectively. After the functionalization of HNTs with APTES, the broad band at 3372 cm⁻¹ is attributed to the N-H₂ asymmetric stretching vibration. The peak at 2920 cm⁻¹ is assigned to the symmetric stretching vibration of -CH₂. The peak at 1305 cm⁻¹ can be assigned the stretching vibration of C-N band. All of these observations prove the presence of the APTES in the functionalized HNTs.²⁵ Compared to N-HNTs, the IR spectrum of N-HNTs/Asp displays a distinct band at 1751 cm⁻¹ originated from C=O stretching vibration according to the IR spectrum of aspirin. Especially, two new bands at 1486 and 1622 cm⁻¹ are respectively from antisymmetric and symmetric stretching vibration of a carboxylate form of aspirin.¹⁷ All these bands are ascribed to aspirin molecules, indicating that the aspirin molecules have been adsorbed on the N-HNTs after drug loading.

A release burst occurs within first hour of both HNTs/Asp and N-HNTs/Asp systems (Fig. 6), while the dissolution rate of aspirin is low. HNTs/Asp delivery system exhibits 89 wt% of aspirin in the initial release stage within first hour, and the release process stops over a period of 100 min. N-HNTs/Asp delivery system exhibits 68 wt% of aspirin in the initial release stage within first

hour, and the release process nearly stops over a period of 600 min. However, for aspirin, only 40 wt% is released within first hour, and it takes about 200 min to reach 68 wt%. Obviously, the drug release from N-HNTs/Asp is faster than that from aspirin, especially during the release burst within first hour. The same effect has happened to the matrix of HY zeolites showing initial burst rates of aspirin release with nearly 50% within first hour,¹⁷ which could be advantage for actual application because the low dissolution rate is the limiting factor for the drug absorption rate and it is not convenient to maintain effective concentration in the body. The difference in aspirin release rate might be due to the nanocrystal and amorphous state of aspirin, which is in agreement with that the dissolution rate of crystalline form of ibuprofen is lower than the amorphous form.¹⁵

In this study, the release data is fit using a Higuchi kinetic model. Higuchi model is governed by Fick's diffusion and can be described using a simplified model, $Q=kt^{0.5}$, where Q is the amount of drug release, k is the Higuchi rate constant, and t is the time. The Higuchi equation has been used to describe the release of drug from functionalized mesoporous materials.²⁶ The amount of aspirin released is plotted against the square root of time and a linear regression is used to fit the data, with the origin included among the data (Fig. 6). It can be seen that the linear regression is obeyed only for release values lower than 80%, *i.e.*, this would be a threshold limit for valid application of the Higuchi's model.²⁶ The linearity of the amount of aspirin release Q ($Q<80\%$) versus $t^{0.5}$ in the Higuchi model of HNTs/Asp and N-HNTs/Asp is in Fig. 7. The linear correlation of HNTs/Asp and N-HNTs/Asp are found to be Fick's diffusion. A decrease of the rate constant brought about by functionalizing HNTs is found, and this effect is dependent upon the aminopropyl groups used in the process. As aminopropyl group is more basic than OH, the

chemical interaction of aminopropyl with COOH of aspirin is stronger than OH with COOH.²⁷ The implanting of aminopropyl groups at the HNTs surface creates an electrostatic attraction between HNTs with aspirin,⁸ which decreases the rate constant from 1.53 ± 0.10 to 1.20 ± 0.05 .

A schematic representation of aspirin loading on HNTs (especially the internal lumen surface) is shown in Fig. 8. The surface of HNTs is fully covered of hydroxyl group. After modification with APTES, the N-HNTs surface is covered by aminopropyl groups of APTES. Aspirin is anchored on the surface of N-HNTs by electrostatic attraction between the carboxylate of aspirin and the aminopropyl groups.⁸ N-HNTs have a stronger affinity (electrostatic attraction) to aspirin, which leads to a higher loading of aspirin in N-HNTs. Besides, on the external surface of HNTs, aspirin is weakly anchored through hydrogen bonding or van der Waals force between the surface hydroxyl group or the siloxane group of HNTs and the carboxyl group of the aspirin.²² The aspirin molecules in solution are further bonded with the anchored aspirin by hydrogen bonding to form hydrogen-bonded aggregates in the lumen surface of HNTs.⁸ Some of these aggregates are nanocrystal and some of them are in amorphous state contributing to the fast dissolution than aspirin.

Conclusions

Natural halloysite nanotubes (HNTs) with pore ranging from 10 to 20 nm are used as carrier of a slightly water-soluble model drug (aspirin). The results indicate that the modification of HNTs could improve the amount of aspirin from 3.84 to 11.98 wt%. The obtained N-HNTs/Asp significantly enhances the dissolution rate by creating a burst release with first hour compared

with the aspirin. The physical state of aspirin is affected as aspirin molecules are entrapped inside the confined space of channels. Nanocrystal and amorphous aspirin could be formed inside HNTs, which significantly enhance the dissolution rate. The linearity of Higuchi equation indicates that the release mechanism for N-HNTs/Asp is fitted to be Fick's diffusion, and the dissolution rate is slower than that of HNTs/Asp. The as-synthesized N-HNTs could have interesting potential application in the drug carrier systems.

Acknowledgments

This work was supported by the National Science Fund for Distinguished Young Scholars (51225403), the Hunan Provincial Natural Science Fund for Innovative Research Groups, the Specialized Research Fund for the Doctoral Program of Higher Education (20120162110079) and the Fundamental Research Funds for the Central Universities of Central South University (2014zzts274).

References

1. F. Catella-Lawson, M. P. Reilly, S. C. Kapoor, A. J. Cucchiara, S. Demarco, B. Tournier, S. N. Vyas and G. A. Fitzgerald, *New Engl. J. Med.*, 2001, **345**, 1809
2. D. J. A. Crommelin, G. Storm, W. Jiskoot, R. Stenekes, E. Mastrobattista and W. E. Hennink, *J. Controlled Release*, 2003, **87**, 81
3. R. Mellaerts, C. A. Aerts, J. Van Humbeeck, P. Augustijns, G. Van den Mooter and J. A. Martens, *Chem. Commun.*, 2007, 1375
4. F. Wang, H. Hui, T. J. Barnes, C. Barnett and C.A. Prestidge, *Mol. Pharm.*, 2009, **7**, 227
5. C. A. Aerts, E. Verraedt, A. Depla, L. Follens, L. Froyen, J. Van Humbeeck, P. Augustijns, G. Van den Mooter, R. Mellaerts and J. A. Martens, *Int. J. Pharm.*, 2010, **397**, 84

6. E. Verraedt, M. Pendela, E. Adams, J. Hoogmartens and J. A. Martens, *J. Controlled Release*, 2010, **142**, 47
7. G. J. Churchman, T. J. Davy, L. A. G. Aylmore, R. J. Gilkes and P. G. Self, *Clay Miner.*, 1995, **30**, 89
8. D. Y. Tan, P. Yuan, F. Annabi-Bergaya, H. G. Yu, D. Liu, H. M. Liu and H. P. He, *Micropor. Mesopor. Mat.*, 2013, **179**, 89
9. W. Y. Zhou, B. C. Guo, M. X. Liu, R. J. Liao, A. B. M. Rabie, D. Jia and J. Biomed. *Mater. Res. A*, 2009, **93**, 1574
10. J. Forsgren, E. Jämstorp, S. Bredenberg, H. Engqvist and M. Strømme, *J. Pharm. Sci.*, 2010, **99**, 219
11. M. X. Liu, Y. Shen, P. Ao, L. B. Dai, Z. H. Liu and C. R. Zhou, *RSC Adv.*, 2014, DOI: 10.1039/C4RA02189D
12. N. G. Veerabadran, D. Mongayt, V. Torchilin, R. R. Price and Y. M. Lvov, *Macromol. Rapid Commun.*, 2009, **30**, 99
13. P. Yuan, P. D. Southon, Z. W. Liu, M. E. R. Green, J. M. Hook, S. J. Antill and C. J. Kepert, *J. Phys. Chem. C*, 2008, **112**, 15742
14. C. Aubrey-Medendorp, S. Parkin and T. Li, *J. Pharm. Sci.*, 2008, **97**, 1361
15. S. C. Shen, W. K. Ng, L. Chia, J. Hu and R. B. H. Tan, *Int. J. Pharm.*, 2011, **410**, 188
16. P. Yuan, D. Y. Tan, F. Annabi-Bergaya, W. C. Yan, M. D. Fan, D. Liu and H. P. He, *Clays Clay Miner.*, 2012, **60**, 557
17. A. Datt, D. Fields and S. C. Larsen, *J. Phys. Chem. C*, 2012, **116**, 21382
18. C. C. Li, L. J. Fu, J. Ouyang and H. M. Yang, *Sci. Rep.*, 2013, **3**, 1908
19. G. Cavallaro, G. Lazzara and S. Milioto, *J. Phys. Chem. C*, 2012, **116**, 21932
20. J. Jin, Y. Zhang, J. Ouyang and H. M. Yang, *Phys. Chem. Miner.*, 2014, **41**, 323
21. D. D. Mei, B. Zhang, R. C. Liu, Y. T. Zhang and J. D. Liu, *Sol. Energy Mater. Sol. Cells*, 2011, **95**, 2772
22. C. Aguzzi, P. Cerezo, C. Viseras and C. Caramella, *Appl. Clay Sci.*, 2007, **36**, 22
23. M. Sliwinska-Bartkowiak, G. Dudziak, R. Sikorski, R. Gras, R. Radhakrishnan and K. E. Gubbins, *J. Chem. Phys.*, 2001, **114**, 950

24. C. C. Liu, L. Yu, Y. T. Zhang, B. Zhang, J. D. Liu and H. Q. Zhang, *RSC Adv.*, 2013, **3**, 13756
25. Y. Zhang, X. He, J. Ouyang and H. M. Yang, *Sci. Rep.*, 2013, **3**, 2948
26. J. C. Doadrio, E. M. B. Sousa, I. Izquierdo-Barba, A. L. Doadrio, J. Perez-Pariente and M. Vallet-Regí, *J. Mater. Chem.*, 2006, **16**, 462
27. B. Muñoz, A. Rámila, J. Pérez-Pariente, I. Díaz and M. Vallet-Regí, *Chem. Mater.*, 2003, **15**, 500

Table 1 Elemental analysis data of different samples

Samples	C (wt %)	Content of aspirin (wt %)	N (wt %)	Molar ratio of C/N
N-HNTs	0.70	—	0.22	3.71
HNTs/Asp	2.30	3.84	—	—
N-HNTs/Asp	7.89	11.98	—	—

Table 2 Pore characteristics of different samples

Samples	BET surface area (m ² /g)	Pore volume (cm ³ /g)
HNTs	59.12	0.24
HNTs/Asp	56.85	0.23
N-HNTs	42.43	0.17
N-HNTs/Asp	27.29	0.13

Figures captions:

Fig. 1 XRD patterns of different samples

Fig. 2 DSC curves of different samples

Fig. 3 Nitrogen gas adsorption-desorption isotherms and pore size distributions (inserted) of different samples

Fig. 4 TEM images of (a) HNTs, (b) single tube of HNTs, (c) N-HNTs and (d) N-HNTs/Asp

Fig. 5 FTIR spectra of different samples

Fig. 6 Drug release profiles of different samples

Fig. 7 Amount of aspirin release (Q) vs $t^{0.5}$ for different samples according to the Higuchi model $Q=k_H t^{0.5}$

Fig. 8 Schematic representation of aspirin loading on HNTs.

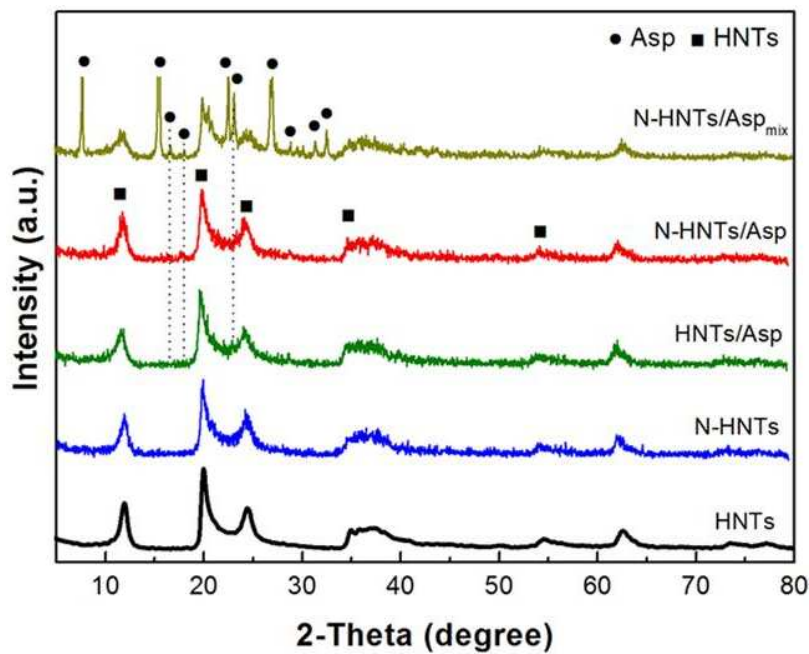


Fig. 1 XRD patterns of different samples

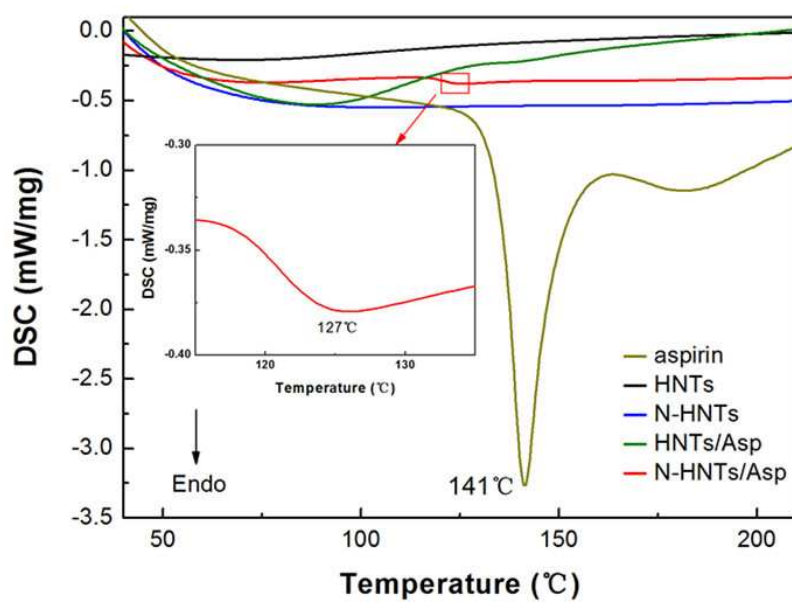


Fig. 2 DSC curves of different samples

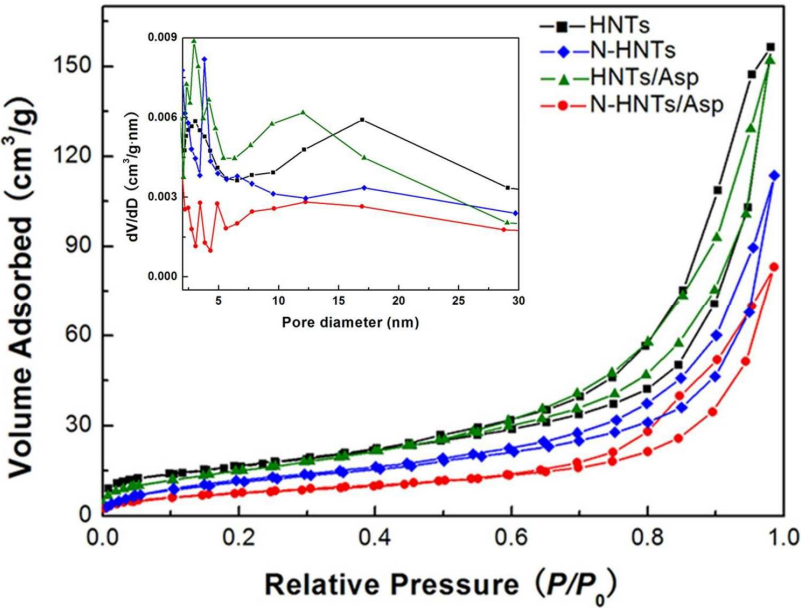


Fig. 3 Nitrogen gas adsorption-desorption isotherms and pore size distributions (inserted) of different samples

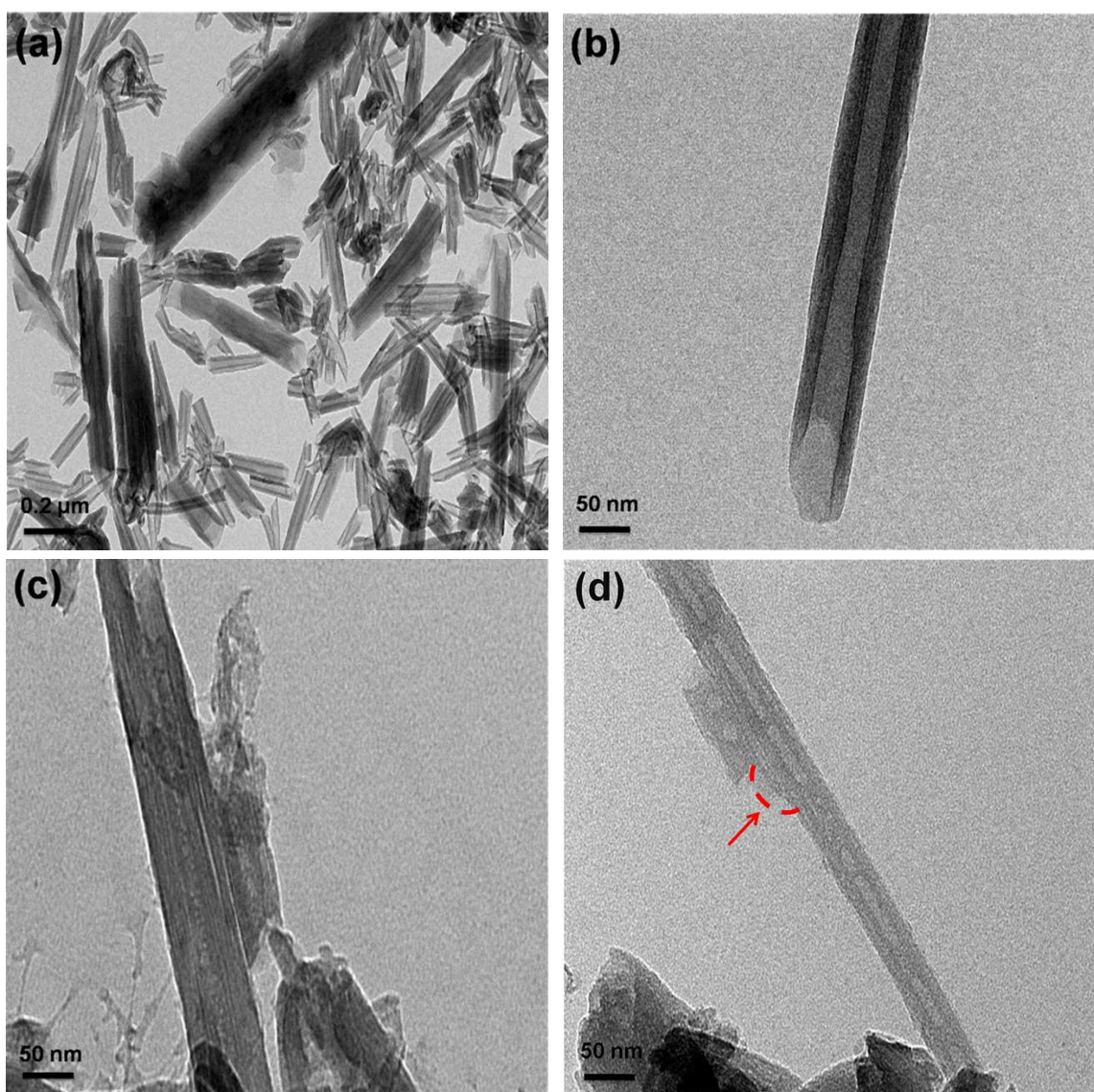


Fig. 4 TEM images of (a) HNTs, (b) single tube of HNTs, (c) N-HNTs and (d) N-HNTs/Asp

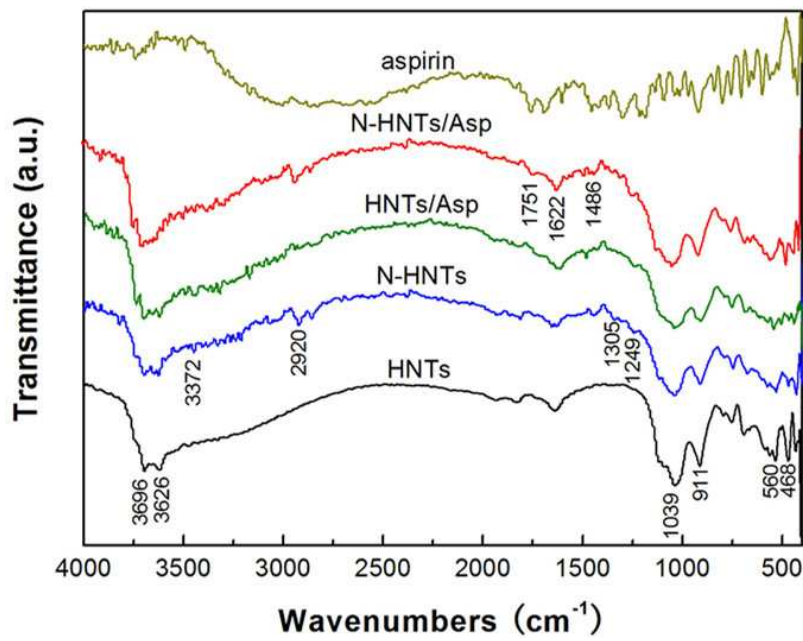


Fig. 5 FTIR spectra of different samples

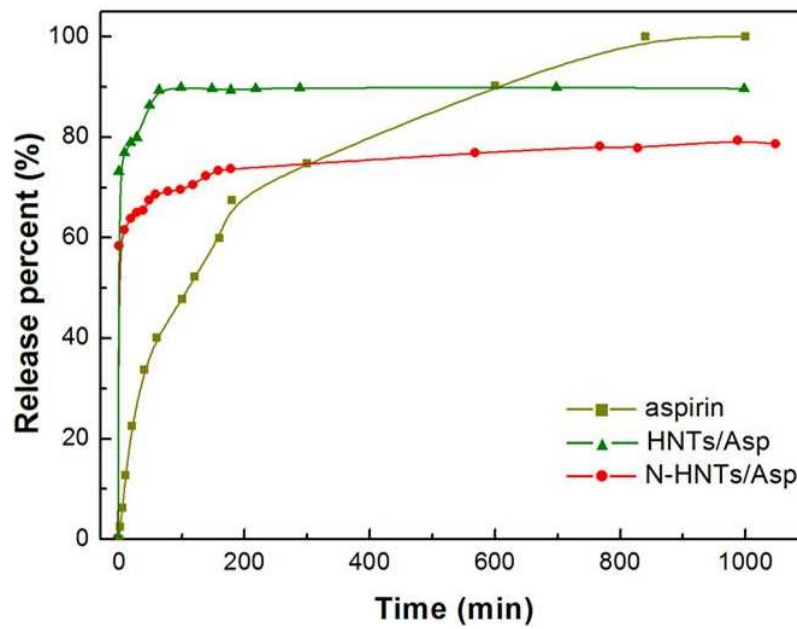


Fig. 6 Drug release profiles of different samples

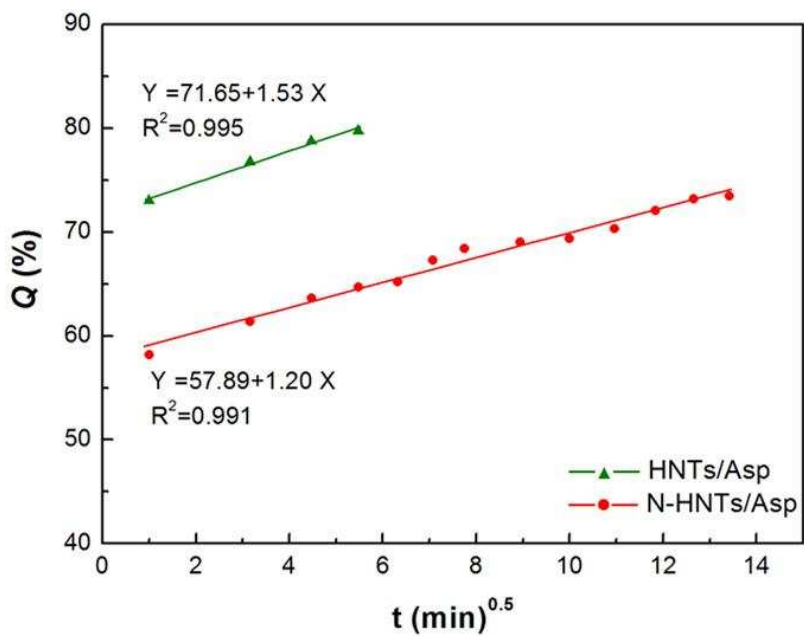


Fig. 7 Amount of aspirin release (Q) vs $t^{0.5}$ for different samples according to the Higuchi model $Q=k_H t^{0.5}$

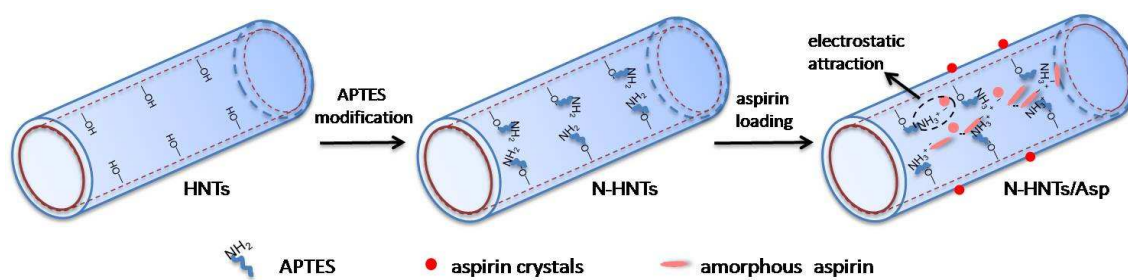


Fig. 8 Schematic representation of aspirin loading on HNTs.