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Modern ionic liquid functionalized silica nanoparticles as carriers for oral drug delivery

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Abstract: The one hand, the N-methylimidazole was covalently attached to the 3-trimethoxysilylpropyl chloride with replacement of all the chlorine atoms. A silica nanoparticle was modified by 1-(3-Trimethoxysilylpropyl)-3-methyl-imidazolium Chloride. On the other hand, Silica-poly(methacrylic acid) (PMA) was successfully prepared via copolymerization of methacrylic acid (PMA) onto vinyl-bond-modified silica NPs. The procedure consisted of surface activation with 3-trimethoxysilyl propyl methacrylate (3-TMSM), followed by free-radical polymerization of methacrylic acid (MAA) in ethyl acetate with 2,2´-azobis-isobutyronitrile (AIBN) as initiator. Finally, these two systems were mixed together. An anionic drug, naproxen was entrapped in each of these carriers and was dry by freeze drying method. Simulated gastric fluids (SGF, pH=1) and simulated intestinal fluids (SIF, pH=7.4) to determination of in vitro release profiles were stablished in an enzyme-free environment.

Keywords: Silica nanoparticles, Ionic liquid, Imidazole, pH-sensitive, Oral drug delivery.

Introduction

A drug should be protected from absorption of the environment of the upon gastrointestinal tract (GIT) and then be instantly released into the "optimum site for colon-targeted delivery of drug" proximal colon. Coating drugs with pH-sensitive carriers is one strategy for trapping orally applied drugs to the colon [1-7]. Our answer to this problem was to scheme that decreased not only the degradation but also the non-specific release of drug molecules in the GI tract that is a porous nanocarrier with a pH-sensitive features and controlled-release function.

Mesoporous silica materials have attracted too interest ever since they were synthesized by Beck and co-workers in 1992 [8], mesoporous silica metal have wide and interesting applications in the fields of chemical catalysts for the big surface area, too pore volume, highly regular pore structure, and correctable pore size, [9] and in the biotechnology [10].

Mesoporous silica material can be applied as a drug carrier for the controlled release of pre-loaded remedial drugs [11, 12]. Recently, mesoporous silica nanoparticles (MSN) have been synthesized. Silica has abundant silanol groups (Si–OH) on the pore surface, which facilitate their conjugation with different functional groups to increase the adsorption and conjugation of relevant biological molecules [13]. Drug loading efficiency usually relies on the affinity between the nanocarrier and the drug molecules. When a drug molecule is loaded inside of the non-functionalized silica matrix through a weak attraction (i.e., hydrogen bonding), a low loading capacity and a fast releasing profile are usually observed. For charge carrying drug molecules, we propose to increase the drug-loading efficiency by strengthening the electrostatic attraction through a modification of the

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silica material's surface to bear more opposite charges [14].

In this paper, we have three different carriers, and the drug delivery system was evaluated. Naproxen as an anionic drug molecule was employed as loading compound with freeze drying method and Simulated gastric fluids (SGF, pH=1) and simulated intestinal fluids (SIF, pH=7.4) to determination of in vitro release profiles were stablished in an enzyme-free environment.

Results and discussion

Figure **1** shows all surface modification of silica NPs with different functional groups for synthesis of new nano carriers. The chemical structures of the modified silica NPs and PMAA-grafted silica NPs were studied by FTIR spectroscopy. That absorption bands at 1105, 1655, and 3435 cm^{-1}, which are attributed to Si–O–Si bond stretching of the silica, vinyl bond stretching of the TMVS, and O–H bond stretching, are present in the SNPV samples. Comparing the spectrum of the PSNP with that of the SNPV, the absorption band at 1730 cm^{-1} is appeared. The results suggest that the PMAA chains had been grafted onto the silica NPs by free radical copolymerization.

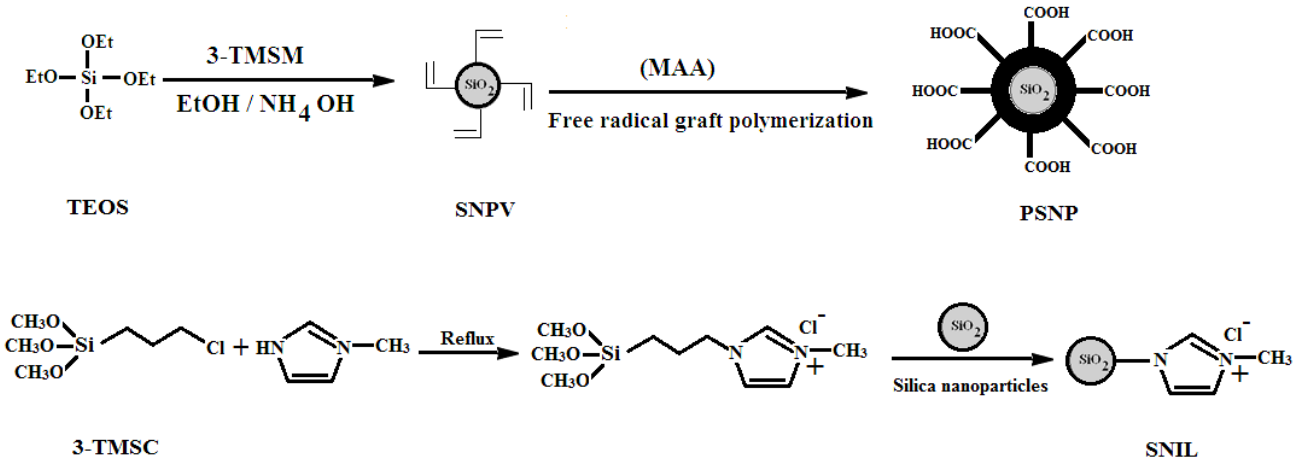

Figure 1: Synthesis of functionalized silica nanoparticles as carrier.

Figure **2** show scanning electron microscope (SEM) of nano carriers bonded drugs. The average diameter of the composite particle is about 100 nm; the particle size is also uniform.

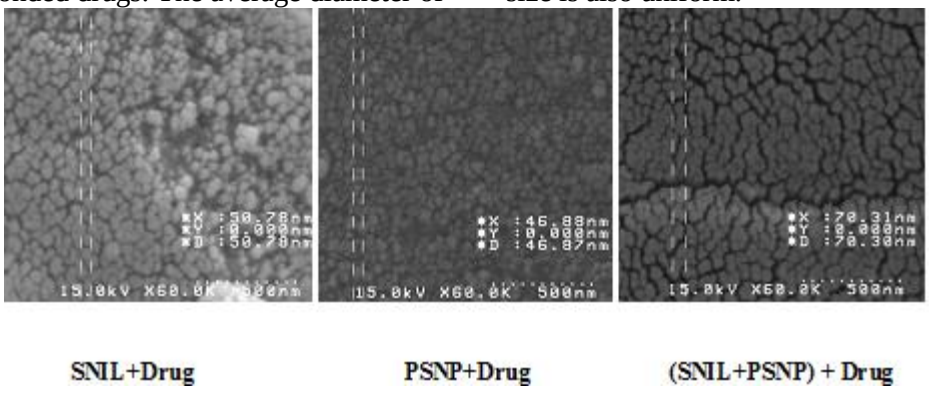

Figure 2: SEM of nano carriers containing drug.

In order to study the potential application of nano-carriers containing drugs as a pharmaceutically active compound, we have studied the drug releases behavior of the pH-sensitive nano-composites under physiological conditions. Although the nano-carriers were not soluble in water, they were dispersed in a buffer solution and the drug release was considered as a heterogeneous system. The percentage of the released drug from nano-carriers as a function of time is shown in Figure **3**. The order of hydrolysis in this series was significantly affected by nano-carrier's composition.

In the simulated gastric fluid (pH 1), the existence of hydrogen-bonding interactions between polar silanol and –COOH groups in the nano composites results in a complex structure formation within the silica network, and therefore the movement of nano composites segments is restricted. This is because, in the presumed pH the naproxen molecules have a tendency to attach to polar silanol and –COOH groups due to hydrogen-bondings caused by the decrease in the release rate. At the physiological buffer (pH around 7.4), the silanol groups (Si–OH) and -COOH in the nano carriers would become deprotonated, and a strong electrostatic repulsion between the negative charges of (SiO^- and $–COO^-$ groups) and the negative charge of naproxen molecule would be generated. Consequently, the pH value of 7.4 promotes the release rate [15-18]. However, the residual drug molecules can be occluded in the channels which would restrict achieving achieve the overall release.

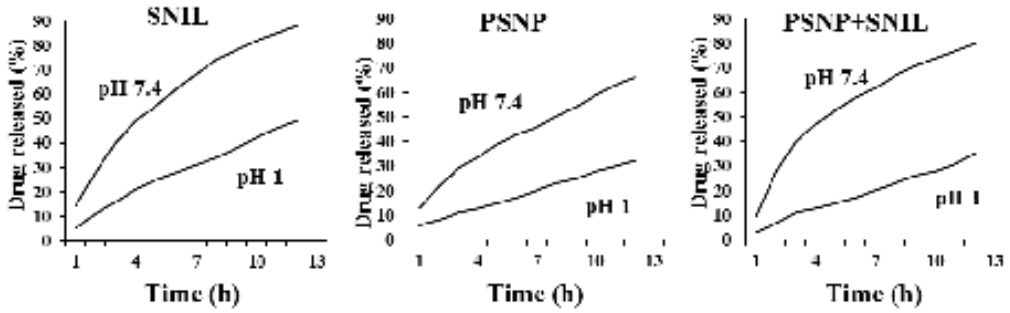

Figure 3. Release of naproxen from nano carriers as a function of time at 37 ºC.

Conclusion

A positive charge pH-responsive controllable drug release system has been designed by incorporating MAA in the framework of silica nanoparticles in such a way that the drug molecules can be efficiently adsorbed inside of the nanochannels with minimal release rate in the acidic pH environments. At pH 7.4 due to the deprotonation of surface silanol and -COOH groups, causing the strong electrostatic repulsion, the release rate of the adsorbed drug molecules becomes much higher. Based on the significant differences in hydrolysis rates at pH 1 and 7.4, these pH-responsive nano carriers appear to be good candidates for colon-specific drug delivery.

Experimental

Methacrylic acid (MAA), tetraethoxysilane (TEOS, 99 wt%), 3- trimethoxysilyl propyl methacrylate (3-TMSM, 97 wt%), 3-trimethoxysilylpropyl chloride (3-TMSC), N-methylimidazole and 2,2-azobisisobutyronitrile (AIBN) and other chemicals were purchased from Aldrich. Methacrylic acid by distillation under vacuum was purified. Initiator of 2, 2´-azobisisobutyronitrile (AIBN) was crystallized by methanol to be purified.

The IR spectra were recorded on a Shimadzu FT IR-408 spectrophotometer. The amount of released naproxen was determined by a Philips PU 8620 UV spectrophotometer at the maximum adsorption of the free drug in aqueous buffered solutions (λmax=315 nm) that use from a 1 cm quartz cell. Surface characteristic studies of the prepared polymeric nanocapsules were performed by scanning electron microscopy (SEM) model LEO 440I (UK).

Synthesis of silica nanoparticles:

In a 250 mL round bottom flask, 60 mL (10 mmol) ammonia solution (32%) and 1.98 g (110 mmol) water are added to 100 mL absolute methanol. The solution is stirred for 5 min before adding dropwise 10.41 g (500 mmol) TEOS. The final solution is stirred for three days at ambient temperature.

Synthesize of 1-(3-Trimethoxysilylpropyl)-3-methyl-imidazolium Chloride:

The synthesis is carried out under argon atmosphere. 1-Methylimidazole (2.060 g, 25.085 mmol) and (3-chloropropyl) trimethoxysilane (6.042 g, 25.091 mmol) were refluxed for three days at 80 °C. The orange suspension is filtered off and the solvent evacuated. By addition of 150 mL dry dichloromethane a precipitate appears and is filtered off under argon atmosphere. The product is then separated by distillation at 150 ºC under

vacuum (1 mbar) and 1-(3-Trimethoxysilylpropyl)-3-methyl- imidazolium Chloride was obtained with a honey-like consistency at room temperature (in 98 % yield) (Figure **4**). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.42 (1H, NCHN), 7.61 (1H, NCHCH), 7.34 (1H, NCHCH), 4.3 (2H, CH_2N), 4.02 (3H, NCH_3), 3.5 (9H, OCH_3), 1.96 (2H, CH_2CH_2), 0.59 (2H, $SiCH_2$).

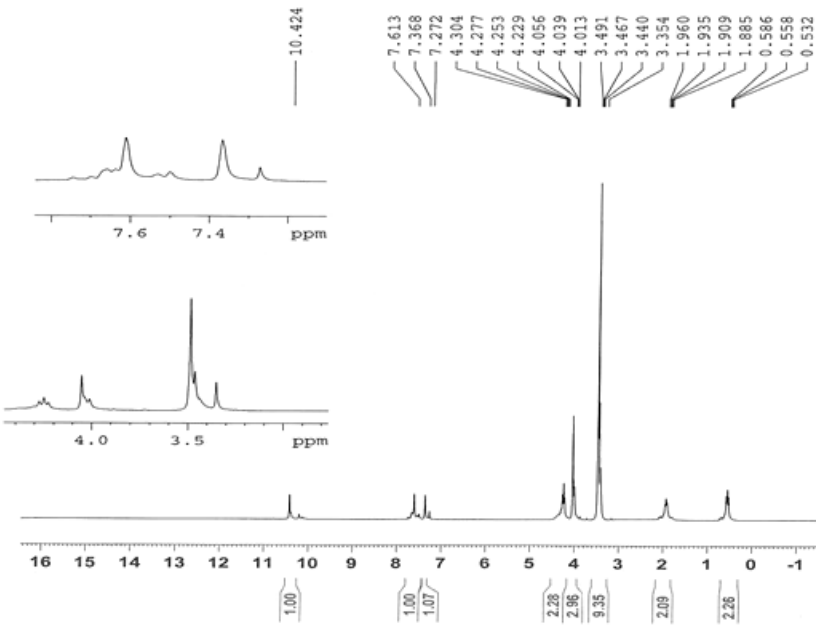

Figure 4: ^{1}HNMR of 1-(3-trimethoxysilyl propyl)-3-methyl- imidazolium chloride**.**

Immobilized ionic liquid: (SNIL):

Then silica nanoparticles suspension are precipitated with n-hexane and extracted through centrifugation (twice at 6000 rpm) before being re-dissolved in dichloromethane. Silica (1.016 g) was suspended in CH_2Cl_2 (5 mL) and 1-methyl-3-(3-trimethoxysilylpropyl) imidazolium chloride (300 mg, 0.929 mmol) dissolved in CH_2Cl_2 was then added. After stirring the mixture for 3 days at ambient temperature, the silica was allowed to settle. The supernatant solution was decanted and the modified silica was extracted with CH_2Cl_2 prior to being dried for several hours in vacuo.

Silica nanoparticles loaded with coupling agent: (SNPV):

Silica NPs modified by 3-TMSM wase prepared by a modified Stöber method (22), which comprises the base-catalyzed hydrolysis of TEOS and in situ coupling agent modification in ethanol. More specifically, 3.6 ml of TEOS, 0.25 ml of 3-TMSM and 88 ml of absolute ethanol were mixed in an Erlenmeyer flask under magnetic stirring at 20 ºC. Then, 12 ml of ammonia was added quickly under vigorous stirring. Gentle stirring was continued for at least 24 h to ensure that the reaction was complete. The silica NPs was washed extensively with absolute ethanol by centrifugation at a rate of 4000 rpm to remove excess reagent.

Synthesis of PMAA-grafted silica NPs: (PSNP):

The polymeric nanoparticles were synthesized by grafted copolymerization of silica modified NPs, MAA in a dried ethyl acetate. Polymerization was done in the presence of 2, 2´-azobis isobutyronitrile (AIBN) as an initiator (0.01 $molL^{-1}$) at 60-70º C in a thermal water bath. All of the tests were done in Pyrex glass ampoules under vacuum. After polymerization, the grafted silica NPs were separated from the suspension by centrifugation and then washed several times by centrifuging/re-suspension in deionized water. Finally, the PMAA-grafted silica NPs was dried at 80 ºC for 6 h in vacuum to perform further characterization. IR (KBr): 3350-2550 (broadened, -COOH group), 1725, 1675, 1610, 1420, 1240, 1225 cm^{-1}.

Using two-carrier composites as a new carrier (PSNP+SNIL):

Solid dispersion of carriers was prepared in the ratio of 1:1 by physically mixing both carriers.

Drug loading in nano carriers:

0.5 g of each carrier containing 25 mg of naproxen as a drug was dispersed with stirring in 25 ml deionized water. After approximately 180 min, the mixture was sprayed into a liquid nitrogen bath cooled down to 77° K, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze-dryer. In the freeze-drying process, the products are dried by a sublimation of the water component in an iced solution.

In vitro release studies:

The powdered PCSN-drug (10 mg) was poured into 3 mL of aqueous buffer solution (SGF: pH 1 or SIF: pH 7.4). The mixture was introduced into a cellophane membrane dialysis bag. The bag was closed and transferred to a flask containing 20 mL of the same solution maintained at 37° C. The external solution was continuously stirred, and 3 mL samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. Triplicate samples were used. The sample of hydrolyzate was analyzed by UV spectrophotometer (λmax=315 nm), and the quantity of drug was determined using a standard calibration curve obtained under the same conditions.

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