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Piperine Loaded Silica Aerogel and Silica Xerogel as NANO-Enabled Drug Delivery System

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Abstract: The feasibility of silica aerogel and silica xerogel as drug delivery carrier for low dosage of piperine is presented. Piperine was loaded into silica aerogel and silica xerogel via three methods: impregnation, direct synthesis and physical mixing. Formulations prepared via direct synthesis shows the fastest release, followed by impregnated and physically mixed systems. Nanoparticulate drug delivery carriers allow for faster drug absorption, controlled dosage releases and shielding from body's immune system which enhance the effectiveness of already existing drugs. Piperine loaded silica aerogel gives the fastest dissolution; where piperine release rate is dependent on particle size and surface area of drug formulation. A decrease in drug particle size increased the surface area and hence dissolution. The ease in collapse of the silica matrices structure in water is observed to favor faster release. The dissolution rate of poorly water-soluble piperine is successfully increased, consequently improves its bioavailability.

Key words: Silica matrix · Drug delivery system · Dissolution · Nanoparticles · Supercritical drying

INTRODUCTION

Interest on the application of silica particles as host matrix for biomaterial has intensified in the last decade. The application of synthetic porous silica based materials such as mesoporous MCM-41, TUD-1 and SBA-1 as potential drug delivery systems have been reported, offering numerous advantages compared to conventionally administrated drugs in dosage forms, such as improved efficiency and reduced toxicity [1-3]. The presence of silanol groups in silica matrices provides possible hydrogen bonding with the drug compounds [4]. This material contains nanosized pores that allow for inclusion of drug into the pores. It also exhibits exciting structural features of large specific surface area (up to 1000 m^2g^{-1}) and ordered cylindrical mesopores with a narrow size distribution. However, the synthesis process includes the presence and removal of surfactants which may be troublesome and not cost effective and unfavourable use of a silicon alkoxide source such as tetraethyl orthosilicate (TEOS) which is toxic and expensive [5]. Therefore, the search for an alternative carrier that is more effective, safer and comparatively cheaper to produce is desired.

Silica aerogel has emerged as ideal drug delivery carrier due to its biocompatibility; having identical chemical composition with that of amorphous silicon oxide (Aerosil) which has been used in the pharmaceutical industry since 1940 [6]. Similarly, as demonstrated by Aerosil, orally administrated silica aerogel is expected to pass through the gastrointestinal tract without being resorbed in detectable quantities. However, with a much larger internal surface area (600-900 m^2/g); compared to that of Aerosil (200 m^2/g), silica aerogel is expected to be superior to Aerosil in drug delivery system [7, 8]. Furthermore, production of silica aerogel via green process and lower heating temperature compared to Aerosil makes it more efficient and energy saving [9]. The feasibility of silica aerogels as drug delivery carrier has been reported; in which no degradation occurred during loading process and the drugs (ketoprofen and griseofulvin) adsorbed on silica aerogels dissolved faster than the crystalline drugs [6, 8]. An extremely fast release – even compared to the nanocrystals - of drugs was

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achieved by loading the drug into hydrophilic aerogel. Meanwhile, hydrophobic aerogels exhibited slower drug release rate; that is governed by diffusion [7]. However, low drug loading (dithranol and niclosamid) was also reported. The application of silica aerogel as carrier material is not limited to inorganic materials only but applicable to biomaterials such as enzymes, bacteria and biopolymer such as chitosan and cellulose [10, 11]. Maury and Pierre [12] reported the increment of the enzyme catalytic activity of lipase encapsulated silica aerogel compared to free lipase. Silica aerogel offers protection for the enzyme from deterioration brought about by the solvent. The immobilization of three other enzymes (PGA, thermolysin and chymotrypsin) in silica aerogel was also demonstrated by Basso *et al.* [13].

Silica xerogel is normally synthesized by sol-gel process and is formed once the gel is dried under ambient condition [14-16] conventional gel drying in the air, however, resulted in considerable shrinkage of the gel. The phenomenon was explained by the formation of liquid-vapour interfaces within the gel network [6, 14, 17]. Thus, silica xerogel possesses lower surface area (less than 300 m^2/g) than silica aerogel. Previous studies on silica xerogel as a carrier material in controlled delivery indicate that silica xerogels are biocompatible and non-toxic materials. Since the incorporation of various biological molecules such as drug and proteins into silica xerogel can be carried out at room temperature, silica xerogel has been explored for various biomedical applications, including oral and implantable drug delivery systems [14-17]. The application of silica xerogel for the controlled release of heparin showed that the released heparin from different xerogels studied retained about 90 % of its biological activity [18]. In addition, the synthesis of silica xerogel is considerably easy, safe and inexpensive. By taking the chemical and physical parameters into account while preparing silica xerogels, different matrixes with different properties can be produced.

Black pepper, *Piper nigrum* Linn (*Piperaceae*), is a well-known spice, widely available in Asia and has been used as Ayurvedic and Chinese traditional medicine. Quoted as 'King of Spices', black pepper is also described as a drug which increases digestive power, improves appetite, cures cold, cough, dyspnoea, disease of the throat, intermittent fever, colic, dysentery, worms and piles [19-20]. It is listed by US Food and Drug Administration (US FDA) as Generally Recognised as Safe (GRAS) and contains 5-9% of active compound, piperine [21]. Piperine (piperoyl-piperidine) is also present in other Piper species for example, *Piper longum, Piper betle* and *Piper aurantiacum.* Piperine has been demonstrated in '*in vitro*' studies to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species [22]. Among other uses, the ability of piperine in improving the bioavailability of other nutrients is its most significant characteristic. Bioavailability enhancement helps to lower dosage levels, shorten the course, which consequently may reduce harmful side effect, toxicity and cost. The effect of piperine on the bioavailability of propanolol has been studied and proven to enhance the bioavailability of this drug [23]. With controlled dosage, it was found that piperine can increase, improve or accelerate the absorption of minerals and trace elements such as vitamin D, calcium, selenium, copper, zinc and chromium [24]. Study on the immunotoxicological effect of piperine shows that the lowest dose of no observed adverse effect level (NOAEL) is 1.12 mg piperine per kg body weight [25]. Unfortunately, piperine is very sensitive towards light and oxygen and the suggested drug dosage for a person is not more than 20 mg per day [26].

This paper reports on the development of a silica aerogel and silica xerogel made from organic cereal waste as suitable drug delivery carrier of low dosage of piperine.

Experimental

Silica Matrices: Silica aerogel and silica xerogel was produced via modified aqueous colloidal sol-gel process. Generally, the synthesis of silica matrices consists of three stages: (i) the preparation of sodium silicate, (ii) synthesis of wet gel and (iii) the gel drying. Rice husk ash (RHA) and sodium hydroxide (NaOH) (Merck; 99 %) were used to prepare sodium silicate solution with mass ratio of 39.13 g RHA: 14.55 g NaOH: 450 g H_2O. The mixture was stirred for two days at 90 °C and filtered to separate the filtrate from undissolved residue. The silicate solution was then diluted to obtain sodium silicate with 4 % silica. This low cost sodium silicate (Na_2SiO_3) precursor was used to prepare silica aquagel through hydrothermal process using concentrated sulphuric acid (H_2SO_4) (Merck; 96 %).

The synthesis of silica aerogel involves two major steps, the preparation of alcogel via soxhlet extraction and the supercritical-CO_2 drying of alcogel to remove the solvent. Silica xerogel was synthesized following similar route as the synthesis of silica aerogel except for the gel drying. For silica xerogel, aquagel is dried at ambient pressure, obtaining white, hard gel. The general procedure of the synthesis process is shown in Figure 1.

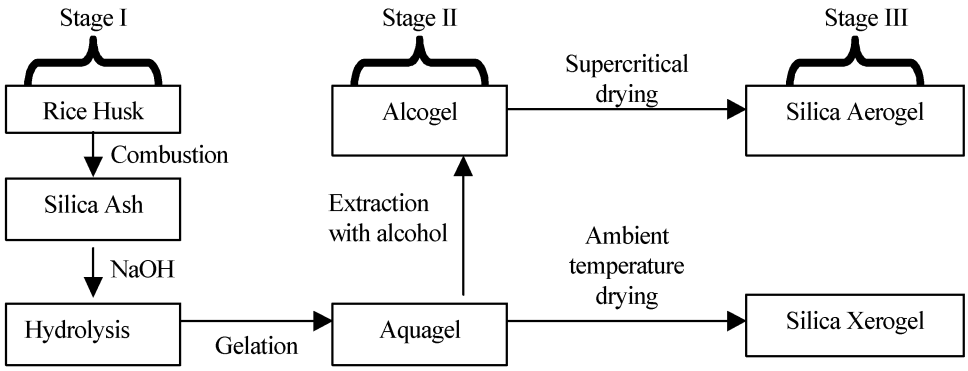
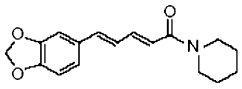


Fig. 1: Synthesis of silica aerogel and silica xerogel

Table 1: Properties of model drug (Piperine)

Structure	Physical Appearance	$T_{Melting}$ (°C)	MW (g mol^{-1})
	Pale yellow, needle like crystals	131-134	285.34

Piperine: The model drug used for the experiment is piperine (piperinoyl-piperidine) (Merck; 98.5 %) and its properties are summarized in Table 1.

Drug Loading: Three methods were used in order to load the silica matrices with piperine: physical mixing (co-grinding), impregnation and direct synthesis. Physical mixtures of piperine and silica matrices were prepared by grinding fine piperine crystals (20, 40, 50 and 60 wt%) with silica aerogel and silica xerogel, respectively, using porcelain mortar until homogeneous. The mixed powder was sieved through 212 µm screen and stored in air-tight sample bottles. The physically mixed piperine-silica powder was also used to prepare piperine impregnated silica matrices by adding ethanol dropwise until a moist mixture was obtained. The mixture was stirred until homogeneous, dried at 40 °C in oven, ground and sieved.

Piperine-loaded silica aerogel was also prepared through chemical reaction during the sol-gel process. In order to minimize denaturation, the drug was loaded at pH ~7, which was slightly before gelation in the following steps. First, a calculated amount of piperine (0.16 g) was dissolved completely in 10 mL ethanol to ensure homogeneous distribution of drug in gel. In a separate container, concentrated sulphuric acid (H_2SO_4) was added dropwise into 20 g sodium silicate (4 wt% silica) solution under mild stirring until gelation was about to occur (pH ~7). The ethanolic piperine solution was then added into the silicate mixture and left to gel. The formed gel which contained 20 wt% piperine was aged for 2 days, followed by washing with distilled water. Then, the gel was aged in ethanol for 2 days. Similar samples were prepared with different drug loading (40, 50 and 60 wt%).

Characterization: All samples were characterized using Ultraviolet-Visible spectrophotometry (UV-Vis), Fourier transformed infrared spectroscopy (FTIR), BET surface area analysis, X-Ray diffraction (XRD) and field emission scanning electron microscopy (FESEM). The UV-Vis spectra were measured on Perkin Elmer Lambda 25 spectrophotometer under ambient conditions using quartz test cuvettes. The absorbance value reading at maximum peak for piperine was used for quantitative analysis using calibration curve. In order to determine the drug concentration in the sample, 10 ppm solution of the samples were prepared by dissolving the sample powders in ethanol (99.7 %). FTIR spectroscopy (Perkin-Elmer Spectrum One at ambient temperature) was used in order to identify the chemical bonding of the samples as well as to determine the degradation occurrence of piperine. The samples were powdered and compressed with potassium bromide (KBr) and placed in the sample holder. The absorption spectra were scanned over the wave number range between 4000 and 400 cm^{-1}. The BET specific surface area of silica drug-loaded silica matrices was measured using ThermoFinnigan Qsurf Surface Area Analyzer M3 series. X-ray powder diffraction patterns of samples were recorded using Bruker D8 Advance diffractometer. Samples were irradiated with monochromatized Cu Kα (λ = 1.5405 Å) radiation and

analyzed at 2è between 5° and 45°. XRD analysis was carried out at a step of 0.05° and step time 1s.

Drug Dissolution Profile: The *in vitro* release study of drug was performed in two simulated fluids: gastric fluid (0.1M HCl, pH ~1) and intestinal fluid (phosphate buffer saline, PBS, pH ~7), using dissolution in a flow through cell. The samples were compacted into 0.1 g disks using two flat face punch and die (d = 13 mm) under pressure (1500 psi). A sample disk was immersed into 500 mL dissolution medium at 37 °C and the solution was continually stirred at 100 rpm. The drug dissolution study was done using custom-made apparatus assembly following USP IV test apparatus (flow through cell) recommended by United States Pharmacopoeia. Triplicate samples (5mL) were withdrawn from the dissolution vessels at selected time interval (10 minutes) and replaced with fresh dissolution medium to maintain the volume. Each sample was analyzed for drug concentration at maximum absorbance of piperine at a wavelength of 340 nm on an UV-Vis spectrophotometer (Perkin-Elmer Lambda).

RESULTS

Silica Matrices: The physical properties of synthesized silica aerogel and silica xerogel are listed in Table 2. The silica aerogel has a surface area of 405 m^2/g and density of 0.064 g/cm^3; that is three times larger and ten times less dense than silica xerogel.

The morphology of silica matrices was investigated and FESEM micrographs are illustrated in Figure 2. The synthesized silica aerogel exhibits porous network structure, which contains s olid clusters of 10-60 nm. As can be seen in Figure 2b, silica xerogel has a highly dense morphology, which appears as aggregates of spherical nanoparticles, approximately 30-60 nm in diameter. These findings correlate the BET surface area analysis result shown in Table 2 and suggest the connection between porosity and the surface area.

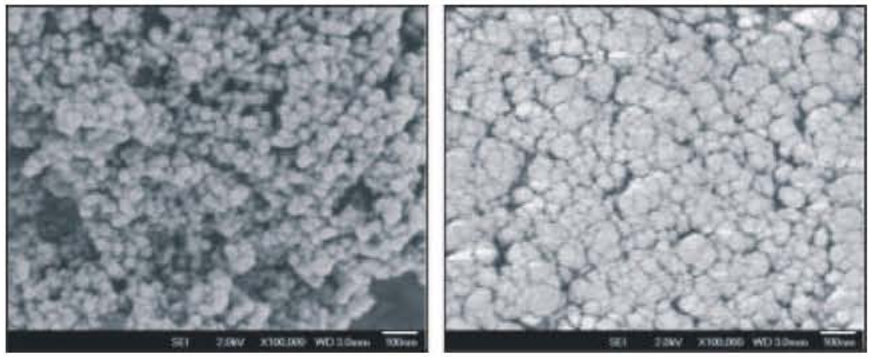
Loading Capacity and Degradation Study: UV-Vis spectrophotometry was used to characterise piperine during the loading process. Figure 3 indicates that characteristic peaks of piperine were detected at the same position (maximum absorbance at 340 nm wavelength) for both pure piperine and piperine-silica matrices formulations, which suggests that the chemical nature of the loaded drug was not influenced by the loading procedure. FTIR spectra of loaded aerogels compared with pure piperine in its crystalline form are shown in Figure 4a and 4b. After loading, it is apparent that the IR spectra consist of peaks which are characteristic of piperine and pure silica matrices with no appreciable change. This strongly suggests that the drug was successfully loaded into/onto silica aerogel and xerogel via physical mixing, impregnation and direct synthesis methods. Since there is no change to the UV-Vis and IR spectra of loaded samples, it can be concluded that crystalline piperine remained intact after loading. Surface properties data in Table 3 indicates that in general silica aerogel with higher surface area (405 m^2/g) increases drug loading capacity.

Table 2: Physical properties of silica aerogel and silica xerogel

Properties	Silica Aerogel	Silica Xerogel
Physical appearance	White, fluffy powder	White, dense, hard gel
Density (g/cm^3)	0.064	0.622
Surface area (m^2/g)	405	116
Pore volume (cm^3/g)	0.23	0.96

Table 3: Loading efficiency and surface area of piperine loaded silica matrices prepared via different methods

Sample	Loading method	Loading efficiency (%)	S_{BET} (m^2/g)
Piperine		100	3
20 wt% Piperine-Silica Aerogel (405)	Physical mixing	82.5	128
	Impregnation	100	124
	Direct synthesis	68	329
20 wt% Piperine-Silica Xerogel (116)	Physical mixing	70	45
	Impregnation	100	47
	Direct synthesis	52	155



(a) (b)

Fig. 2a,b: (a)FESEM micrograph of silica aerogel (b) FESEM micrograph of silica xerogel

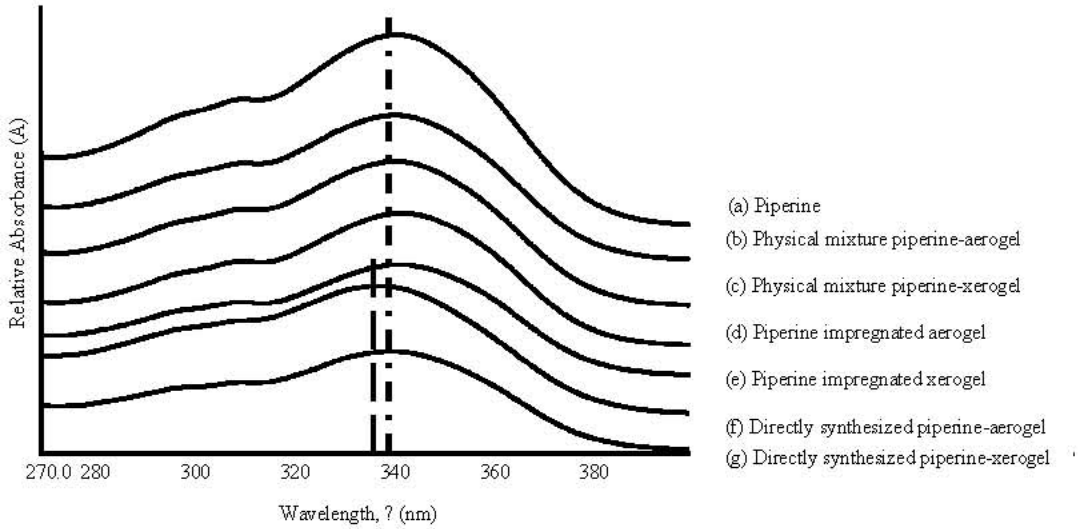


Fig. 3: Ultraviolet-visible spectra of piperine and piperine loaded silica matrices

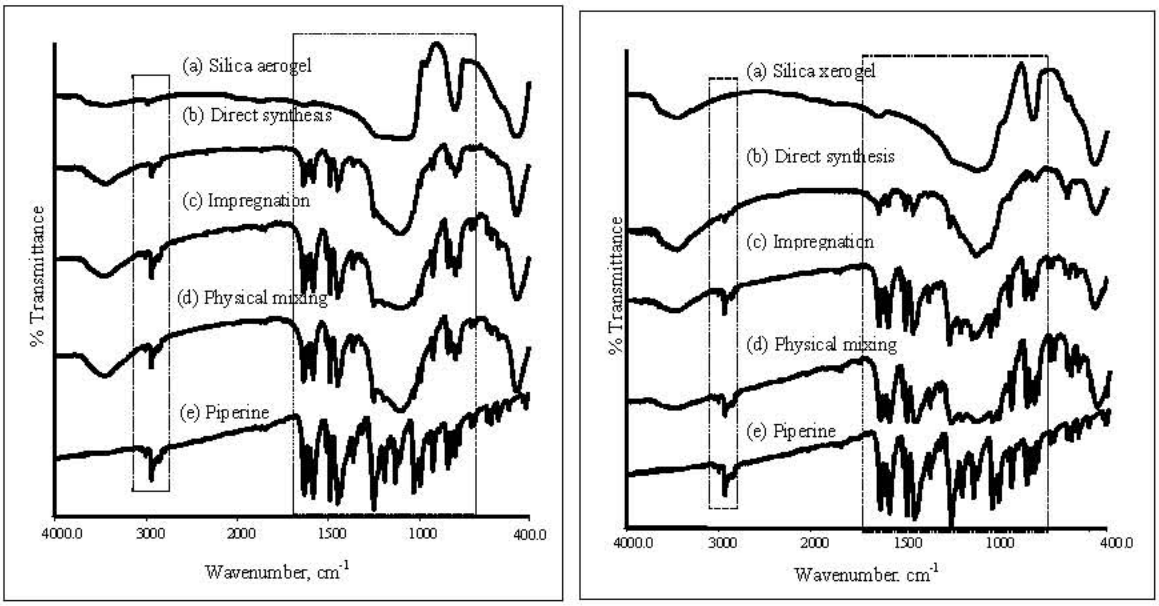


Fig. 4a,b: (a) Infrared spectra of silica aerogel, piperine loaded silica aerogel and piperine, (b) Infrared spectra of silica xerogel, piperine loaded silica xerogel and piperine

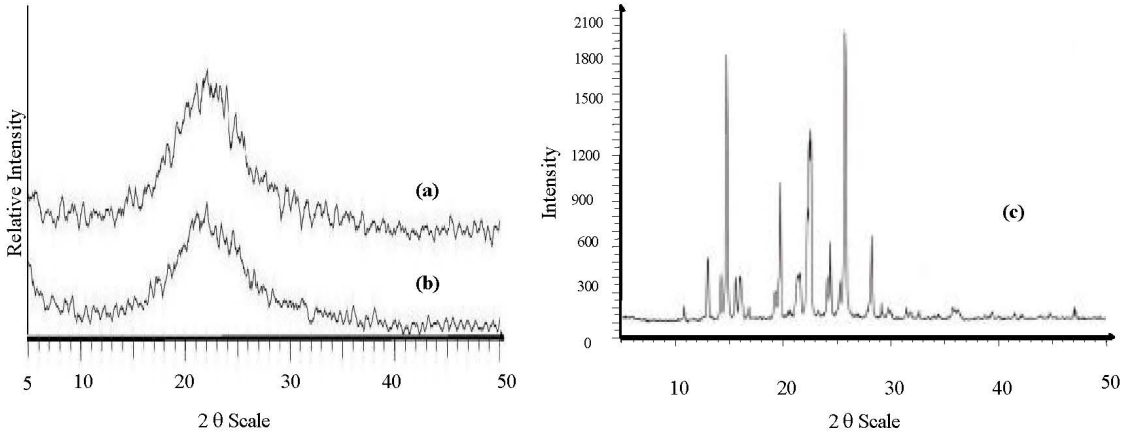


Fig. 5: X-ray diffraction patterns of (a) silica aerogel, (b) silica xerogel, and (c) crystalline piperine

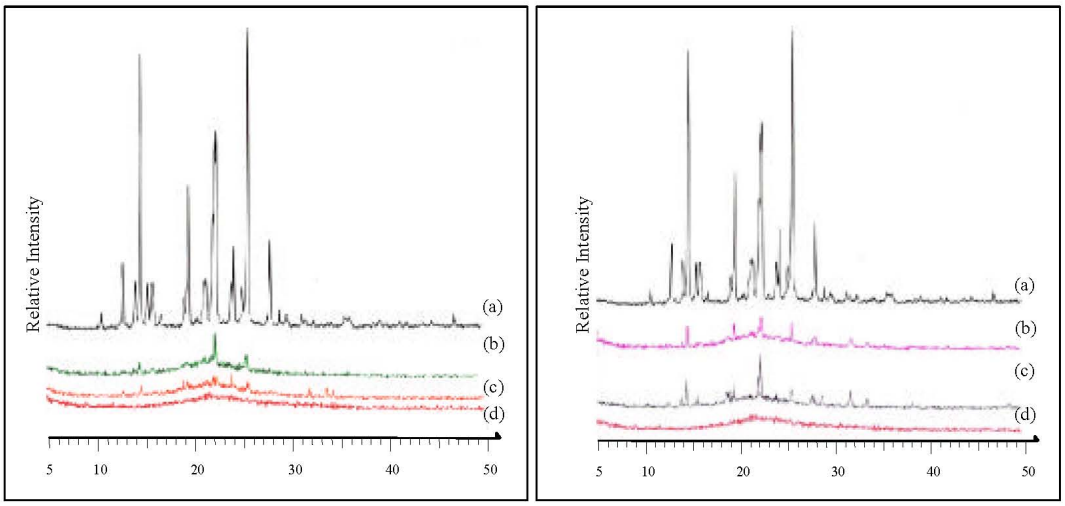


Fig. 6a,b: (a) X-ray diffractograms of (a) piperine, (b) physically mixed piperine-aerogel, (c) piperine impregnated silica aerogel and (d) directly synthesized piperine-aerogel
(b) X-ray diffractograms of (a) piperine, (b) physically mixed piperine-xerogel, (c) piperine impregnated silica xerogel and (d) directly synthesized piperine-xerogel

Surface Structure: X-ray diffractograms reveal that silica aerogel and silica xerogel are amorphous (Figures 5a and 5b), whereas piperine exhibits crystalline structure (Figure 5c). Crystalline piperine remained unchanged after loading with either amorphous silica aerogel or xerogel as shown in Fig. 6a and Fig. 6b. Comparing the x-ray diffractograms of 20 wt% piperine loaded silica by various methods, it is evident that piperine is homogeneously distributed in the amorphous silica network by direct synthesis, resulting in a featureless pattern in Fig. 6a (iv) and 6b (iv).

Surface Morphology: FESEM micrographs of physically-mixed piperine-aerogel shows homogeneous mixture without appearance of large crystals, indicating that low drug loading resulted in successful micronization of drug crystals (Fig. 7a). Meanwhile, the morphology of drug surface changed dramatically upon addition of silica xerogel during co-grinding process (Fig. 7b). The microscopic observation revealed the presence of nanoparticles of the carriers coating the coarse particles of piperine. In case of piperine-loaded silica aerogel, the drug crystals are fully covered with silica aerogel and do not have such a smooth surface as the pure piperine. The coating of drug crystals with silica aerogel may form a protective layer that prevents recrystallization of drug particles, hence crystalline piperine particles were not observed (Fig 7c). Homogeneous mixtures were also observed in piperine impregnated silica xerogel, directly-synthesized piperine- aerogel and directly synthesized piperine-xerogel (Fig 7 d-f).

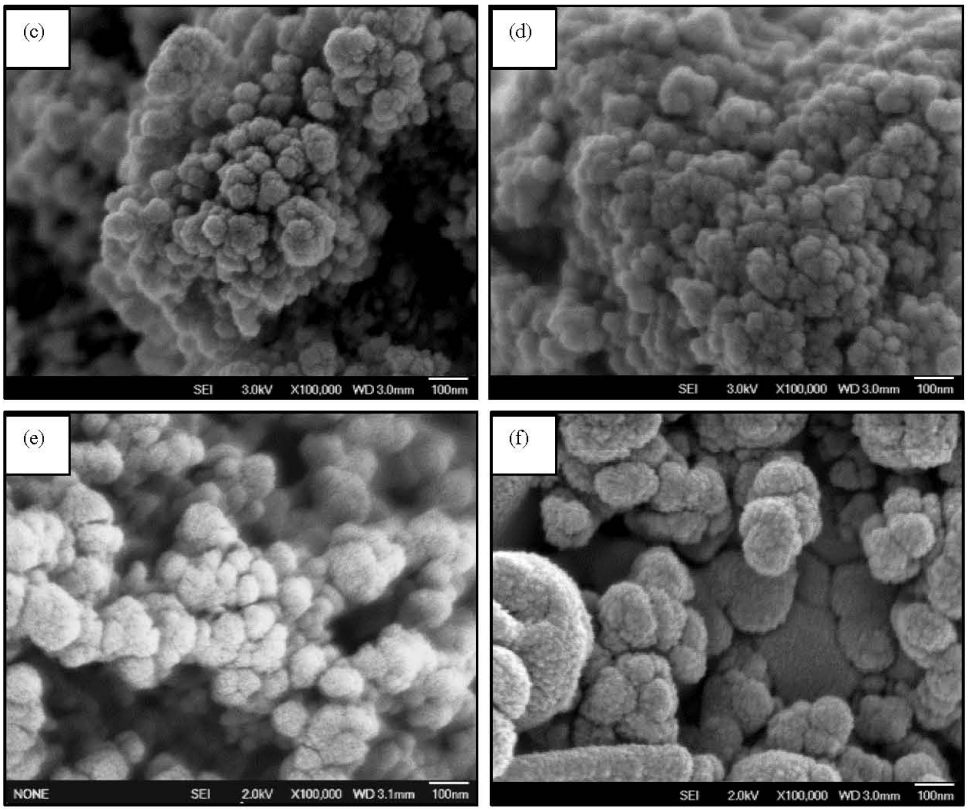


Fig. 7: FESEM micrographs of 20 wt % piperine loaded silica matrices (a) physically-mixed piperine-aerogel, (b) physically-mixed piperine-xerogel, (c) piperine impregnated aerogel, (d) piperine impregnated xerogel, (e) directly-synthesized piperine-aerogel and (f) directly-synthesized piperine-xerogel

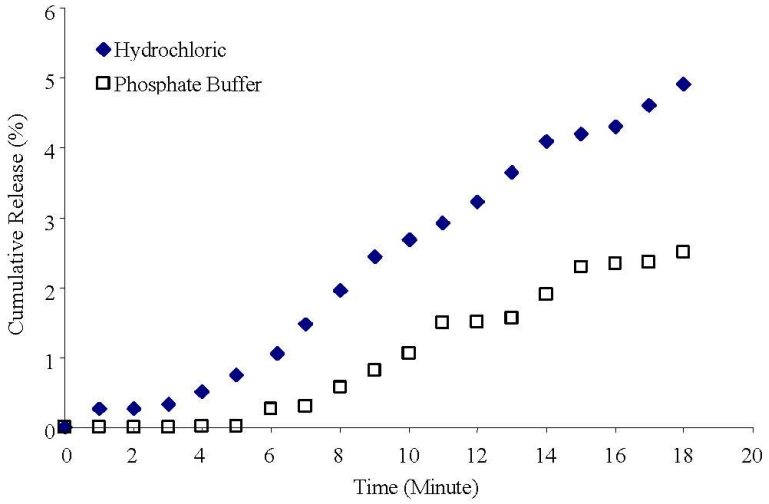


Fig. 8: Dissolution profiles of crystalline piperine in (a) 0.1 M HCl and (b) PBS

Dissolution Study: Crystalline piperine shows very poor dissolution (< 5 %) in both simulated gastric and intestinal fluids (Fig. 8). Investigation on the release profile of piperine from loaded silica matrices found that piperine loaded silica matrices dissolved faster than crystalline drug. The dissolution profiles of piperine-aerogel and piperine-xerogel formulation in 0.1 M HCl are shown in Figs. 9a and 9b. Directly-synthesized piperine loaded silica aerogel gives the fastest dissolution, followed by piperine impregnated silica aerogel and physically mixed

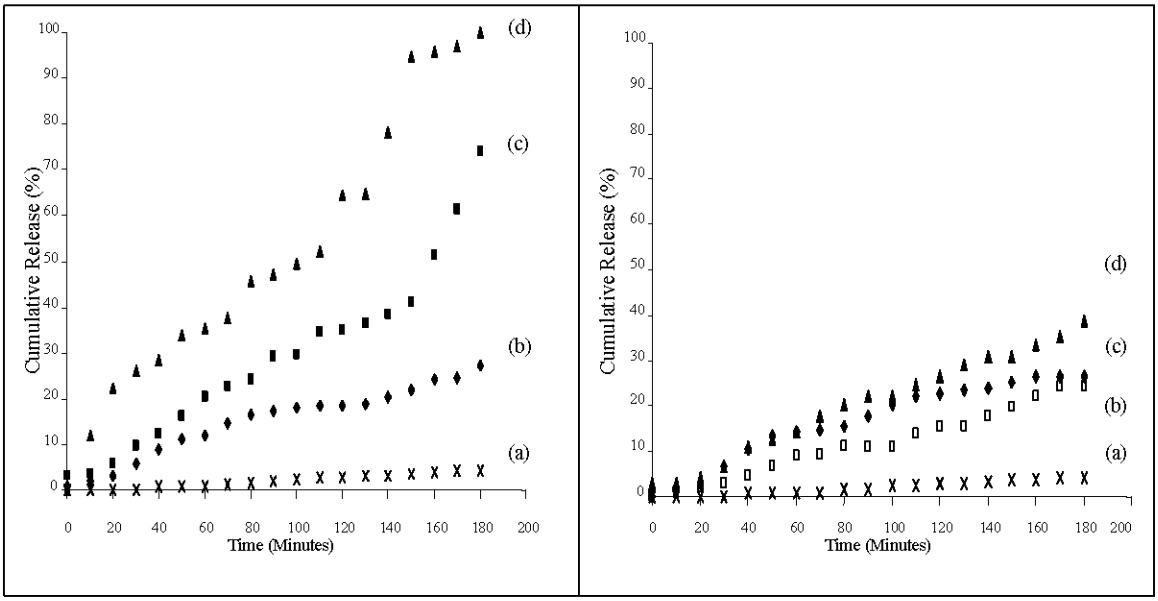


Fig. 9a,b: (a) Dissolution profiles of (a) crystalline piperine, (b) physically mixed piperine-aerogel, (c) piperine impregnated aerogel, and (d) directly synthesized piperine-aerogel, in 0.1 M Hcl
(b) Dissolution profiles of (a) crystalline piperine, (b) physically mixed piperine-xerogel, (c), directly synthesized piperine-xerogel and (d) piperine impregnated xerogel, in 0.1 M HCl

piperine-aerogel. In piperine-xerogel system, piperine impregnated silica xerogel gives the best dissolution profile, followed by directly-synthesized piperine-xerogel and physically-mixed piperine-xerogel. Dissolution profiles of all samples in potassium phosphate buffer (pH 7) follow similar trend.

DISCUSSION

Silica aerogel and silica xerogel have surface areas of 405 m^2/g and 116 m^2/g, respectively. The relatively low surface area of silica xerogel as compared to silica aerogel may be explained by the gel shrinkage due to capillary pressure during ambient pressure drying. These results are consistent with those of other studies, whereby the supercritical drying technique applied in the production of silica aerogel may have avoided the gel network shrinkage [65, 128, 143-145]. This type of technique prevents the formation of liquid-vapour meniscus from receding during the emptying of pores in the wet gel. Thus the liquid surface tension and capillary pressure may be eliminated which consequently avoid collapse of the gel pore volume and results in high porosity and remarkably large surface area.

The drug loading depends on different process parameter, surface area and density of drug carrier. Physical mixing is the simplest method of preparation of drug formulations. The size of drug particles could be easily reduced by grinding and milling. However, without silica matrices or other excipients, ground drug tends to agglomerate, creating a surface with higher energy than that of original crystals. The agglomeration will then reduce effective surface area essential for faster drug dissolution. The interactions between drug and carrier such as electrostatic bonds, Van der Waals forces and hydrogen bonding may retard self association of drug molecules, thus inhibit crystallization and increase solubility. In physical mixture of piperine-silica matrices, sufficient amount of carrier is needed to cover the drug surface in order to avoid agglomeration of its particles. Theoretically, same amount of carriers gives different coverage due to their densities, resulting in different loading efficiency in physically-mixed system. Meanwhile, in impregnated system, the concentration of piperine in silica aerogel is higher compared to piperine-silica xerogel formulations attributed to high surface area of silica aerogel in addition to its porosity and hydrophobicity. It is assumed that there was no reduction in silica aerogel volume due to collapse of framework in ethanol. Besides, impregnation process has affected the hydrophobicity-hydrophilicity of silica aerogel, where the piperine impregnated silica aerogel formulations show hydrophilic properties. The hydrophilicity of these samples is expected to favour the dissolution rate of piperine.

Relatively lower loading in directly-synthesized system was achieved; due to losses of drug from washing, aging and drying procedure.

UV-Vis spectrum of directly-synthesized piperine loaded silica aerogel shows slight shifting of its maximum absorbance. The *n* electrons in a molecule are highly affected by formation of hydrogen bonds. The energy levels of *n* electrons decrease significantly in a solvent that has the ability to form hydrogen bonds. This causes a shift in the maximum of an $n > \lambda^*$ transition to shorter wavelength. Thus, shifting of directly synthesized piperine-aerogel spectrum showed the presence of hydrogen bonding between drug molecule and other molecules containing O-H and N-H functional groups. This may be due to the presence of silanol groups in silica aerogel or ethanol used in the sample preparation.

In general, the peak intensity of piperine-loaded silica aerogels are extremely low compared to pure piperine, which shows strong interaction between the drug and silica aerogel surface, compared to the drug-loaded silica xerogels, which show more intense peaks. Observations on directly synthesized samples showed no diffraction peaks of piperine, indicating homogeneous distribution of drug in the amorphous aerogel and xerogel phase. On processing via direct synthesis, the entrapment of drug inside nanosize pores of aerogel and xerogel thermodynamically prevents it from being detected as a separate crystalline phase. Low drug loading in directly synthesized formulations also contributes to this finding as there is limited crystalline species in those samples. Theoretically, the generation of amorphous phase as proven by the BET data, will increase the surface area of drug particles. Amorphous form due to absence of an ordered crystal lattice requires minimal energy and thus provides maximal solubility advantage as compared to the crystalline and hydrated form of drug. The study has successfully demonstrated that efficient piperine loaded silica aerogel formulations evidently improve solubility and enhance dissolution rate of crystalline piperine.

Morphology study on piperine loaded silica matrices show micronization of piperine crystals. Inclusion of silica matrices avoided agglomeration of crystals and prevented nucleation or larger particles. In directly synthesized piperine-silica, by dissolving in ethanol, piperine is molecularly dispersed within the matrix, thus creating monolithic drug delivery device. In the case of poorly water-soluble drug like piperine, homogeneously distributed system can be used to increase drug release rate in the human body compared to conventional dosage forms.

The dissolution rates of piperine in both dissolution media were very poor, whereby during 180 min dissolution testing, a maximum of 5 wt% drug was released. The reason for poor dissolution of drug could be poor wettability, high crystallinity and /or agglomeration of particles. Presences of silica matrices profoundly affect the dissolution rate of piperine. Both piperine-aerogel and piperine-xerogel formulations showed the same trend, which was increased drug dissolution rate with increased amount of carriers. A prerequisite of efficient dissolution from the formulations was fast dissolution of the hydrophilic carrier particles, delivering a fine particulate suspension of drug particles. As an effect of swelling and collapse of silica matrices, the wetted surface of carrier increased and promoted wettability and dispersibility of piperine. Thus, the desired release was controllable by adjusting the amount of carrier or drug itself. In general, the release rate of piperine-aerogel formulations was about two times faster than piperine-xerogel, due to its larger surface area which provides a wider contactable area with the dissolution medium. Comparing the different methods used, directly synthesized piperine-aerogel system shows extremely faster release rate than piperine-xerogel system. Through supercritical-CO_2 drying, the collapse and shrinkage of gel network were minimized, thus piperine-aerogel system with remarkable high surface area was produced. As drug dissolution rate is strongly correlated with surface area, directly-synthesized piperine-aerogel system presents the best conditions for rapid drug release. Faster dissolution of piperine-aerogel formulations may also be due to the homogeneity of the resulting amorphous phase. Although directly synthesized piperine-xerogel possesses higher surface area compared to piperine impregnated xerogel, it showed slower release. This may be due to successful entrapment of piperine in silica xerogel matrix. Thus, dissolution was controlled by rate of diffusion of drug through the pore. Meanwhile, drug release in physically mixed and impregnated piperine-xerogel was triggered by direct wetting with dissolution medium and collapse of silica xerogel. Different dissolution media did not affect the rate of drug release.

CONCLUSION

Piperine loaded silica aerogel gives the fastest dissolution (up to 100%), followed by piperine-xerogel (up to 45%) and crystalline piperine (< 5%), within three hours. Piperine release rate is dependent on particle size and surface area of drug formulation. A decrease in drug particle size increased the surface area and hence

dissolution. As silica aerogel readily possesses higher surface area compared to silica xerogel, its application evidently enhanced the dissolution profile of water-insoluble drug. Formulations prepared via direct synthesis shows the fastest release, followed by impregnated and physically mixed systems. The ease in collapse of the silica matrices structure in water is observed to favor faster release. The dissolution rate of poorly water-soluble piperine is successfully increased, consequently improves its bioavailability. Dissolution study also revealed that all formulations show similar releases either in simulated gastric juice or intestinal fluid. Thus, the formulations can be released and absorbed in both stomach and intestine. As piperine is well recognized as bioavailability-enhancer, thus the newly designed nano-enabled piperine loaded silica matrices can be co-administered with other nutrients for different target sites. While overcoming solubility issue, nano-enabled delivery system using silica matrices synthesized from rice husk ash promises versatile applications in pharmaceutical industry.

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