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REVIEW ARTICLE

State of the Art Review on Emerging Applications of Mesoporous Silica

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Abstract:

The recent advances in the drug delivery system using a variety of technological platforms have resulted in innovation in the attitude towards diagnosis and therapeutics alike in the present times. Mesoporous Silica possesses favourable chemical properties, thermal stability, and biocompatibility. The unique structure of mesoporous silica makes possible the effective loading of drugs and their subsequent release in a controlled manner at the target site. The properties like pore size, high drug loading, and porosity as well as the surface properties of Mesoporous silica make them a suitable platform for many drug delivery applications. This review focuses on the applications and the advances made in the mesoporous silica to broaden the spectrum of its use especially in the field of medicine. The Mesoporous Silica carrier has proved its use in the field of biosensing, controlled and targeted drug release, gene delivery, water treatment, solubility and bioavailability enhancement and wound healing.

Keywords: Mesoporous Silica, Theranostic, Biocompatible, Biodegradable, Biosensing, Drug delivery system.

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1. INTRODUCTION

Modern nanotechnology has evolved as the boon to the medicine and diagnostic sector [1].

The diagnosis of diseases and their therapy are constantly achieving heights of success due to the application of nanotechnology in the field of biomedicine. Mesoporous Silica carriers have been used for many applications ranging from biosensing and targeted drug delivery to nano adhesives [2] and solubility enhancement as well as water treatment [3, 4]. Due to their biocompatible and biodegradable nature, a tremendous amount of research is in progress on Mesoporous Silica Nanoparticles [5] (MSNs). The synthesis of MSNs is also simple and cost-effective which enables their use in multiple applications. Moreover, these provide uniform and tunable pore size, functionalization of the surface, gating mechanism of the pore opening, thus making these a distinctive and promising drug carrier [6]. The structure of Mesoporous Silica resembles that of the Honeycomb and can be visualised through Transmission Electron Microscopy. Conventional MSNs have the capacity to load a dose of active pharmaceutical moiety up to 200-300 mg which can be extended up to 600 mg/1g of MSNs. However, hollow MSNs with hollow core-mesoporous shell structures are able to achieve a super-high drug loading capacity because these provide more space to load drugs due to the hollow cores, typically >1 g drug/1 g of silica [7].

The biocompatibility of mesoporous silica depends upon the shape, size, surface charge and porosity. The MSN materials having a size in between 100-200 nm are considered safe and biocompatible. Spherical MSNs are internalized faster by Chinese Hamster Ovarian (CHO) and normal human fibroblast cells than the rod-shaped nanoparticles, possibly due to the lower tendency of the former to form aggregates. MSNs with fewer silanol groups on their cell-contacet surfaces are considered to trigger the haemolysis of RBCs lesser than their nonporous silica counterparts containing a higher density of cell contactable surface silanol groups [8, 9].

Fig. (**1**) shows the multidisciplinary nature of MSNs.

Fig. (**2**). depicts the porous nature of mesoporous silica and its capacity to load the drug.

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The present review especially emphasizes on following applications:

[1] Biosensing Applications
[2] Targeted and Controlled Drug Delivery
[3] Solubility Enhancement
[4] Gene Delivery
[5] Wound Healing

2. BIOSENSING APPLICATIONS

The surface to volume ratio of NPs is quite high which allows the incorporation of abundant functional ligands, and also enables multivalency on NP surface which increases the interactions with targets. Capping and gating of MSN derivatives are frequently done to exploit their applications in Controlled-release Systems (CRS). Different detection technologies have been coupled with the CRS to develop diverse biosensors. Zhonghui Chen and his colleagues developed a simple, low cost and highly sensitive Cocaine Biosensor based on Chemiluminescence (CL) system of luminol/H2O2. Controlled released mesoporous silica had been coupled with a chemiluminescent detection technique to develop a sensitive biosensor for the target which does not cause an effect on the CL system itself. Initially, MSNs are loaded with glucose, then positively charged MSN reacts with the aptamer Cocaine which is negative in charge and closes the mesopores of MSNs. In the presence of the target, cocaine binds with its aptamer with high affinity; the flexible linear aptamer structure undergoes non-Watson & Crick interaction and gets converted to branched stems which lead to the release of glucose into the solution. The released glucose reacts with the dissolved oxygen to produce gluconic acid and H2O2 in the presence of Glucose Oxidase (GOx), which further enhances the CL of luminol in the NaOH solution. The increased chemiluminescence intensity is directly related to cocaine concentration. The present method successfully detected cocaine in serum with high selectivity [10]. Zhu and co-workers developed an ATP biosensor that used aptamer-modified Au nanoparticle and closed the pores of MSN; these pores opened in the presence of adenosine triphosphate (ATP) through the competitive binding and the cargo was released. This study demonstrated that the aptamer-target interaction could be used as a stimuli-responsive mechanism in controlled-release systems. As a broad range of targets have been exploited to obtain the aptamers including several cancer biomarkers, so it can be concluded that this aptamer-based controlled-release system should have an equally broad spectrum of applications [11]. Zhang Xueao and other Co-workers, in 2009, developed a Biosensor based on acetylcholinesterase immobilized on mesoporous silica thin films. The sensor properties of the biosensor were investigated by using acetylthiocholine iodide as the substrate and Cyt c as the electron transfer mediator. The inhibition versus the logarithm of concentration was found to be linear to organophosphorus pesticide dichlorvos [12].

3. TARGETED AND CONTROLLED DRUG DELIVERY

Fig. (**3**). illustrates the ability of MSN to target and offer the diagnostic application in the form of bioimaging.

Different functionalization and conjugations are done with MSNs to provide smart drug delivery systems [13]. The drug release rate can be retarded by modifying the functionalization or surface charge. It also depends on the pore size and loading capacity. Moreover, drug targeting can be facilitated by suitable surface functionalization; *e.g.* Folic acid conjugation for cancer cell targeting. Properties like spherical shape prove to be more efficacious in targeting cells compared to the rod shape. The properties like pore size are highly important in case of targeting larger molecules [14]. Capping and gating associated with mesoporous silica are responsible for target-specific activity and controlled release of the drug [13, 15, 16]. In the case of cancer which requires the destruction of tumor without harming host cells can be achieved with the help of different gated MSNs [17].Various gates are attached to MSNs which are responsive to different stimuli, including pH, light, enzymatic activity and temperature, *etc*. The tumor microenvironments having different pH and temperature conditions are employed while designing gated mesoporous silica nanoparticles [18]. The gating not only provides site-specific release but also protects the external environment [19]. Folic acid conjugations add to the target specificity of the MSNs in cancer therapy [16]. The therapeutic efficacy of the drug also gets enhanced as the MSNs enhance the solubility and bioavailability of the drug [20]. Photodynamic therapy can also be employed to cure cancer and other infectious diseases by passive targeting [21]. Vishal Pande and colleagues, in 2018, developed a Gemcitabine loaded, dye loaded, folic acid conjugated MSNs platform for the treatment of pancreatic cancer. They found out that the drug uptake of Gemcitabine in malignant cells was enhanced from the platform as compared to the plain drug. Moreover, dye loaded MSNs could be visualized which made the platform an excellent diagnostic agent and sustained release of the drug took place which was confirmed by *in-vitro* dissolution testing [16]. Nihal Elbialy *et al*., in 2019, synthesized the smart theranostic platform of PEGylated mesoporous silica nanoparticles loaded-curcumin for the prevention and treatment of cancer. This nanocarrier increased bioavailability of curcumin as well as provided a self-fluorescent system for bioimaging of cancer cells. A sustained pH-triggered drug release in the acidic environment of cancer cells was observed and also it was found to be safe, chemopreventive, therapeutic and diagnostic agent. The *in-vitro* study proved that the cell cycle arrest at G2/M of liver cancer cell line took place. The *in-vivo* study indicated that Tumour Chemoprevention Protocol (TCP) exhibited high therapeutic efficacy over Tumour Reduction Protocol (TRP) [22]. Chen and other investigators, in 2018, developed a pH-responsive Doxorubicin loaded Hyaluronic Acid (HA) capped mesoporous silica nano reservoir for targeted drug delivery. HA served as a targeting agent which inhibited the premature drug release and facilitated the release in an acidic environment only. The *in-vitro* anticancer study of the carrier showed the targeting toward CD-44 overexpressing cells. The platform proved to be safe for other host cells and successfully targeted the cancer cells [23]. Chen and other scientists, in 2018, developed a self-targeting and controllable drug delivery system by fabricating chitosan film formed over doxorubicin-

loaded MSNs and functionalized with folic acid having multi-stimuli responsive drug release for cancer treatment. They formed a layer of chitosan crosslinked by disulfide bond on drug-loaded mesoporous silica which was susceptible to pH and GSH stimulated drug release. Morever, folic acid conjugation targeted the platform to cancer cells. *In-vitro* study on HepG-2 cancer cell line showed folate-receptor mediated endocytosis to occur successfully. It increased the cellular intake of the nanoparticle and showed antitumor activity toward malignant cells and provided safe controlled release and targeted delivery of the anticancer drug [19]. Erik Niemela and other scientists, in 2015, developed a platform for celastrol drug delivery for cancer treatment. They developed sugar decorated mesoporous silica nanoparticles as a vehicle for increasing solubility of celastrol and increasing its anticancer activity. They functionalized the glucose by conjugating directly to the MSN surface or mediated by a hyperbranched poly(ethylene imine, PEI) layer; the latter approach provided an overall positive surface charge which increased the cellular uptake as well as increased the reaction sites for sugar conjugation. The glucose functionalization increased the specificity of drug release in cancer cells and remained non-toxic to other cells. The uptake in HeLa and A549 cells as cancer cell models, as compared to mouse embryonic fibroblasts (MEFs) as representatives for normal cells, proved the target-specific efficacy of the particles. The analysis was done by flow cytometry, confocal microscopy, and spectrophotometer. The analysis concluded that the solubility of the drug increased. Glucose moiety could successfully target the cancer cells. Moreover, the anticancer activity of the drug markedly increased due to the platform; MSNs proved to be an excellent DDS for Celastrol in the cancer treatment [20] (Table **1**).

4. SOLUBILITY ENHANCEMENT

Fig. (**4**). depicts the ability of MSNs to load the crystalline drug into pores and convert it to amorphous in order to enhance the solubility of the drug.

Fig. (1). Different Applications of Mesoporous Silica Nanoparticles

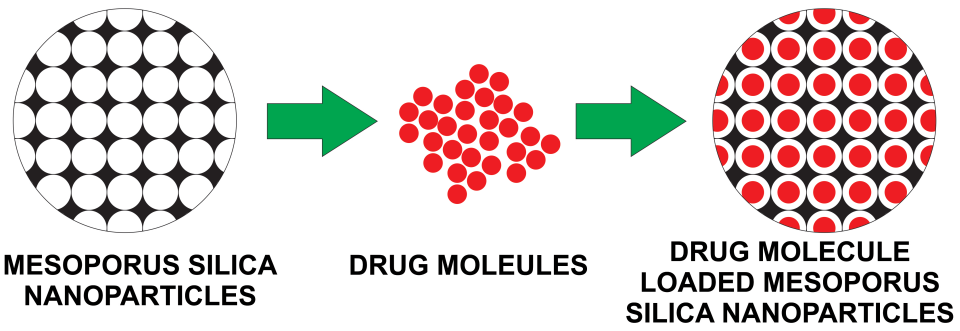

Fig. (2). Drug Loaded Mesoporous Silica Nanoparticles for Different Applications

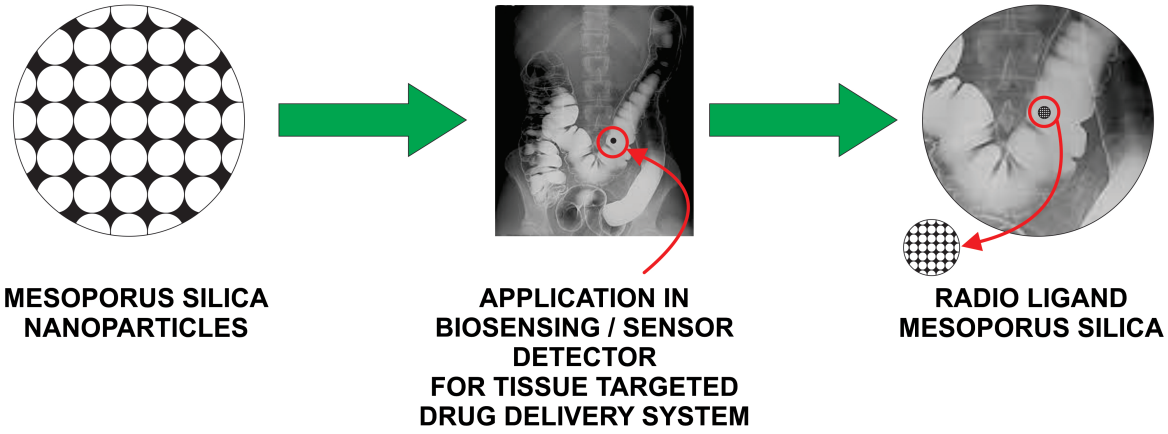

Fig. (3). Tissue Targeting and Bioimaging

Table 1. Drug Loading capacity and release profile of different MSN Templates.

Sr no.	MSN Template	Model Drug	Loading Capacity	Drug Release	Reference
1.	MCM-41 HMSNs	Ibuprofen	35.9 74.5	Complete release in 10 h Initial burst release of 50% in 10 h followed by 100% release in 3 days	[80 - 82]
2.	MCM-41 SBA-15 SBA-15 (C8) SBA-15 (C18)	Erythromycin	29 34 13 18	60% release within 5 h total release within 14 h Complete release in 10 h 25% in the first 24 h, sustained beyond 80 h	[83 - 86]
3.	SBA-15	Gemcitabine hydrochloride	76%	47.3% in 10 H	[16]
4.	SBA 15	Palperidone	62.44%	95% in 120 min	[30]
5.	SBA 15	Gemcitabine	60%	49.3% in 10 h	[87]

Fig. (4). Application of wound healing by Mesoporous Silica

Mesoporous silica has proved to be advantageous for poorly soluble drugs in increasing its solubility [24 - 26]. MSNs have a high specific surface area, high pore volume and appropriate pore sizes in the molecular range, ordered pore structures and silanol groups on their surfaces that can interact with a variety of drug molecules [27]. The solubility of the drugs markedly increase due to the confinement of the drugs into the tiny pores of MSNs having a size of 3-50 nm range [28]. The entrapment of the drug in MSNs is done by the solvent impregnation method [16, 29, 30]. Not only the drug solubility increases due to entrapment but also the drug can be protected from different destructive environments [31]. This

nature of the MSNs has proven to be an excellent solubility enhancer and bioavailability enhancer as well [24, 32]. The solubility enhancement mechanism of the mesoporous silica is clearly associated with the conversion of unstable crystalline form to stable amorphous form [33]. Katarina Bukarawhile working with her co-workers in 2016 developed a proof of concept of solubility enhancement in humans using ordered Mesoporous Silica Nanoparticles and Fenofibrate as a model drug. The study was performed as an open-label, randomized, two-way cross-over study, in which 12 healthy human volunteers were made to fast overnight. Fenofibrate formulated with ordered mesoporous silica or a marketed product based on micronized fenofibrate was given as a single dose. Plasma concentrations of fenofibric acid (pharmacologically active metabolite of fenofibrate) were monitored up to 96 h post-dose. The rate (Cmax/dose increased by 77%; tmax reduced by 0.75 h) and extent of absorption (AUC0–24h/dose increased by 54%) of fenofibrate significantly enhanced following administration of the ordered mesoporous silica-based formulation. This proof of concept developed a novel formulation strategy for the delivery of poorly soluble drugs using MSNs [34]. Nikhil Biswas, in 2017, studied solubility and bioavailability enhancement of a poorly water-soluble drug valsartan using functionalized Mesoporous Silica Nanoparticles. During the study, he developed amine-functionalized mesoporous silica loaded Valasartan [VAL] and coated it with pH-sensitive polymer eudragit L100-55 for pH-dependent sustained release of anionic VAL. During the animal study, he found out that there was a 1.82-fold in bioavailability as compared to the marketed tablet. The blood pressure of rats was under control for 840 minutes as compared to the marketed tablet which lasted for about 360 minutes. From this study, he concluded that the marked increase in solubility and bioavailability was observed due to the amine-functionalized MSNs [35]. Vishal Pande and his colleagues, in 2018, studied the solubility and dissolution enhancement of poorly water-soluble drug Palperidone using MSNs. They synthesized amine-functionalized MSNs and loaded the drug Palperidone with the help of the wet impregnation method. The *in-vitro* and *in-vivo* drug releases were studied which were found to be significantly enhanced. The *in-vitro* drug release in 120 min for MSN loaded drug was 96% while that of the plain drug was 30%. The *in-vivo* study also confirmed the enhancement of solubility and dissolution of Palperidone [30].

5. GENE DELIVERY

The drug delivery applications are most common and have already been reviewed earlier. Various developments have taken place in this context using different functionalizations, different gates, different trigger mechanism**s,***etc* [16, 36 - 39]. The study of specific molecules like gene, proteins and peptide is noteworthy [40]. The size of mesoporous silica nanoparticles varies from template to template. Moreover, the pore size can be increased by agents like Trimethyl Benzene [TMB]. The size ranges from 2-40 nm. The size of protein molecules entrapped is up to 100 kDa [41]. The target specific delivery [42] of the genes to the selected cells is the most important challenge in gene delivery [43]. In general, gene delivery vectors can be classified into two categories: viral vectors and non-viral vectors; each of them has been widely reported for gene delivery [44, 45]. Though viral and non-viral vector systems are available for gene delivery, there are many problems associated with them like biocompatibility, immunogenicity, *etc*. but as mesoporous silica is an approved biocompatible and biodegradable [5, 46] carrier by the FDA (US), it is suitable for targeted gene delivery [47 - 49]. It is important to note that Mesoporous silica has those three major properties which are required to deliver the gene successfully.

1) While there exist nucleases in the bloodstream and intracellular matrices, MSNs can protect the gene from degradation.

[1] MSNs have the capacity to pass the gene through the plasma membrane, endosome and/or nuclear pore complexes.

3) MSNs are nontoxic in nature [49]

Flow cytometer study was employed to evaluate the cellular transfection efficiency of hollow MSNs which suggests that a two-fold increase in transfection efficiency was observed due to MSNs [48]. MSNs have been proven as an excellent gene carrier because of their ability to achieve a positive charge on their surface. The positive charge has the capability to interact with nucleic acids which are negatively charged to form the delivery complex. The rest of the positive charges of the complex are favourable for cell entry. These groups include amine group [50] and cationic polymers like PEI [51], PLL [52], PDEAEMA [53], PAMAM [54].

Small amino-functionalized MSNs are far better for the delivery of gene as compared to the cationic polymer grafted MSNs. They have some of the disadvantages like reduced pore volume [55], abundant positive charges on the polymer, thus the negatively charged nucleic acids may hinder the release of the gene [56]. The large range of properties of MSNs which facilitate efficient loading and release of gene make them a strong alternative and future source for gene delivery. It can be strongly mentioned that efficient, reliable and exact gene delivery can be achieved by MSNs [57].

6. WOUND HEALING

Fig. (**5**). demonstrates the nano bridging and tissue gluing effect.

Currently available options for fast gluing of tissues are fibrin glue, cyanoacrylate adhesives, *etc*. [58 - 68] The problem associated with the cyanoacrylate adhesives is the immunogenic reaction of severe heat produced at the point of application and the damage of tissue may take place at this site. Also, these may liberate formaldehyde which is severely toxic [5, 69 - 74]. Moreover, the surgical stitches and staples are also available but the after marks remain in case of stitches so these are also not acceptable. There should be a platform that may glue the tissues and serve as liquid stitches. Mesoporous silica has found its application in this field as well [2, 5, 75]. Nanoparticles have the ability to glue together the tissues by nano bridging effect [76 - 78]. Nanobridging requires a particle size less than 100 nm while the clotting of blood depends on the porosity and the particle size of MSNs. Various metal oxide

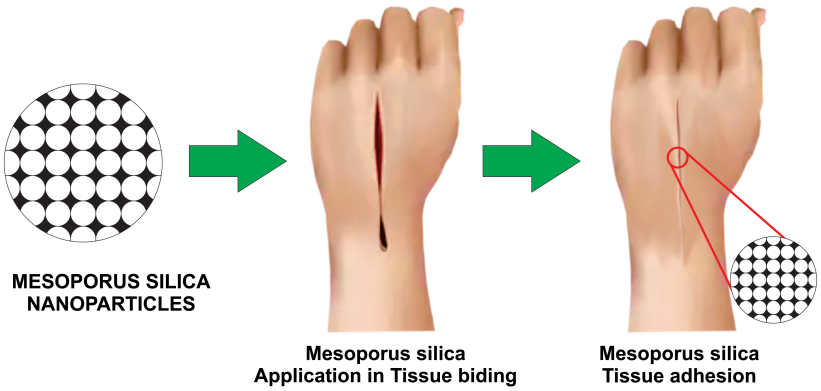

Fig. (5). Application of wound healing by Mesoporous Silica

nanoparticles have already been proven as effective tissue adhesives but it is worthy to know the ability of Mesoporous silica combined with metal oxide nanoparticles to be an effective tissue adhesive and antibacterial platform for wound gluing and healing [76]. As the mesoporous silica is biocompatible, it does not have any toxic effect post-application. It is biodegradable hence it will get degraded to a maximum extent [5, 79]. Meng-meng Lu and Co-investigators, in 2018, designed a silver nanoparticle decorated biodegradable mesoporous silica for rapid wound closure. They studied the platform for its wound healing ability in the Wistar rats. They concluded that the wound closed in 30 seconds while it healed in 5 days. Biodegradability was also confirmed which took place completely in 96 hours. It showed excellent antibacterial activity against *E coli* and the *S.aureus* which are major wound infecting organisms. MSNs proved to be an excellent nano adhesive and aesthetic wound healer as well [5]. Wu and other associates, in 2017, developed a Ceria nanocrystal decorated mesoporous silica nanoparticle as a tissue glue for wound healing. They immobilized the ultra-small Ceria nanocrystals on the surface of the MSNs. It not only healed the wound but also significantly inhibited ROS exacerbation mediated deleterious effects, which potentially accelerated the wound healing process. Also, it did not allow to form any scar. Moreover, the platform can be much useful where wound healing and ROS Scavenging activity will be required simultaneously [2]. It may be interesting to note the haemostatic efficacy of MSN. It could significantly promote the blood clot. There is a direct relationship between pore size and clotting efficiency, while the particle size of MSN has a little influence on the blood clot. The accessibility and diffusion of clotting–promoting proteins to and from the interior surfaces of MSN may be associated with each other as pore size gets directly impacted, and pores on the MSN surface get removed due to the curvature difference caused by the particle size. The ability of MSN to promote cell viability was proved in biocompatibility analysis of MSN where larger pore size resulted in better biocompatibility, but particle size had a negative influence on the cell viability. Rapid haemostasis of MSN in rabbit femoral artery injury testified the superb haemostatic efficiency of MSN [75]. So, we can conclude that MSN has a haemostatic effect and it can be successfully implemented in wound healing; furthermore, if it iscombined with other metal oxide nanoparticles, it will enhance its effect and broaden its applicability. Moreover, the nano bridging effect [78] of the MSNs could prove itself as a liquid stitches formulation for rapid wound closure.

CONCLUSION

Mesoporous Silica possesses tremendous desirable properties. The exploitation of all these properties can lead to benefits and gains in numerous applications. The pore size and loading capacity facilitate the controlled release of the drug; moreover different functionalizations of MSNs can be used to target drugs at specific sites. The release of these drugs can be monitored by ultrasonic waves, light, pH, magnetic properties, *etc*. The crystalline drugs are converted to amorphous by entrapment into MSNs which provide enhanced solubility and dissolution rate. The nano bridging effect associated with MSNs is utilised by combining with drug or metal nanoparticles, which has proved to be a significant tissue adhesive and an excellent wound healer. Maximum porosity and the adsorption capacity of MSNs make their use feasible in the loading of drugs, NPs, *etc*. and in drug therapy. MSNs can also be used as a bioimaging tool by combining them with an MRI active agent.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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