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Mini Review

Mesoporous Silica Nanoparticles And its Current Approach's to Curtail Multi Drug Resistance in Malignant Tumour: A Mini Review

Sankha Bhattacharya*

Associate Professor, Department of Pharmaceutics, ISF College of Pharmacy, Punjab, India

***Corresponding Author:** Sankha Bhattacharya, Associate Professor, Department of Pharmaceutics, ISF College of Pharmacy, Punjab, India.

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Abstract

Nanotechnology is playing a palpable role to circumvent any forms of cancer. But multi drug resistance (MDR) in malignant tumour tissues is a serious concern for nanotechnology to address. Among all the nanocarrier, mesoporous silica nanoparticles (MSNs) could be a promising candidate to tackle this challenge. This review is mainly focused on MSMs based approaches which are showing exciting results while treating MDR. The review is also highlighting the upcoming challenges associated with MSMs formulations while tackling MDR using MSMs approach.

Keywords: Cancer Treatment; Multidrug Resistance; Co-Delivery; Combination Therapy; Dual Targeting; Mesoporous Silica Nanoparticles

Introduction

Cancer is a pivotal disease which is affecting almost 25% of the world populations throw-out the years [1]. However, chemotherapeutic medicaments are playing an uncompetitive role while treating cancer [2]. But it has also many limitations like, tissue toxicity, cellular toxicity, secondary alopecia etc. But most challenging part of cancer is its frequent recurrent profile after treatment using chemotherapy or using radiotherapy [3]. There are many formulations are postulated by scientists in recent years. But vary few has good quality of drug delivery and target specificity [4]. The increase payload of nano formulations often produces non receptive action within the cells and cause multi drug resistance in some cases [5]. Among all reported nanoparticles Mesoporous Silica Nanoparticles (MSPs) is showing high field of interest in recent years because of its higher drug loading capacity, specificity, selectivity and vivid narrow range of size (50-300nm) with larger surface area (700-1000 $m^2 g^{-1}$) [6]. MSNs is a good candidate to incorporate various medicaments which engulf within its surface [7]. This mini review will highlight about recent findings and effects given in the filed of MSPs to target multi drug resistance (MDR) of malignant tumours or cancer cells.

Basics of Mesoporous Silica Nanoparticles (MSNs):

In 1992 Mesoporous silica materials was discovered by Mobile Oil Corporation [8]. But throughout the years and almost 3 decade of innovation, MSNs are now a key carrier for drug delivery system.A proper drug carrier can improve bioavailability, biodistribution, drug loading capacity hence it is necessary to have limited particle size of the nanocarrier system. MSNs is one of the finest candidates for this task [9]. The hydrophilic surface coating of MSNs makes it's a good candidate for surface engineered nano formulations [10]. Basically, MSNs can be obtained using liquid crystalline templating with sol-gel chemistry [11]. The obtained MSNs possessed good level of chemical stability, biocompatibility, surface functionality. Due to the presence of porous structure and large surface area, MSNs become a best carrier for many functional groups to target drug moiety to the targeting site [12]. The honeycomb like structures of MSNs has more active surface area to bind with any molecule [13]. Compare to other metal oxide Viz. iron oxide, zinc oxide, titanium dioxide, silica is abundantly available in environment and most importantly silica is biocompatible [14]. The beauty of MSNs is its unique drug loading capacity in high quantities with controlled drug release properties [15]. Due to the presence of Si-O bonds in MSNs as compare with the other nano formulations i.e, polymeric nanoparticles, solid lipid nanoparticles, polymeric hybrid core-shell type nanoparticles, niosomes, liposomes and dendrimers, it is more physically stable and ridged [16]. In recent era researchers are trying to develop multifunctional MSNs, which could be use for diagnostic and theragnostic purpose [17]. The multifunctional MSNs can be prepared by surface functionalization through chemical linkage [18]. As far as synthesis is concerned MSNs are prepared using sol-gel and spray drying technique. New research suggesting that, incorporation of gold plating on MSNs is on demand. The nano formulations which are produced using pyrolysis method can effectively coated with silica which insanely produces good stability in aqueous environment. During 2000-2019, many researches has been exercised to control the drug delivery, gene transport, genes expression, biomarking, imaging agent, considering MSNs as a carrier. Eventually the conventional MSNs can hold upto 200-300mg drug inside; however, hollow-core-mesoporous shell structure is able to hold more drug inside i.e., >1 g drug/1 g of silica [19].

Application of MSNs in cancer theranostics

Delivery of cytotoxic drugs and small interfering RNAs (siRNAs)

The multidrug resistance in tumour is once of such focal issue in recent time. All though some research claiming to circumvent such problems, but immediate application is certainly unclear. Eventually Multi Drug Resistance (MDR) define an ability of cancerous cells to become resist to usual chemotherapeutic agents [20]. There are many mechanisms involved in it, one of such mechanism is ATP-dependent membrane protein (Pgp) efflux from cells [21]. Therefore, this mechanism continuously exile drug within the cell to extracellular fluid; which ultimately reduces the therapeutic efficacy. This type of efflux mechanisms is very common in pancreatic, breast and stomach cancer [22]. The non-pump resistance mechanism includes the activation of anti-apoptotic proteins i.e., Bc-1 and Bc-2 or Heat-Shock protein (HSP), which exaggerated expression prevent cellular death [23].

As per conventional chemotherapeutic medicaments, it basically disrupts the resistance pathways and inhibits those mechanisms [24]. The small interfering RNAs or silencing RNAs are basically a one type of nucleic acid which could able to interface with the normal gene expression of mamma line cells by computing with messenger RNAs [25]. To emphasis these approach, MSNs based nano formulation are of special interest because, they can deliver cytotoxic or chemotherapeutic medicaments and siRNAs simultaneously in more effective way then any other nanocomposites and therefore increase the therapeutic profile by maximizing the concentration of chemotherapeutic while mildly effect the protein which is responsible for drug resistance [26]. It is very essential to know that anchoring of siRNAs to the nanocarrier must be irredeemable as its action requires to detach nucleic acid to perform its therapeutic effects (Figure 1). In this circumstance MSNs plays a significant role as it can easily tailored to undergo electrostatic interaction with nucleic acids. In a recent research conducted by Chen., *et al.* Doxorubicin loaded MSNs shows positively charge generation [27] 2(G2) amine terminated polyaminodomine (PAMAM) dendrimer via electrostatic interactions that disapper under acidic liposomal pH.

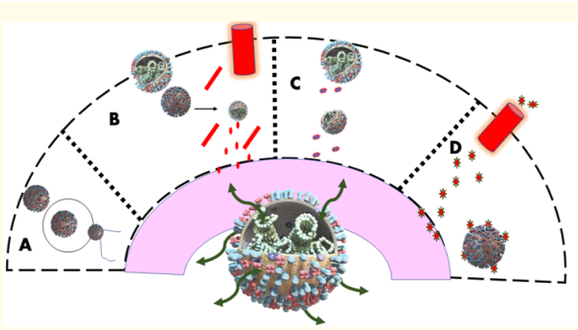

Figure 1: Schematic way of action of different reported strategies to overcomse MDR in cancer cells. A) Cellular-nuclear targeting; B) Drug-siRNA co-delivery; C) Drug codelivery. D) Drug efflux pump modulation.

Multiple cytotoxic drugs delivery

In MDR treatment in cancer or malignant tumour, multiple chemotherapeutic medicaments co-administration could hamper cellular adaptation and integrity [28]. One of the best approaches for enhancing or sensitizing against chemotherapeutic compound could be hybrid drugs with single pharmacophore in a single molecule [29]. But some common issues related to hybrid design is the drug could not allow conjugation without comprising their activity, secondly a misplacement of pharmacophore while both the compound act in different place, third a poor pharmacokinetic/dynamic profile of hybrid compound as compared to individual compound.

The role of MSNs in cancer therapy is very vivid, as it does not allow nanocomposites to come out from the shell until proper drug delivery environment obtained. Based on infusibility, aqueous solubility of drug, the co-loading of several gust molecule into MSNs is obtained.

Physical stimulation and MSNs in cancer treatment

Combination of classic cytotoxic drugs with additional physical stimulation can able to sensitize the cancerous tissue [30]. Combination of cellular killing pathways enhance therapeutic profiles in drug resistance cancerous cells. MSMs based formulations could trigger apoptotic pathway and minimise undesired side-effects [31].

Photodynamic therapy

In this technique a photosensitiser (PS) is used which could able to absorb desire wavelength of electromagnetic radiations [32]. This excitation results in reactive oxygen species (ROS); which are potentially cytotoxic and causes irreversible cellular damage and thus providing cellular damage [33]. In a relevant research Gary-Bobo., et al. mannose targeted MSMs with water soluble prophirin sulfonate PS and loaded with CPT [34]. In this research CPT excreted a cancer static action which ultimately reduces vialbility of cellular lines tested to ca. 60%.

Magnetic hyperthermia and MSMs

Magnetic induced hyperthermia is one of such approach in which increase temperature can alter magnetic field [35]. In recent years Shi., *et al*. has reported the proper synthesis of HMSNs conjugated iron oxide nanoparticles [36] which ultimately allows nano capsules which ultimately helps in DOX drug delivery system. The presence of hollow structural arrangement of HSMSNs permeates hosting of high chemotherapeutic amount. In another research by Tang., *et al.* suggested that in the presence of alternating magnetic field, iron oxide nanoparticles acting as a DOX delivery system [37]. The DOX-loaded magmatic MSNs were showing excellent drug release in the presence of pH 5.0 medium in Tao and Zhu research. In addition effective heat generation was established upon exposure to alternative magnetic field (AMF).

Radiotherapy

Radiotherapy is also a parallel approach besides chemotherapy and surgical removal procedure of solid tumours [38]. But it has also had some own limitation like poor selectivity between healthy and malignant tissue and higher amount of cytotoxicity. Fortunately, radiotherapy focuses malignant and nearby tissues only, but its wide angel toxicity sometime even causes bone marrow depletion and increase myelosuppression properties in cytosol [39]. Nevertheless, subsequent development of nanotechnology improvising radiotherapy as well as new research suggesting improving EPR effects within the tumour cells by modifying radiotherapy [40]. Mostly radio isotopes in healthcare sector are used in diagnostically. But researchers are doing great to transmute radiotherapy to theranostic use. A new research by Shen., et al. suggesting nano system for reversing multi drug resistance in tumour by imbibed with topotecan (TPT) [41]; a topical radio sensitizing drug and outer surface of the formulation were anchored by using PEG to improve bioavailability.

Future approaches of MSNs in multidrug resistance therapy for malignant tumours

Even though MSMs are exposed in different dimensions to treat MDR in malignant tumours, but there are many fear factors and challenges need to be addressed in upcoming days. In recent years focused was given to improve the bioavailability and drug release from nanocomposite and to manipulate lagan-based tissue specificity of MSMs. In near future, preparation of multifunctional MSMs using coupling and anchoring of biomacromolecules (antibodies, aptamers, proteins and new generation peptide) would be an exciting task. In future possible use of ultrasound with MSMs based drug delivery could be possible to tackle MDR.

Conclusion

The recent research outcomes suggesting that MSNs is playing a significant role to overcome current limitations of cancer therapy. Nanocarrier like MSNs are versatile and outstanding carrier for increasing payload of any oncological medicaments. Advanced strategy is considerably taking to curve the multidrug resistance in tumour by using MSMs approach. The overall outcomes of this mini review was to give an outline about MSNs approach and its applicability to curve multi drug resistance in tumour tissue cells. Number of repots suggesting MSMs has good in-vitro drug release profile but entering in clinical trial is still in infancy for MSNs. New researchers are now focused on biodistribution, excretion, elimination and genomic toxicities of MSMs; which is indeed an emerging filed as far as MSMs research is concerned. But most burning question for be near future would be proper standardization of MSMs as in maximum research it was witnessed the researches used certain fragments to link with MSMs; which is not fully evaluated which may presume certain toxicity in clinical research.

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Conflict of Interest

The authors have no conflict of interest.

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