ABSTRACT

Introduction: Recent medical improvements have not much of an influence on cancer patients' life expectancy throughout the world. Nano medicine is a cutting-edge topic in cancer therapy, with various well-tested techniques for delivering drugs. Objectives: Liposomes and other nanostructures are often used in therapeutic contexts and scientists in numerous countries are currently investigating polymer micelles. These structures will become more lucrative if they include chemicals that help with site-specific delivery and tailored release. The objective of the current review is to provide comprehensive information on nano-drugs. Methods: Liposomes, polymer micelles, and dendrites, among other well-known nanoparticle technologies, can be controlled and regulated to generate a more long-lasting and effective non-therapeutic modality. Occasionally, the term "multistage drug delivery" is used. This method, which employs a well-designed Nano-carrier, overcomes several biological barriers to medicine delivery. Results: Several multistage drug delivery system papers were reviewed for this study and their advantages were discussed with some pharmaceutical drug examples as well. Conclusions: We emphasize developments in nanoparticle design that overcome heterogeneous delivery barriers and contend that intelligent nanoparticle design can boost effectiveness in general delivery applications especially cancer treatment while enabling customized designs for precision applications, ultimately improving patient outcomes.

Keywords: Nano Medicines, Nano Particles, Treatment, Systematic Injection
INTRODUCTION

Despite decades of advancement in clinical research and medicines, Cancer is still one of the most common and dangerous diseases for which no clinical cure has been invented till date. It has recently become the leading cause of death among those aged 50 and up (1). The main objective of cancer treatment is to stop their uncontrolled proliferation. Chemotherapy has been a successful cancer treatment approach when used in conjunction with other medicines. However due to patient discomfort, serious side effects and low long-term survival rates researchers are striving to create newer tools for effective drug delivery of anticancer agents. Discovery of nanoparticles, monoclonal antibodies, vaccines, cytokines and T cell chimeric therapies have proven to be safe and effective in cancer treatment (2). However, the delivery of anti-cancer agents to the target area for treatment and diagnosis is proven to be much more controlled by nano medicine approach. Liposomal doxorubicin (DoxilTM/CaelyxTM) was the first anti-cancer nano medicine licensed by the FDA in 1995. It was designed to take advantage of the increased permeability and retention (EPR) effect. DoxilTM/CaelyxTM achieves differential doxorubicin dispersion vs the free medication and is currently licensed for various applications based on better safety and equivalent or higher effectiveness to conventional therapy. DoxilTM achieved a roughly 300-fold increase in area under the curve in patients when compared to free doxorubicin, albeit this includes both free (bioavailable) and liposome encapsulated (non-bioavailable) doxorubicin (3). Various nanostructured formulations are being synthesized such as nanoparticles with transition metals such as gold, silver, iron and zinc, with solid lipid nanoparticles, polymer nanoparticles, liposomes and with dendrimers. The nanomaterial is selected on the basis of target physiology, size and volume specific surface area (4) and the drug encapsulated within the nanocarriers may include any chemotherapeutic agents or nucleic acids that may target the tumor cells. These formulations can thus help in increasing the permissibility and retention of poor soluble drugs, furthermore, increasing half-life of drugs and accumulation of drug in tumor cells. This targeted approach is helpful in protecting healthy cells from cytotoxic effects and reducing adverse effects of therapy. Several studies have shown that nanoparticles of drugs such as doxorubicin (5), paclitaxel (6) were less harmful to healthy cells, showed reduced adverse effects and circumvented drug resistance in tumor cells.

Figure 1. Nano-medicine synthesis with drug combination. Reproduced with permission.
Scientists have spent decades trying to apply Ehrlich’s "magic bullet” notion to
chemotherapy by developing liposome and polymer-drug conjugates (7). These platforms are widely used in the interdisciplinary field of nano medicine, which uses the nano scale (1–100 nm) to improve the efficiency of chemotherapy and the most typical use of these carriers is to help with pharmaceutical solubility and stability. The term nano and cancer are often seen together as the anticancer research is expanding and new advancements are seen in the field (8).

Nano medicines have been studied for the targeted delivery of pharmaceuticals to treat a wide range of disorders. This industry viewpoint focuses solely on oncology-based nano medicinal treatments, which garner around two-thirds of research effort (9). The notion that nanomedicines strive to increase the therapeutic index of anti-cancer therapies by changing their pharmacokinetics and tissue distribution to better delivery to the site of action is widely known and has been clinically proved. In a few crucial cancer cases, Nano medicine has already shown promising effects. First in human dose escalation docetaxel entrapped nanoparticles-based phase I clinical trials were held in Netherlands and Belgium in 2015-2018. The study showed potential treatment against solid tumors with manageable toxicity and small risk of neutropenia (10). The approval of novel nanomedicines has been based mostly on improved therapeutic benefit via increased safety, with patient survival being comparable to that obtained with traditional therapies. Many innovative nanomedicines' strong anti-cancer effectiveness has yet to be replicated clinically, and as a result, the development of marketable nanomedicines has frequently been sluggish. Though important, the absence of or limited improvement in overall survival calls into question the field's ability to enhance patient survival further with more effective nanomedicine-based therapy (9). Applying a 5Rs framework to nanomedicine development necessitates the identification of key biological-technology relationships, such as the impact of tumor pathophysiology on nano medicine accumulation, distribution, retention, and efficacy, and the relationship between delivery system properties and in vivo behavior. Until date, the focus in nano medicine research has been drug delivery system engineering. However, there has been little emphasis on defining nano medicine design based on tumor biology, and nano medicine application has been mostly empirical (11). The majority of approved anti-cancer nano medicines have been designed to take advantage of the EPR effect, with a small subset of nano medicines attempting to change nano medicine behavior further through ligand-mediated targeting (e.g., BIND-014 (BIND Therapeutics;) and MM-302 (Merrimack Pharmaceuticals). EPR-based therapies, in general, attempt to increase effectiveness and tolerance by altering the pharmacokinetics and biodistribution of the drug (12). In general, EPR-based therapies strive to increase effectiveness and tolerance by altering the drug's pharmacokinetics and biodistribution. They can reduce the peak free drug concentration (Cmax) in plasma and tumor while often increasing the area under the curve to offer sustained exposure to
therapeutic levels of medication at the target. Several nano medicines have bestowed a considerably increased therapeutic index to an existing therapy or permitted new novel treatment techniques by obtaining the proper target' and suitable exposure (13). The nano medicine sector has made great efforts to gain understanding of the technical and biologic benefits and disadvantages of various nano medicine systems. Many nano medicines have been created to enhance the stability, solubility, pharmacokinetics/biodistribution, toxicity, and/or effectiveness of cytotoxins and other payload types. Size, charge, shape, kind of surface modification, and biocompatibility of the delivery mechanism all have an impact on the biodistribution and clearance of the nano-medicine (14). Using more clinically relevant models to evaluate nano medicines will allow the biology of the target population to drive system fine-tuning. It will be feasible to construct data sets supporting translatable clinical development and patient pre-selection techniques by modifying our approach to nano medicine development (9). Similar studies and trials suggest novel ways to use Nano medicine in the creation of new chemotherapeutic formulations, with a focus on platforms and developing trends.

**Synthesis of Nano-Medicine Liposomes**

Liposomes are composed of hydrophilic phospholipids with hydrophobic anionic or cationic long-chain tails. They are explored for targeted delivery of anti-cancer drugs owing to their active or passive mechanism. Liposomes can be made with saturated hydrophilic drug solution, with lipophilic drugs by pH exchange or even by solvent exchange method. FDA-approved liposomal doxorubicin (Doxil) has been used to treat Kaposi's sarcoma since 1995 (15). Since then, several liposomal nano medicines are now in market for targeting the proliferating cancerous cells. Even more advancements are being researched to improve and enhance the Doxil targeting (16). The concept of liposomal therapy is not only to enhance the permeability and bioavailability but also to enhance the delivery of hydrophilic drugs unable to cross the lipid membranes, similar they are modified to increase drug stability and half-life (17). The platform significantly reduced cardio toxicity by extending the half-life of doxorubicin in the blood from 10 minutes to 50 hours (5, 18). One more phase II trial at SEQUUS Pharmaceuticals delivered liposomal doxorubicin every three weeks to 238 patients with AIDS related Kaposi sarcoma. The results showed that the PEGylated drug was well tolerated and only four patients left the trials due to neutropenia. Fifteen patients showed complete response to drug, 177 showed partial response and 44 showed stable disease (19). Other drugs are presently undergoing clinical testing due to the success of liposomal doxorubicin. Not only drugs but antisense oligonucleotides can also be encapsulated in liposomes. The RAF anti-sense oligonucleotide is included in the liposomal formulation LErafAON. It stops the protein c-RAF from making cancer cells more resistant to radiation and chemotherapy (20). Four of the twelve patients treated with radiation for advanced solid tumors in a
phase I study had a partial response, while the other four did not. Only three patients showed lower amounts of C-RAF-1 protein, although four had lower levels of C-RAF-1 mRNA (21).

Figure 2. Proven nanoparticle delivery techniques for anticancer medications. Capable of harboring hydrophilic medicines, liposomes with a hydrophobic membrane and an aqueous core (A). Lipophilic drugs are encapsulated in polymer micelles with a hydrophilic corona and a hydrophobic core (B). Dendrimers contain several branches emanating from a central core (C). Reproduced with permission of publisher.

Polymers Micelles
Amphiphilic-block copolymers spontaneously generate spherical nanostructures with diameters of 10–100 nm termed polymer micelles (Figure 2A). These polymer micelles, which have a PEG hydrophilic shell and a hydrophobic core and are mainly generated from polymers like poly (e-caprolactone) (PCL) or poly (D, L-lactic acid) (PLA), can disseminate liposomal medicines. Additional ligands or polymer core-forming polymers can be added to polymer micelles to improve their capacity to cling to tumors or allow for controlled disintegration (22). Several micelle formulations are now being tested in clinical studies at different stages of development (23). NC-6004 (a polymeric micelle containing cisplatin) has been demonstrated in clinical studies to treat patients with various types of solid tumors. Clinical trials confirmed the results of preclinical trials (24-26) which claimed that cisplatin toxicity can be controlled if not eliminated by administering cisplatin incorporated micelles ad improved therapeutic indices. Seven of the seventeen individuals showed disease stability with lesser chances of nephrotoxicity with total hydration (Figure 2B) (27).

Dendrimers
Dendrimers, which are 10 nm-sized nanoparticles made up of several units that branch out from a central core, can have their terminal groups modified (Figure 2C). These nanostructures can store a wide range of medicinal drugs by connecting therapeutic molecules to the functional end groups, positioning them within the central cavity, or constructing several pathways between the dendrons (28). A reproducible pharmacokinetic behavior is present in all of the dendrimers which assures the intended bioavailability and efficacy. Thus, dendrimers are being used as a nanotheragnostic platform that encapsulates a variety of therapeutic, imaging, and targeting moieties for the detection and management of cancer (29). Ligands can be added to the polyamidoamine (PAMAM) chemical
structure of dendrites to increase their biocompatibility or capacity to detect tumors. PAMAM was one of the first class of dendrimers to be synthesized and fully characterized in 1985 (30). Due to their exceptional abilities to deliver genetic material, drugs, controlled release, easy modification by functional groups, less cytotoxicity and, if not most important, autofluorescence property they are used as therapeutic and diagnostic tool, making easier detection of fate of drug (31). Dendrimers offer much potential for cancer therapy, according to preliminary research. A recent study utilizing polyline dendrites showed that activated a5b1-integrin is required for tumor development and spread and PHSCN dendrimers can be immensely helpful in targeting the tumor cells. According to Yao and his colleagues' results, these dendrimers were 700 to 1,100 times more efficient than the free peptide in targeting the a5b1-integrin of tumor cells without effecting the a5b1 receptors of healthy tissues (32). Polyamidoamine (PAMAM) dendrimers to get carbon quantum dots-PAMAM conjugates (CDPs) that helped identify and treat triple negative breast cancer (33).

**Advancement of Nano-Medicine for Cancer Treatment**

Targeting methodologies are used in conjunction with strategic planning. Passive targeting of nanoparticles enhances the permeability of drugs by leaking or leaching the blood vessels surrounding the tumor cells so less nutrients reach the tumor cells, the phenomenon known as angiogenesis, hence the porous vessels allow for more drug to reach the periphery of tumor cells, indirectly targeting the cancer cells. It also has the advantage of active targeting, of being selective to tumor cells (34). Similarly, a substantial amount of research is being done on nanoparticles that contain "targeting moieties", an approach of active targeting treatment. These nanoparticles can recognize and bind to over expressed specific receptors on tumors and the endothelium surrounding them. One of the projects aims to locate and collect tumors more accessible (Figure 2). Folic acid receptors (35), G protein coupled receptors (36, 37), Transferrin receptors (38-40), Luteinizing hormone-releasing hormone (LHRH) (41), epidermal growth receptors (42) and other receptors (43, 44) that are over expressed in tumor cells are specific target sites for action and penetration of anti-cancerous drugs by nanoparticles delivery system. The receptor targeted approach is also applicable for theranostic purposes such as folate bound probes (45) can make locating and determining the folate receptor induced cancer very manageable (46). Folate linked metal nanoparticles (47) and nanoaggregates (48) with PEG and other materials are used for diagnosis and disease intervention in several tumor indices.

Folate receptors are highly over expressed in several types of tumors at a level that is 100 to 300 times higher than the average amount. Singh and his colleagues synthesized and studied the effects of 5-fluorouracil-folate functionalized PAMAM dendrites on mice. PEGylated folate-functionalized dendrites resulted in 15.5%, 20% and 10% increased injected dosage at 2nd, 4th and 8th hour, respectively, after two
injections (on days 0 and 7), compared to non-targeted control specimens. This resulted in a 40 per cent decrease in the formation of tumors compared to what had previously been seen (49). Several more studies with folate conjugated with dendrimers are underway and giving major breakthrough in specific targeting of tumor cells, conjugated doxorubicin (50) and methotrexate (51, 52) bifunctional dendrimers for folic acid targeted cancer therapy allows selective binding and killing of KB tumor cells that over express folate receptors. These studies were done in both in vitro and in vivo environment and showed preferential binding to the target sites with enhanced permeability and selectivity with respect to unconjugated drugs (51).

Figure 3. It depicts the functionalizing nanoparticles for active targeting and controlled release utilizing external inputs. Targeted nanoparticles are more likely to bind to receptors and integrin’s overexpressed in cancer endothelia or tumors, increasing site-specific accumulation. This is the result of the increased likelihood of this happening. Following the tumor localization, external signals like ultrasonography or a temperature rise can be used to start the drug's release. Reproduced with permission. Copyright 2021, Publisher.

In targeted delivery approach, Trastuzumab can be used as a component of a targeted moiety and used as a medication. Trastuzumab decorated doxorubicin nanoparticles contained 47 μg/mg doxorubicin and 33.5 μg/mg Trastuzumab and showed higher expression into targeted HER2 overexpressed cell line when compared to control cell lines. The difference was also obvious in non-targeted nanoparticles (53). Another study with nano liposomal formulation of topotecan was invested with significantly enhanced stability of drug with enhanced antitumor activity in overexpressed prostate and breast model of mice. The results were obvious in just two doses in addition to decreased side effects when compared to non-nano liposomal drug (54). scFv F5 antibody and liposome-encapsulated topotecan were used to target BT-474 breast cancer cells precisely. Anti-HER2-targeted liposomes exhibited more than fivefold higher anticancer effects than free topotecan in model studies. Another approach by angiogenesis is the overexpression of a variety of target integrin’s, such as the Trans membrane protein avb3 (55). Another feature of this process is the production of amino acid-rich peptides. The crude peptide functions as a targeting ligand on the surface of nanocarriers for tumor imaging and therapy (56, 57).

It is possible that active nanoparticle targeting will be investigated. The cRGD targeting ligand, according to Nasongkla and colleagues, has the potential to be used in
the functionalization of PEG-PLA polymer micelles containing doxorubicin (58). Overexpression of avb3 resulted in an increase in cellular absorption in SLK endothelial cells compared to non-targeted micelles. Micelles containing super paramagnetic iron oxide nanoparticles were shown to target and concentrate in tumor tissue more than non-targeted controls, as evidenced by better MRI contrast in mice with A549 lung tumors (59).

**Nano medicine Delivery Methods**

Advance techniques and formulations are being introduced for the purpose of controlling the quantity of drug delivered at selective target site, reducing the adverse effects and enhancing permeability and drug half-life to increase patient compliance to nano medicines (60). The objective of the current research is to quickly expose advance methods for treating malignant tumors to therapeutic doses that can be sustained over time. Customizing the drug release from nanoparticles does this. pH controlled delivery methods are introduced that limits the therapy to the point where extracellular compartments where tumors occur have pH values that are lower than blood. This provides us with many options for releasing the cargo at specific sites. Hence the pH responsive nanoparticles are a powerful strategy to engineer the nanoparticles delivery system (61). The release of B-poly (ethylene glycol)-poly (ethylene glycol) [N-(2-hydroxypropyl) meth acrylamide-lactate] (N-(2-hydroxypropyl) meth acrylamide-lactate) (N-(2-hydroxypropyl showed prolonged release of drug doxorubicin as Talelli and coworkers discovered that (peg-b-p [Hama- Lack]) micelles may covalently, yielding a pH-sensitive polymer micelle (62). When the pH was 7.4, just 5% of the medicine was freed in the first twenty-four hours of therapy. Micelles sensitive to

<table>
<thead>
<tr>
<th>Nanoparticle</th>
<th>Medicinal Ingredients</th>
<th>Generic Name</th>
<th>Cancer Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposome NP</td>
<td>Paclitaxel</td>
<td>EndoTAG-1</td>
<td>Pancreatic cancer</td>
<td>53</td>
</tr>
<tr>
<td>Albumin NP</td>
<td>Paclitaxel</td>
<td>Abraxane</td>
<td>lung</td>
<td>14</td>
</tr>
<tr>
<td>Lipid NP</td>
<td>siRNA against KSP</td>
<td>ALN-VSP02</td>
<td>Solid tumors</td>
<td>39</td>
</tr>
<tr>
<td>Colloid gold NP</td>
<td>TNF</td>
<td>CYT-6091 AuNPs</td>
<td>Late-stage cancers</td>
<td>37</td>
</tr>
<tr>
<td>Colloid gold NP</td>
<td>Paclitaxel</td>
<td>Genexol-PM</td>
<td>lung cancer</td>
<td>43</td>
</tr>
</tbody>
</table>

The use of ultrasound may induce medicinal compound-containing nanoparticles to seep into the surrounding environment (Figure 3). ‘The action is based on the generation of
free radicals, which can lead to the breakdown of polymers, a rise in local temperature, and cell membrane penetration (63-65). According to Schroeder and colleagues’ findings, (66) after being treated with low-frequency ultrasound, mice with the J6456 lymphoma strain had liposomes injected intraperitoneally into their abdominal cavity. A time frame of one hour when ultrasonography was utilized instead of radioactive cisplatin, around 70% of the cisplatin was freed. The concentration of cis-plating in tumors that received ultrasound was three times greater than in tumors that did not get the therapy. C-26 colon tumors in mouse footpads were given an intravenous injection of liposomes before being irradiated with ultrasound after being left alone for 24 hours. Compared to free cisplatin treatment, which could be given with or without ultrasound, cisplatin-containing liposomes significantly reduced tumor development when ultrasound was used for 29 days (67).

Table 2. PX-loaded polymeric nanoparticles

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Modification</th>
<th>NP Preparation Method</th>
<th>% EE</th>
<th>Status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA</td>
<td>—</td>
<td>emulsion-solvent evaporation</td>
<td>85</td>
<td>in-vitro</td>
<td>14</td>
</tr>
<tr>
<td>PLGA, PLGA-PEG, PCL-PEG</td>
<td>nanoprecipitation</td>
<td></td>
<td>70</td>
<td>in-vivo</td>
<td>15</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>interfacial deposition</td>
<td></td>
<td>&gt;90</td>
<td>in-vitro</td>
<td>16</td>
</tr>
<tr>
<td>TPGS (emulsifier)</td>
<td>emulsion-solvent evaporation</td>
<td></td>
<td>100</td>
<td>in-vitro</td>
<td>24</td>
</tr>
<tr>
<td>DLPC (emulsifier)</td>
<td>emulsion-solvent evaporation</td>
<td></td>
<td>15-56</td>
<td>in-vitro</td>
<td>28</td>
</tr>
<tr>
<td>DPPC (emulsifier)</td>
<td>emulsion-solvent evaporation</td>
<td></td>
<td>34-45</td>
<td>in-vitro</td>
<td>29</td>
</tr>
<tr>
<td>PLGA</td>
<td>Chitosan</td>
<td>emulsion-solvent evaporation</td>
<td>75-79</td>
<td>in-vitro</td>
<td>19</td>
</tr>
<tr>
<td>PLGA</td>
<td>DMAB</td>
<td>emulsion-solvent evaporation</td>
<td>47</td>
<td>in-vivo</td>
<td>21</td>
</tr>
<tr>
<td>PLGA</td>
<td>MMT</td>
<td>emulsion-solvent evaporation</td>
<td>~50</td>
<td>in-vivo</td>
<td>30</td>
</tr>
<tr>
<td>PLGA</td>
<td>MMT, HER2 (targeting)</td>
<td>emulsion-solvent evaporation</td>
<td>~50</td>
<td>in-vitro</td>
<td>31</td>
</tr>
<tr>
<td>PLGA</td>
<td>RGD (targeting)</td>
<td>emulsion-solvent evaporation</td>
<td>60-65</td>
<td>in-vitro</td>
<td>32</td>
</tr>
<tr>
<td>PLGA</td>
<td>Pluronic P85, transferrin (targeting)</td>
<td>nanoprecipitation</td>
<td>70-76</td>
<td>in-vivo</td>
<td>33</td>
</tr>
</tbody>
</table>
According to the findings of a recent study, delivering drugs to tumors via externally generated heat spikes might be a viable way. Nanoparticle instability is caused by the hydrophobic effects of polymers with lower critical solution temperatures (LCST), such as poly (N-isopropyl acrylamide) (pNIPAM) (68). Poon and his colleagues used doxorubicin liposomes to create thermo sensitive doxorubicin liposomes that could be heated. At 37 degrees Celsius, it was revealed that thermo sensitive liposomes produced relatively little doxorubicin (less than 10% over 30 minutes) (less than 10 per cent over 30 minutes) (69). Approximately 90% of the medication was already out in the open after only 10 minutes of being heated to 45 degrees Celsius.

Medicines are delivered in a modular format working by creating a unique multistage drug delivery system capable of overcoming the various biological hurdles that nanoparticles face on their way to the tumor and maximizing site-specific localization and therapeutic release. The work that has been done over the last few years has enabled this breakthrough. Because cancer displays differentials in the mass transfer of its constituents, this technique is driven by the need to utilize knowledge of "oncophysics" to avoid bio barriers (70). Finally, the idea is to wrap drug-containing nanostructures inside MSPs, which will protect and transport these nanoparticles until they recognize and dock with the tumor vasculature (Figure 4). As a result, the platform divides the different drug distribution operations, ranging from injection to delivery at the tumor site (71).

Figure 4. It shows the medicine distribution used to treat tumors at various stages. The multistage drug delivery approach's proposed mechanism of action calls for successful Margination and attachment to cancer endothelia, accumulation at the tumor site, and the release of medications incorporating second-stage nanoparticles. Reproduced with permission. Copyright 2019, Publisher.
mice. Whenever statistical significance is addressed, an asterisk should be used. The longitudinal relativities of MSP, which included the gadolinium contrast agents Magnetism (MAG), gad fullerenes (GF), and gad nanotubes (GNT), as well as related gadolinium contrast agents, were assessed.

Figure 5. It offers a graphic picture of chemotherapeutic delivery particles with several phases. A single mesoporous silicon particle was enclosed in a single PEG-FITC-SWNT, which was colored green, and quantum dots, which were colored red, for bright-field confocal imaging (MSP). Reproduced with permission. Copyright 2021, Publisher.

Mesoporous Silicon Particles
The platform's first stage comprises mesoporous silicon particles, which will be injected into the patient's bloodstream and residence. In contrast, the platform's second step comprises nanoparticles, which will be loaded with anticancer medications and referred to as the third stage (also known as the third stage) (72). Porous silicon was chosen as the housing material since it is FDA-approved and biodegradable under physiological circumstances. This was the initial stage. Nanostructures built of porous silicon represent a lesser risk throughout their lifetime because they degrade into innocuous silicic acid metabolites. Chemical compositions and iodization settings can alter pore widths and porosity, but the size and shape of MSP are determined by the photolithographic masks used in the production process (73). We established processes at our research Centre that allow us to make particles with an outer diameter ranging from 500 to 1.6 nm and a mean pore size ranging from 5 to 80 nm (74). Because silicon chemistry is flexible, it may be functionalized with PEG and target moieties to accelerate tumor growth. Its enormous size also allows it to hold a large number of nanoparticles. Mice who have received an intravenous injection do not coagulate, indicating less likely to develop thrombosis (75).

Furthermore, the second step can utilize a variety of nanoparticles in several different combinations. Quantum dots (QD) and PEG-FITC-SWNT-single-walled carbon nanotubes (SWNT) were used to demonstrate this in Fig. 5. Although SWNT and QD were co-localized in a single MSP, SWNT was spread throughout the particle, while QD was concentrated in the Centre (green and red, respectively).

Multistage Drug Delivery
There is no doubt that multistage drug delivery allows for more versatility and the capacity to change the pharmacokinetics of injectable drugs dramatically. In silicon mathematical modelling and in vitro and in vivo studies were utilized to construct MSP
with optimum shapes and sizes and limit RES absorption as feasible (74). Margination dynamics, firm adhesion, and internalization control were mathematically separated into three critical components for this endeavor. The tendency of nonspherical particles to migrate laterally within the blood flow was discovered in vitro tests. A range of particle shapes was introduced into a parallel-plate flow chamber and exposed to carefully regulate hydrodynamic conditions. These experiments were carried out in a lab setting. When particles are oblong rather than spherical, they have a better probability of colliding with the walls of blood arteries, and they may more easily attach to specific vascular targets. Because they have a more significant number of ligand-receptor interactions, platelet-like oblate-spherical particles stick to artery walls more tenaciously than spherical particles (76). Bio distribution experiments on MDA-MB-231 breast tumor-bearing mice demonstrated that various particle shapes delivered intravenously had various effects (Figure 5). Hemispherical particles accumulated significantly faster in tumors than spherical, discoid, or cylindrical particles. According to our findings, the buildup of MSP in arteries linked with tumors is assisted by hemodynamic features and bio distribution (77). This discovery emphasizes the necessity of considering the best Nano carrier shapes for applications that need site-specific medicine delivery. The efficacy of a particle is ultimately determined by cell-to-cell interactions that occur after a particle has travelled to the circulation and microenvironment of a tumor.

**Endothelial Cells During the Serum Opsonization Process**

Negatively (due to oxidation) or positively (due to APTES alteration) charged macro pinocytosis (Figure. 5). As can be observed from these findings, APTES-modified MSP was shown to be more quickly absorbed by endothelial cells during the serum opsonization process. In order to maximize the consequences of cell death, finding the proper release rate for the therapeutic payload is critical to MSP's success. Researchers discovered a link between the biodegradation of porous multistage particles and the release of second-stage nanoparticles from MSPs under physiological conditions. Manipulation of this link can affect the kinetics of nanoparticle second-stage release. The breakdown of porosity-limited multistage particles occurs in hours rather than days, allowing the payload to be delivered slowly over time (78). Furthermore, the functionalization of the MSP surface was demonstrated to be closely connected to the degeneration of the MSP surface. The effectiveness of a two-stage drug delivery strategy that incorporated liposomes that carried sienna against EphA2, an oncogenic tyrosine kinase receptor, was investigated using an ovarian cancer mouse model (SKOV3ip1). Over two weeks after loading liposomes into MSP, more than 80% of the sienna was released (approximately 80 per cent after two weeks) (79). For three weeks, mice were given sienna-liposome injections into their veins twice a week. Each EphA2-siRNA injection included 5 LG of EphA2-siRNA. Those in a different group were given a single dose of
EphA2-siRNA-liposomes, which were made from EphA2-siRNA-liposomes that had gone through many rounds of preparation. The multistage delivery strategy produced a more significant response to treatment than a single injection of the EphA2 protein from the SKOV3ip1 tumor (Figure. 5). Compared to control sienna-liposomes and multistage sienna-liposomes, EphA2-siRNA-liposomes were able to reduce the weight of the tumor by 54.2 per cent and 65.3 per cent, respectively (80). EphA2-siRNA-liposomes given as a single dosage had an anticancer effect similar to six intravenous doses. There is little question that the liposomal sienna formulation's better bio distribution and sustained release at the tumor site contributed to this result.

**T1 Contrast Agents**

MSP was used to encapsulate MRI contrast compounds and research their magnetic properties to produce a theranostic Nano platform that may be used for imaging and treatment. T1 contrast agents such as Magnetism (made by Bayer Schering Parma in Berlin), gad fullerenes, and gad nanotubes were encapsulated with MSP (81). Fig.5 shows a strong relationship between increased image contrast and increased longitudinal proton relativity of gadolinium-loaded MSPs following encapsulation. In some of these situations, the relativity values were 4–50 times greater than those of commercially available formulations due to gadolinium Nano confinement and clustering in the MSP. Because gadolinium was present in the MSP, this is most likely the case (82). According to preliminary data, multistage delivery has much promise in accurately identifying and treating cancer.

**Challenges for Nano-Medicine**

The power of nanotechnology, potentially carcinogenic compounds may now be recognized promptly and accurately. To explore the effects of molecular shifts in this manner, just a few cells are required. When applied in the field of medicine, nanotechnology has the potential to throw open entirely new doors for the diagnosis and treatment of disease. The challenges associated with nanotechnology include, among other things: a) the prohibitively high costs of research and products; b) the intricacy of their production. The integration of nanotechnology with a wide variety of medical specialties is what's meant to be referred to as "nanomedicine" (83-85).

**CONCLUSION**

Chemotherapy is challenging to come by in large enough doses to be provided locally, even though it is an excellent cancer adjuvant treatment. Although Nano medicine platforms like liposomes and polymer micelles have considerably improved drug delivery, several physical challenges remain. Ultrasound has recently been used in Nano medicine and the integration of highly selective chemicals that target cancer receptors (such as folic acid) (e.g., ultrasound). Our team recently looked at the development of a medicine that went through several stages. This delivery technique uses mesoporous silicon carrier particles as the medium for delivering nanoparticles containing medicine to cancer cells. As a result of the increased cargo protection, superior targeting, and delayed drug release, it has been established that the multimodal chemotherapeutic strategy has
higher anticancer effectiveness. Despite the advances made in this field, the future of Nano medicine will result in new platforms for the treatment of tumors. These platforms may pave the way for individualized treatment, which will enhance patient outcomes.

ACKNOWLEDGEMENTS

The authors thank their parental university for providing the necessary facilities to accomplish this work.

DECLARATIONS

Authors’ Contributions

UN and TA contributed to study concept. SK, MK and AS contributed to study design and data collection. IN, WW and IJ contributed in data analysis and interpretation. FNK, ZSZ and UK did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical Approval

Not applicable

Conflict of Interest

The authors declare no conflict of interest among them.

Funding

None

REFERENCES


45. Alberti D, Protti N, Franck M, Stefania R, Bortolussi S, Altieri S. Theranostic nanoparticles loaded with imaging probes and rubrocurcumin for combined cancer therapy by folate receptor