International Journal of Drug Delivery 4 (2012) 275-288

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Nanotechnology in drug delivery systems

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Abstract

Nanotechnology is the engineering of purposeful systems at the molecular scale. It has an impact on every industry counting semiconductors, manufacturing, and biotechnology. Biomedical nanotechnology, bionanotechnology and nanomedicine are increasing biomedicine offered hybrid fields. The oncoming generations of nanoscale biomedical/pharmaceutical products will have object specificity, carry multiple drugs, and potentially release the payloads at desired unreliable time periods. Nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferable to the use of injectable drugs, for the reason that the latter frequently show first order kinetics that may ground toxicity and decreased drug ability. Bioadhesive polymers have broadly been used in transmucosal drug delivery systems. These materials can be combined into pharmaceutical formulations, drug absorption by mucosal cells can be increased or the drug can be released at the position for an expanded duration of time. Over the past few years, nano particle ceramics have been broadly handled in a wide spectrum of biomedical requests, and drug delivery is one of the wildest developing and increasing areas for nanoceramics, drawing growing consideration. Certainly, researchers are recognizing that the amazing characteristics of nano particle ceramics exhibit excellent platforms for drug transportation and controlled release compared with polymeric platforms. This review defines various nano particle ceramics and bio/mucoadhesive polymers used in drug delivery. The presented data displays that these systems can be used excellently for continued release applications. They assure the basic demands of biocompatibility, drug loading and tolerated release sketches spreading to several weeks, and are proper materials for present implant technologies.

Keywords: Nanotechnology, nanomedicine, drug delivery, Biotechnology

Introduction

Nanotechnology is the study, design, creation, synthesis, manipulation, and application of materials, devices, and systems at the nanometer scale [1]. The prefix"nano" refers to one-billionth. When applied in the metric scale of linear measurements, a nanometer is one-billionth of a meter. The term "nanotechnology" is now normally used to mention to the construction of new objects with nanoscale dimensions between 1.0 and 100.0 nm [2-4]. Nanotechnology is used to define materials, devices and systems with constructions and constituents displaying new and significantly increased physical, chemical and biological properties as well as the occurrences and procedures enabled by the capability to control properties at nanoscale [3].The application of nanotechnology in the field of health care have come under great attention in current periods. There are numerous behaviors today that take several time and are also very pricey. Using nanotechnology, faster and much cheaper behaviors can be developed [1,4]. Simultaneous with the rising life width in today's world, the numeral of age recounted diseases has enhanced. Hence, a need for new treatments, implants, prostheses, long term pharmaceutical usage as well as the need for elongating the life period of the present techniques has risen [5,6]. Nanotechnology, when used with biology or medicine, is mentioned as nanobiotechnology. This technology should be used very cautiously because the lives of human presences are being dealt with. If used correctly, it can be very operative in providing behaviors with minimum side-effects [1]. The current period of medicine growth started with the finding of vaccines in 1885 and methods for cleansing of drugs from plant bases in the late nineteenth century, tracked by the introduction of penicillin after its detection in 1929, and a following age of creative drug innovation. The increment and manufacture of numerous pharmaceuticals includes the genetic modification of microorganisms to convert them into drug-producing factories. Examples are recombinant deoxyribonucleic acid (DNA), human insulin, interferon, erythropoietin (for the dealing of anemia connected with chronic renal failure/AIDS/antiretroviral agents,

chemotherapy associated anemia in nomnyloid malignancy patient), and tissue plasminogen activator [7]. According to Ochekpe et al[3] some of the encounter with most drug delivery systems contain pitiable bioavailability, in vivo constancy, solubility, intestinal absorption, tolerated and targeted delivery to site of action, therapeutic efficiency, side effects, and plasma fluctuations of drugs which either fall below the minimum effective concentrations or surpass the safe therapeutic concentrations. Nevertheless, nanotechnology in drug delivery is a method schemed to overwhelmed these challenges due to the enlargement and construction of nanostructures at submicron scale and nanoscale which are mostly polymeric and have numerous benefits[3]. Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures. The size of nanomaterials is similar to that of most biological molecules and structures; consequently, nanomaterials can be valuable for both in vivo and in vitro biomedical investigation and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, different agents, analytical tools, physical therapy applications, and drug delivery vehicles [1]. Perspective drug delivery systems can be described as mechanisms to introduce therapeutic agents into the body. Chewing leaves and origins of medical plants and inhalation of dust from the burning of medical materials are examples of drug delivery from the initial times. Nonetheless, these primeval methods of delivering drugs lacked homogeneity. This managed to the improvement of dissimilar drug delivery techniques in the advanced part of the eighteenth and early nineteenth century. Those techniques contained pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulizers, and many other traditional delivery mechanisms. Numerous of these delivery mechanisms use the drugs derived from plant extracts [7,8]. The main methods to deliver drugs are oral and injection, which has limited the development of drug growth. New biologic drugs for instance proteins and nucleic acids need new delivery skills that will diminish side results and help to improved patient compliance [1,2]. New drug delivery processes may permit pharmaceutical companies to progress new formulations of off-patent and soon-to-be off-patent drugs. Reformulating old drugs can decrease side results and rise patient compliance, therefore saving money on health care delivery [9].Normally, nanostructures have the capability to defend drugs encapsulated inside them from hydrolytic and enzymatic degradation in the gastrointestinal region; target the delivery of an extensive range of drugs to numerous parts of the body for sustained release and thus are capable of deliver drugs, proteins and genes through the per oral route of administration [9,11]. They deliver drugs that are extremely water insoluble; can bypass the liver, thereby avoiding the first pass metabolism of the combined drug [3,9,10]. They enhance oral bioavailability of drugs because of their particular approval mechanisms for instance absorptive endocytosis and are able to continue in the blood circulation for a extended time, releasing the combined drug in a sustained and incessant style leading to less plasma variations thus diminishing side-effects produced by drugs[3,11,12]. As a result of the size of nanostructures, they are able to infiltrate into tissues and are taken up by cells, permitting effective delivery of drugs to sites of action. The acceptance of nanostructures was found to be 15-250 times larger than that of microparticles in the 1- 10μm range [13,14].

Controlled drug delivery demands have expended quickly with new developments in biomedical sciences besides parallel improvements in advanced materials and technologies [15,16]. The purpose of controlled drug delivery is to control the essential quantity of drug safely and effectually to specific sites in the human body and to control the temporal drug profile for maximum therapeutic benefits. The knowledge of controlled drug delivery happens around 1960s when Folkman et al, realized that a rabbit can doze off by mingling its blood inside a tube which had been described to an anesthetic gas. This was the first proposal of a drug delivery implant [3,9]. He suggested that small, closed sections of such tubing inclosing a drug could be implanted, and if the silicone didn't vary in dimensions or composition, the implant would become a continual rate drug delivery device. [15] He also displayed that the rate reduced as the tubing thickness enlarged, which is apparent today, but back then it was the first recommendation of a zero order controlled drug delivery implant in vivo [15,16]. Controlled release over an extended duration is highly valuable for drugs that are quickly absorbed and removed from the body after administration [17]. A controlled drug delivery system needs simultaneous attention of numerous aspects, for example the drug property, method of management, nature of delivery vehicle, apparatus of drug release, capacity of targeting, and biocompatibility. These have been potted in Fig. 1.

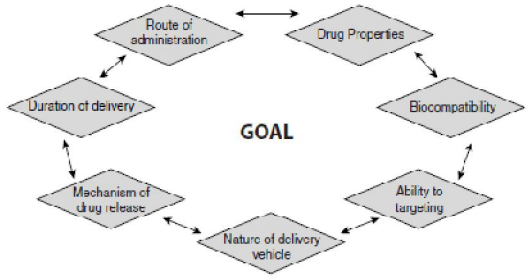

Figure 1. Design requirement for a drug delivery systems[Adapted from Ref. 7].

In this review article, we discuss a class of drug delivery applications which are done by facilitating metallic, ceramic or silicon implantable devices. We analyze a select few of the best known inorganic nanoporous implant coatings used in drug release applications, explore their fabrication and biocompatibility.

Nanotechnology in Drug delivery System

The US national nanotechnology initiative (NNI), invested in October 2000, affords a federal idea for nanotechnology-based investment concluded the coordination of 16 US departments and self-determining agencies. The efficacy of drug delivery to innumerable parts of the body is unswervingly modified by particle size. Nanostructure refereed drug delivery, a basic technology for the substantiation of nanomedicine, has the potential to increase drug bioavailability, progress the timed release of drug molecules,

and suitable accuracy drug targeting [6,18,19]. Additionally, nanotechnology suggests a number of innovative styles to control drug transportation through the body, whereby pharmaceuticals can be released in precise, well-timed, targetable or environs-receptive ways[7]. Nanoscale drug delivery schemes can be applied within pulmonary therapies [6], as gene delivery vectors [11], and in stabilization of drug molecules that would then reduce too quickly [19-21]. Complementary profits of using targeted nanoscale drug carriers are decreased drug toxicity and more well-organized drug delivery [14,21]. Anatomic structures for example the blood brain barrier, the branching pathways of the pulmonary system, and the tight epithelial junctions of the skin make it problematic for drugs to spread many wanted physiologic targets. Nanostructured drug transporters will help to infiltrate or overwhelmed these obstacles to drug delivery [6]. Nanotechnology is fixed to enhance quickly over the coming years. Investigators are increasing modified nanoparticles the size of molecules that can deliver drugs straight to unhealthy cells in your body. This manner should seriously decrease the damage treatment such as chemotherapy does to a patient's healthy cells, When it's achieved, [1]. Table 1 shows some examples of nanotechnological applications [3]. We have newly seen the introduction of the first nano-delivery system, a reformulated sort of the anticancer agent doxorubicin. Here the drug is covered within polyethylene glycol (PEG)-coated liposomes less than 200nm in diameter. As a consequence of the sustained release of the drug from the liposome and its elongated movement time from the "stealth" capability deliberated by the PEG, intravenous treatment is desired every four weeks. The use of PEG to mask a drug from our natural resistances has also been used for antibody grounded therapeutics [1]. Rewards of nanostructure-mediated drug delivery contain the capability to deliver drug molecules straight into cells [19] and the capability to goal tumors inside healthy tissue [20,21,6].Concluded accurate controller of the drug transporter architecture, the release of the drug can be adjusted to accomplish a preferred kinetic contour. Three of the most common kinetic profiles are zero order, first order, and Higuchi; these are illustrated in Figure 2 and stated mathematically in Eq. 1. The delivery of most drugs is done via oral administration or by injection and tracks first-order kinetics. The perfect release profile for most drugs would track a fixed release rate so that the drug levels in the body continue steady while the drug is being managed. Extra new transdermal drug delivery mechanisms pursue the Higuchi model [22]. As will be revealed in following units, nanostructured polymeric and silica nanoparticles are being developed as drug carriers which gain near zero-order kinetics.

Zero order : $Dt = D_0 + k_0 t$

First order : $\ln Dt = \ln D_0 + k1t$ (1)

Higuchi : $Dt = D_0 + kH\ t1/2$

where Dt is the quantity of drug released at time t, D0 is the original quantity of drug released, consequence of original fast release, k0 is the zero-order release constant, k1 is the first-order release constant, and kH is the Higuchi release constant[6].

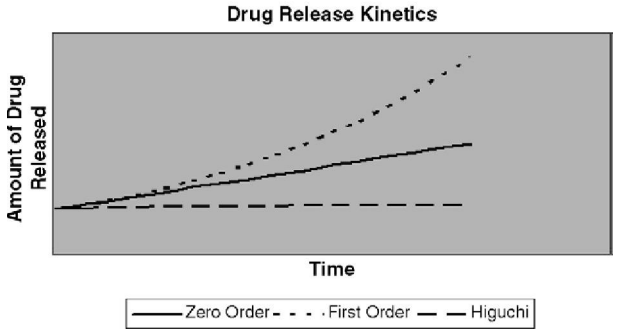

Figure 2. Drug release profiles from zero order, first order, and Higuchi kinetics [Adapted from Ref. 6].

Drug loading and release

A significant condition for nanoporous coverings is that they must be able to load and release the drug, additionally to having biocompatibility, mechanical and chemical constancy. Overall, a substrate must have the capability to combine a drug, preserve it and deliver it regularly over the time to a particular target site [23]. For particular requests, some extra properties might also be essential such as being flexible to the implants, being biodegradable or being non-erodible. The holy grail of controlled drug delivery is to transport the therapeutic amount of the drug to the spot in necessity for the required quantity of time. The amount of the drug and required release time vary depending on the request. Nevertheless, since traditional drug delivery techniques already cover the short period drug organization, continued drug delivery has attracted more attention. There is dissimilar style for controlled drug delivery such as targeted drug delivery, controlled drug delivery, sustained drug delivery, response controlled drug delivery, and implantable controlled drug delivery [7]. Drug loading for the nanoporous templates generally is achieved through capillary achievement by either dipping the patterns in the concerted drug resolution or dipping the solution gradually on the pattern surfaces [2,24]. Different methods have been used to rise and accelerate the consumption of the drug, counting surface improvement, sonication or solution aids [2]. Urano and Fukuzaki [58] calculated desorption kinetics of bovine serum albumin (BSA) from alumina particles. They described the desorption kinetics with the first order kinetic model by Bourne and Jennings [25] as:

$$-dI^f/dt = k^f I^f \text{ and } -dI^s/dt = k^s I^s \quad (2)$$

where I^f and I^s are the quantities of faster and slower desorbing BSA respectively and k_s are the desorption rate constants. Drug release measurement investigates rely on the kind and properties of the drug used. For self-fluorescent or fluorescent-tagged drugs, for instance doxorubicin or fluorescein isothiocyanate-conjugated dextran, respectively, fluorometry is an easy way to measure the

Table 1: Applications of nanotechnology [Adopted from Ref.3]

Nanotechnology area	Application
Nanoelectronics	
Information and computing	Quantum dots and nanowires in cameras and personal computers. Nanotubes instead of cathode rays in televisions. Semi conductor – silicon nanowires containing functioning electronic and optical devices.
Sensors	Nanomaterials used to assess the quality of the soil and water, and determine the state of plants, food and other products.
Nanomaterials	
One-dimensional materials	Thin films and layers used in waterproof fabrics and electronics. Surfaces in fuel cells and as catalysts
Two-dimensional materials	Inorganic nanotubes such as molybdenum disulphide for catalysis and energy storage.
	Nanowires such as silicon nanowires for data storage, electronic and optoelectronic devices.
	Carbon nanotubes for sensors, electric current transmission and antistatic packaging.
	Nanotubes as containment for hydrogen in hydrogen fuel cells
	Biopolymers such as DNA molecules
Three-dimensional materials	Nanoparticles employed in cosmetics, textiles, paints, catalysis and drug delivery.
	Fullerenes are carbon materials which are employed as lubricants, drug delivery vehicles and in electric circuits.
	Dendrimers are polymeric molecules used in coatings and inks, for drug delivery and environmental remediation by trapping metals such as copper (II) which is then removed by ultra-filtration.
Nanobiotechnology	
Bionano-sensors	Combinations of enzymes and silicon chips implanted in humans or animals to monitor health and administer corrective doses of drugs.
Biomimetic structures	Diagnosis of diseases, molecular imaging and drug delivery
Drug delivery	New formulations for drug and gene therapies
Tissue engineering	Reproduction and repair of damaged tissues using nanomaterial-based scaffolds

drug release [26]. UV spectrometry can be used to control the quantity of drug particularly if the drug has a high UV absorbance [25]. Additional release measurement approaches contain high performance liquid chromatography (HPLC) [2,26] and micro-BCA assays to measure the protein content [2].

Nanophase ceramics for improved drug delivery

After more than a period of study and improvement, nanotechnology has reformed the traditional thinking of using ceramics for drug delivery [27]. Even though drug delivery has been a polymer-dominated field, the developing of nanotechnology means that ceramic materials are now displaying much ability for many drug delivery requests. Nanophase ceramics already have been broadly used in a wide spectrum of biomedical applications, and now drug delivery is one of the fastest developing and emerging fields for nanoceramics, drawing rising consideration over the past few years [27]. Definitely, investigators are recognizing that the unexpected characteristics of nanophase ceramics recommend that they can be outstanding stages for drug transportation and controlled extended release compared with polymeric platforms [28]. The developments nanophase ceramics are creating in drug delivery seem to potential that these materials will resolve many of today's challenging medical problems. Based on their architectural

variances, the nanophase ceramics can be located into two general groups: nanoparticles and nanoscaffolds [27,28].

Ceramic nanoparticles

Particulate drug transporters (as opposite to two-dimensional coatings or three-dimensional scaffolds) have a variability of benefits for use in drug delivery and are possibly the greatest common ceramic drug delivery platforms today[27].Particulate transporters can simply carry drug objects in volume-confined organization ways and, thus, can deliver drugs in slightly aggressive procedures just as their polymeric counterparts. Particulate transporters also have great surface area-to-volume ratios that permit for a high drug load and a extended drug-release profile [3,4]. Developments in nanotechnology have additional reinforced these benefits by providing extreme slight particles of high pureness and enormously high surface area-to-volume ratios along with reasonable manufacture procedures with a high controller of particle size, morphology or porosity [2,4]. Nanoscale drug-carrying particles can increase endocytosis of drugs by target cells and can also enable bottomless diffusion into capillaries and through fenestrations to, finally, improved cellular acceptance. High surface part-to-volume ratios of nanoparticles and their related high surface actions can additional expand drug-loading competences and constancy. These incomes that medical specialists can accomplish superior drug control and continued release [1,2,4,7,28]. Nevertheless, all of the above benefits are generally true for polymers too, and are associated primarily with their nano size. Ceramic nanoparticles keep numerous single properties compared with polymeric or metallic nanoparticles. First; ceramic nanoparticles typically have longer biodegradation times, an exclusivity essential to diffusion-controlled drug release kinetics. Second, dissimilar polymers, ceramic nanoparticles in aqueous situations usually do not great or change porosity and are more constant when variations in pH or temperature are encountered. Third, fictitious ceramic nanoparticles can have the same chemistry, crystalline structure and size as the components of targeted tissues. Their construction develops the material's bioactivitiy and biocompatibility even before releasing drugs [28,29].

Ceramic nanoscaffolds for drug delivery

Nanotechnology-generated ceramic scaffolds have also proved remarkable potential for controlled drug delivery. The ceramic scaffolds were originally considered as helpful architectures to control and straight cellular manners by generating a biomimetic environs. Ceramic nanoscaffolds are regularly 3-D and porous, even though in some cases they are 2-D coverings or films. They mimic the in vivo environment of cells more totally than do nanoparticles [27]. The improvement of ceramic scaffolds for biomedical applications that imitator inherent tissue structure is progressively correlated with nanotechnology. These methods have been playing an enormously essential character in the scheme, construction and modification of sophisticated drug-delivery scaffolds. The structural benefits of ceramic nanoscaffolds consist of high porosity, high volume-to-area ratios, high surface area, high structural constancy and extended degradation times [27,28]. These properties create them powerful methods for the storage and controlled release of drugs, particularly drugs for in-situ anti-infection and anti-inflammatory targets. Consequently, most drug-eluted ceramic nanoscaffolds work numerous purposes, for instance drug delivery, directing cell growth or tissue generation, and mechanical amplification. Definitely, the mechanical amplification furnished with ceramic scaffolds far exceeds that furnished with polymeric scaffolds [26,27].

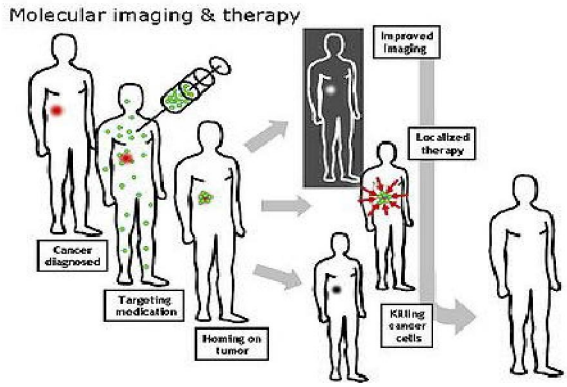

Figure 3: A schematic photograph viewing how nanoparticles or other cancer drugs might be used to treat cancer [Adapted from Ref. 1].

In summary, nanophase ceramics have excellent prospects for contribution targeted drug delivery attempts attributable to their single capability to control drug release kinetics, integrate multifunctional molecules and object definite focus positions. Even though the challenges that nanophase ceramics face are solemn and the harmfulness of nanomaterial's is a growing affection, the supernatural properties of nanophase ceramics and the continuous progresses in accepting their metabolism and abolition tracks from the body proposal more favorable opportunities to diagnose, recognize and treat several diseases through drug delivery[27].

Nanoporous Templates

Supervisory the session of nanoelements is one of the serious methodical fences in nanomanufacturing. There is a requirement to manner fast concentrated session of nanoelements at high rates and over great regions [26,30]. Additional request of nanoporous templates are well-known for continued drug release. Formal drug delivery organizations, using different pharmacological quantity forms, make quick organization of the drug. To preserve drug concentration in therapeutically actual range, numerous drug organizations is compulsory in the conventional techniques. With the improvements in technology, controlled drug delivery systems have been advanced [2,4].

Drug Release from Nanotemplates

Controlled drug delivery requests have extended rapidly with new developments in biomedical sciences as well as equivalent progresses in advanced materials and technologies [27,30]. A

main necessity for nanoporous coatings is that they must be capable to load and release the drug, besides possessing biocompatibility, mechanical and chemical stability. Overall, a substrate must have the capacity to integrate a drug, reserve it and deliver it regularly over the time to a particular goal site [31]. One of the unparalleled aspects of these nanoporous coatings is the capability to exactly control the surface properties. By changing the pore size, distribution and density, drug loading and release can be reformed. Surface charges of these pores can also be adjusted to hydrophobic or hydrophilic to accommodate multiplicity of drug molecules [26,31]. The pore size of the sheath is particularly imperative specially when it becomes comparable with the size of the molecule since the diffusion rate turn into pore size dependent a phenomenon mentioned to as delayed or limited diffusion [1,2,27].The experimental process of in-situ drug release measurements is potted in Figure 4.

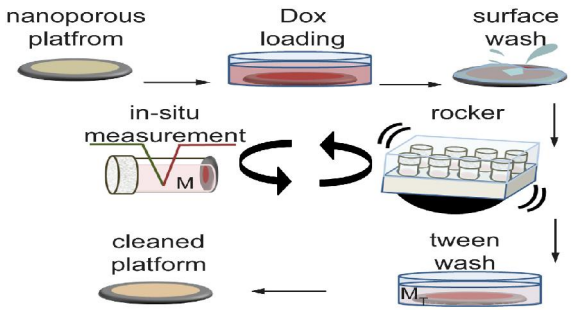

Figure 4: Diagram of the experiment protocol [Adapted from Ref. 2,4]

The most common process to make the release assays for the measurements is assembling aliquots from the release medium periodically and substituting it with new solution. When the amount of the drug is measured in the aliquots by any of the dimension methods, the whole drug quantity in the release medium can be accounted [2].

Nanoporous Aluminum oxide platforms

Newly, anodic aluminum oxide (AAO) has developed one of the greatest general self-ordered episodic, porous templates. Overall the highly advanced, greater organization of nanopores in AAO templates is achieved by using a two-step anodization procedure [1], relatively simple processing technique. The AAO porous construction can be outstandingly changed based on processing factors and both porous and tubular shapes can be accomplished and customized with pore diameters amongst 5 nm - 10 μm and film thicknesses reaching over 100 μm [32]. In relations of biological uses, the characteristic episodic porous films of AAO has been used for compressing enzymes [33], implant surface layers on Ti alloys for bone in growth [34], sheaths for hemodialysis [35], circulatory stentapplications [36], biofiltration [37], and drug delivery[33,38,39].

AAO platforms were organized by two-step anodization of aluminum foil underneath 15 V constant voltages in 5 wt% oxalic acid solution. The next step anodization was completed for 4 hours causing 20nm pore diameter and 2μm array thickness. AAO platforms were also organized by the same two-step anodization technique but under 130 V and in 0.3 M phosphoric acid solution. Resulting 4 hours of second step anodization, the platforms were dipped in 5%phosphoric acid for 80 minutes for pore broadening. The AAO of 200 nm pore diameter and 10μm array thickness was accomplished, after the pore spreading [2,4,33].

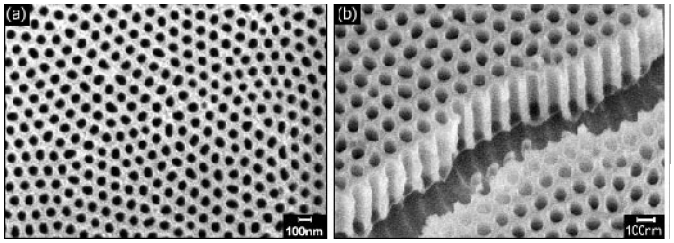

Figure 5:SEM images of nanoporous alumina nanotemplate. (a) Planar observation image of the template with uniform episodic nanoholes over large length scales, scale bar=100 nm and (b) cross-sectional vision of the template displaying smooth cylindrical nanochannels about 250 nm in height spreading to the aluminum substrate at the bottom, scale bar=100 nm.[Adapted from Ref.[2,4].

AAO nanotubes are an example of a multidisciplinary method for joining nanotechnology, biomedical engineering, and precise drug delivery where antibiotics, growth aspects, etc. are suitably required as well as accurate biointegration is preferred [11]. The usage of AAO nanotubes is a novel medical method not only for orthopedics, but also for cure of numerous other drug eluting implants which preferably would release for elongated episodes of time, on the order of days, weeks, even months[2,33].

Anodic Titanium Oxides (ATO)

Titanium and its alloys have been expansively used in orthopedics and dental implant techniques because of its mechanical strength and outstanding biocompatibility. Upon exposure to oxygen titanium progresses a coating of oxide TiO_2 or titania on its surface which is accountable for its biocompatibility. Nevertheless, it is probable to produce this cover of titania on an implant surface in a well-ordered fashion to simplify confined drug delivery. Titania nanotube templates are made-up using an anodization process (Figure 8). Most regularly used electrolytes for titania nanotemplate fabrication are hydrouoric acid (HF) [5], fuoride ion inclosing baths with organic electrolytes [16] or chlorine based electrolytes [40]. The tube size and ultimate length of titania template can be well-ordered by the sort and pH of the electrolyte along with the functional voltage like fabrication of alumina [2,41].Popat et al. [42] studied the effects of titania nanotube templates as continued drug release platforms on the serious or chronic contagion rising after orthopedic implant operations. For this contagion presently used solutions are not completely operational as a result of delivery route difficulties: oral process is not effective and even intravenously the drug cannot spread to the

infection spot in the bone tissue because of necrotic or avascular tissue after the surgery.

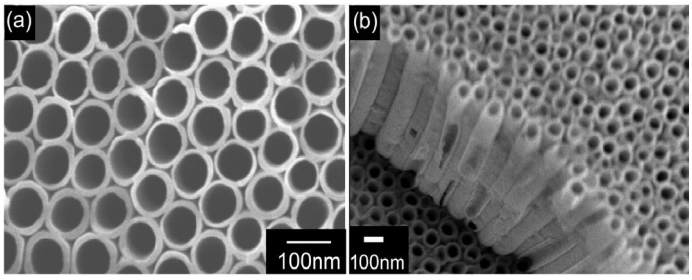

Figure 6. Titania nanotube templates fabricated (a) surface view and (b) cross-sectional view [Adapted from Ref. 4].

They examined measured antibiotic release from the titania templates to stop bacterial adhesion and also to protect Osseointegrative possessions of the nanostructured surface. Their studies presented that there is nearly 70% decline in the populace of the bacteria colonies with drug-releasing nanotemplate compared with titanium or titania nanotemplate devoid of any antibiotic after 4 h of development. Additional encouraging in vitro revision has been completed by Aninwene et al. [43] to progress properties of titanium for orthopedic requests by anodizing and consequently covering the titanium with antibacterial and anti-inflammatory drugs. The drugs were overloaded by two dissimilar techniques: modest physical adsorption which contains dripping the templates in the drug solution and simulated body fluid (SBF) in which templates saturated in the mixture of drug and SBF solutions. The release measurements exposed developed elongated release of both kinds of drugs in case of SBF supporting loading comparing with modest adsorption [4].

Porous silicon templates

Silicon-based structures can be made-up by photolithography, etching, and deposition methods generally used in the production of semiconductors and microelectro mechanical systems (MEMS). The most generally examined silicon-based materials for drug delivery are porous silicon and silica, or silicon dioxide. Figure 7 displays a nanoporous membrane made-up on a silicon substratum [6,44].

According to Gultepe et al, [2,4] porous silicon is fundamentally a net of holes within an interrelated silicon matrix. It has a numeral of properties that create it a striking material for controlled drug delivery requests: controlled pore size, well studied surface chemistry and the unbeatable optical properties that permit in vivo observing [4,45-47]. For construction of porous Si, the anodization is normally done by using hydrofluoric acid based electrolytes (Figure 8). Porous Si has a very broad pore size range; it is possible to accomplish nano-, meso- or macroscale pore sizes by anodization [48]. Additional talented study has been done by Eduardo Ruiz-Hitzky et al,[49] that Silica-based bio-nanocomposites for drug delivery targets have been managed as nanospheres by incomes of spray-drying or CO2 supercritical drying methods. Hybrid nanoparticles created by algalpolysaccharides for instance alginate and carrageenan are

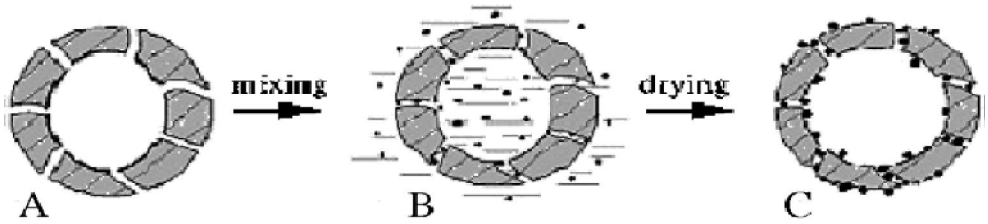

Figure 7. Preparation of hollow silica nanoparticle - based drug carriers. A, Silica nanoparticle. B, Suspend drug molecule with silica nanoparticle.C, Dry blend to catch drug molecule. Reprinted with permission from Biomaterials [Adapted from Ref. 6,45].

potential transporters for the targeted delivery of drugs because of their capability to go into the intracellular space of cells and to their lack of cytotoxicity [49].

In other cases, silica nanoparticles help as a reinforcement of biocide molecules and their dispersal in hydroxypropylcellulose permits the procurement of coverings films with fungicide and insect killer acting [49].

Calcium Phosphates nanoporous structures

Biomineral containing calcium phosphate, hydroxyapatite (HA), calcium silicate, calcium carbonate, and calcium sulfate, are essential calcium-based inorganic biodegradable materials and have been broadly used in biomedical field [50]. Amongst the half of the biomineral, calcium-based inorganic biodegradable nanomaterials (CIBNs) counting calcium phosphate, hydroxyapatite (HA), calcium silicate, calcium carbonate, and calcium sulfate, etc, are essential materials and have been broadly used in biomedical fields for example bone cements, drug delivery, tooth paste additives, dental implants , gas sensors, ion exchange , catalysts or catalysts assistances , and host materials for lasers. Calcium silicate is used in drug delivery and bone tissue regeneration due to its good biocompatibility, bioactivity, and degradability [50].The drug loading and emancipating materials are frequently prepared of the biodegradable polymers.

With the development of CIBNs, their application can also be prolonged to controlled drug delivery system. Some studies have been done on calcium silicate transformation to bonelike apatite/HA, however few have prolonged their applications in drug delivery organisms [51,52]. The calcium silicate hydrate has the

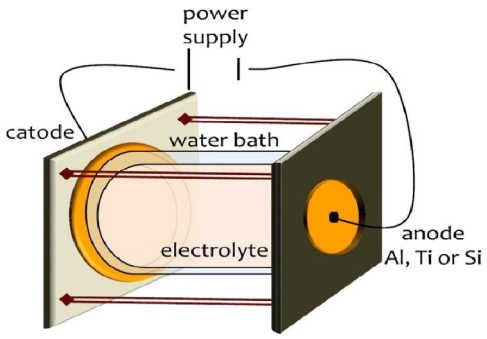

Figure 8: Anodization setup for nanoporous alumina, titania and Si fabrication Adapted from Ref. [2,4]

benefits of great definite surface area, large pore volume, enormously high drug-loading capability, adaptable drug-release rate, qualified bioactivity, and acceptable biodegradability. Furthermore, calcium silicate hydrate can completely transform to HA after the drug release in simulated body fluid, suggesting the good bioactivity and biodegradability.

In addition the hierarchically nanostructured mesoporous ranges of calcium silicate hydrate, they also organized HA and calcium silicate nanostructured porous hollow ellipsoidal capsules, which were created by Nano plate nets using the mineral $CaCO_3$ pattern (Figure 9) [53].The drug loading and release manners of HA hollow capsules designated that HA hollow capsules had a high definite surface area and high storage capacity. This is consist with Gultepe et al, [4] investigation that they have shown hydroxyapatite (HA) is nanostructured biomaterial which is used for drug deliver applications. As a result of their exceptional properties such as biocompatibility, capability of self-setting within the bone crater, moldable and osteo-conductive nature. The probability of using HA as a drug delivery system on highest of being a bone successor is a very valuable scheme for skeletal diseases such as bone tumors, osteoporosis, osteomyelitis or diseased composite ruptures which all need extended term drug administration [4,54,55].

Clay Minerals and Organoclay Bio-nanocomposites

In Earth, in addition phosphates and carbonates, one of the greatest plentiful groups of mineral solids in collaboration with the Biosphere is exemplified by the family of the so-entitled clay minerals [49]. Chitosan–clay bio-nanocomposites are very established materials minus important desorption of the biopolymer when they are cured with aqueous salt solutions for extended stages of time. Chitosan–clay bio-nanocomposites displaying the capability to integrate anionic sorts can be used to make functionalized biohybrids. Chitosan–clay bio-nanocomposites are biocompatible materials and also demonstrate capability to absorb ionic kinds, they could be used as directions for controlled drug delivery of anionic drugs[49,50].Layered Double Hydroxides (LDHs), named hydrotalcite-like materials or evenanionic clays, are blended hydroxides that can be defined by the common formula$[M+^2{}_{1_x}M^{+3}x(OH)_2]$ $[A^{+n}{}_{x/n\_}zH_2O]$ in which M^{+2} and M^{+3} are metal ions and $A^{n-}$is the anion that recompenses the shortage of negative charge in the layers. The capability of LDHs to cooperate with deleteriously charged biopolymers has been used to the procurement of biohybrid materials integrating negatively charged DNA in Mg-Al LDH, as initially described by Choy and coworkers. These bio-nanohybrids reveal the exceptional trait of activity as non-viral vectors in gene therapy to carry nucleic acids to the cell internal via an endocytosis device (Figure 10). LDH-based biohybrids can also be employed as transporters for controlled drug delivery, as various bioactive mixtures are negatively charged. LDHs can also be gathered with enzymes creating their actual immobilization among the inorganic layers, while at the same time permitting the diffusion of substrates and products (Figure 1.11B).

Yang et al. [27] studied about drug and gene delivery of LDHs. They are bioresorbable and have a great anionic-exchange ability, high enlargement properties and pH-interceded solubility that create them talented for drug and gene delivery [27]. Especially, investigators have established that the anticancer drug methotrexate immingled to LDH has a much superior in vitro anticancer result contrasted with clinically used doxorubicin. They daresay this is perhaps as a result of improved cellular drug uptake via clathrin-mediated endocytosis and controlled release inside cells. Current in vitro and in vivo studies additional designated that LDHs in the size range of 100–200 nm might have the maximum delivery efficacy of drugs, and decreased toxicity agents compared to LDHs of other sizes [27, 56,57].

Metal structures

Hollow metal nanoshells are being examined for drug delivery applications [58]. Classic metal contain gold, silver, platinum, and palladium. When connected to or implanted within polymeric drug carriers, metal nanoparticles can be used as thermal release activates when exposed with infrared light or incensed by an alternative magnetic field [59]. Biomolecular conjugation procedures of metals consist of bio practical connections, lipophilic interplay, silanization, electrostatic attraction, and nanobead interactions [6,60]. Figure 11 displays patterns of silanization and electrostatic attraction techniques of metal nanoparticle conjugation.

Carbon structures

Carbon nanotubes (CNTs) were revealed in 1991 by Iijima and meanwhile then they have concerned much consideration in many investigation fields. CNTs can be designated as tubular structures wrapped up from a graphite foil. As regards the number of tubular walls CNTs can be categorized as single-walled carbon nanotubes (SWCNTs) that indicate diameters in the range 0.7–1.5 nm, and multi-walled carbon nanotubes (MWCNTs), which are designed by 2–30 concentric tubes with diameters in the 2–10nmfor the inner tubular layer and extra thickness of about

0.7nm for each extra layer [49]. Surface-functionalized carbon nanotubes (CNTs) can be adopted inside mammalian cells [61], and when connected to peptides may be used as vaccine delivery structures [62]. With use of molecular dynamics (MD) simulations, the movement of water molecules via CNTs has been demonstrated and suggested their potential use as small molecule carriers. Other simulations have contained the transport of DNA through CNTs, representing potential use as a gene delivery tool [6].

Mucoadhesive polymer drug delivery platforms

The polymeric characteristics that are relevant to high stages of retaining at practical and directed sites via mucoadhesive bonds contain hydrophilicity, negative charge possible and the existence of hydrogen bond creating groups. The polymer should take adequate flexibility to infiltrate the mucus net, be biocompatible, non-toxic and economically desired [63]. The polymers that are normally engaged in the production of mucoadhesive drug delivery stages that stick to mucin–epithelial surfaces may be suitably distributed into three expansive groups as defined by Park and Robinson [64]:

(1) Polymers that come to be tacky when located in aqueous media and owe their bioadhesion to tackiness.

(2) Polymers that stick to through non-specific, non-covalent connections those are mainly electrostatic in nature.

(3) Polymers that fix to definite receiver locations on the cell surface [65]. Polymer materials display numerous wanted properties for drug transferor use counting biocompatibility, biodegradability, and functionalization capability. Tricking or encapsulating the drug within a polymer permits for larger controller of the pharmacokinetic manners of the energetic drug molecule. The drug can be released with a more model, near zero-order kinetic outline, which founds a more continuous flow of the drug out of the carrier. This pharmacokinetic manner keeps more suitable stable stages of the drug at the position of delivery. In contrast, formal oral drug delivery naturally tracks first-order release kinetics where the drug release speed is commensurate to the quantity of drug remaining in the drug carrier [2]. Biodegradable polymer nanoparticles, classically involving of polylactic acid (PLA), polyglycolic acid (PGA), or a copolymer of PLA and PGA, are being examined for the delivery of proteins and genes [64,65],vaccines , anticancer drugs, ocular drugs, and cytokines Other polymers being examined for nanoscale drug carriers contain polyalkylcyanoacrylate [74], poly(3-hydroxybutanoic acid) (PHB) ,poly(organophosphazene) ,, poly(ethylene glycol) (PEG), poly(caprolactone) (PCL), poly(ethylene oxide) (PEO), and copolymers such as PLA-PEG [2,64-67].For drug delivery goals, the term bioadhesion suggests connection of a drug carrier organization to a definite biological position. Developments in bioadhesive-based drug delivery and, especially, the delivery of innovative, highly-active and mucosacompatible polymer, are generating new profitable and scientific occasions for delivering narrow absorption window drugs at the objective positions to make the most of their effectiveness.

Mucoadhesive drug delivery schemes are being considered from dissimilar directions, counting enlargement of new mucoadhesives, design of the method, mechanisms of mucoadhesion and infusion improvement. With the influence of a large amount of novel drug molecules from drug finding, mucoadhesive drug delivery will display an even more significant character in delivering these molecules [68]. The wrapped process of mucoadhesion can permit for the target-controlled delivery of a series of APIs. Specified polymer properties for example charge, hydrophilicity, molecular weight between other strictures can touch the achievement and stability of sticky bond. Moreover, environmental elements such as the tonicity and mucus turnover rate must also be measured previous to construction. The most effective first-generation mucoadhesive polymer organizations have been concentrated on hydrophilic, high molecular weightiness, anionic types such as carbomers. Such polymeric systems have originated extensive use inside the mucus-lined organelles of the nose, buccal hollow and the vagina to name but a few. In specific the holy grail of mucoadhesive drug delivery has been focused around postponed transportation and/or aiming of adhesive polymer drug delivery stages to specific "absorption windows". Such an organization could have many potential requests, for development in the bioavailability of present poorly absorbed GI drugs. More lately consideration has lifted away from these more outdated mucoadhesive polymers towards schemes founded on the novel second-generation mucoadhesives. These second- generation mucoadhesives typically include the supplement of lection .Third, numerous other bond purposeful groups to outdated first-generation polymers nets. As such the compulsory of these kinds of platforms proposal, the opportunity of controlled release and a larger grade of supplement specificity, maybe even within the GI region [65].

Micro robots for Drug-Delivery

Developments in the synthesis of new pharmacologically active agents simultaneously with current improvements in system miniaturization are transforming new medicine. In the close upcoming, tiny released devices occasionally mentioned to as micro and nanorobots, may be authoritative of not only discovering human vasculature but also detecting definite biomolecules and delivering drugs to exact tissues. A talented method for realizing slightly aggressive medicine (MIM) is via microrobots wirelessly power-driven by exterior magnetic arenas [69].Numerous approaches using wireless magnetic controller have been effectively established to activate dissimilar microrobot schemes using multifaceted nonuniform magnetic field gradients [70], revolving [71] or oscillating magnetic fields [72].

Each approach is powerfully connected to the exact actuation origin of the microdevice and its design. Many features must be lectured when designing a MIM platform well-ordered by exterior magnetic fields (Figure 12).

Electro synthesized polypyrrole (Ppy) coverings incapacitated with sodium dodecylbenzenesulphonate (SDBS) are capable applicants for drug-delivery applications. The main usages a

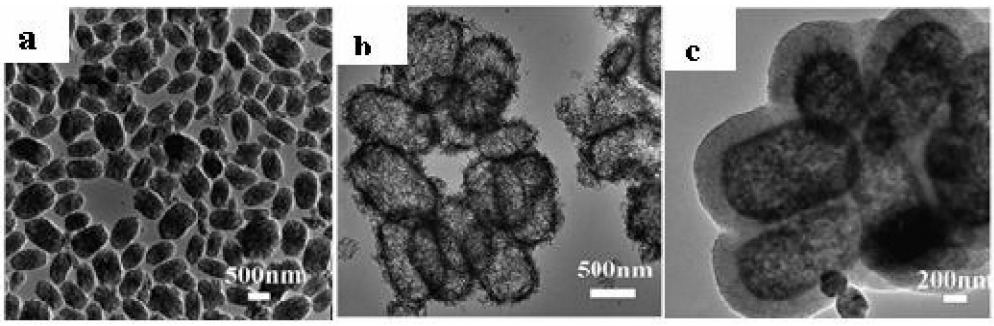

Figure 9. TEM micrographs of (a) $CaCO_3$ cores, (b) HA nanostructured hollow ellipsoidal capsules, (c) calcium silicate nanostructured hollow ellipsoidal capsules [Adapted from Ref. 50,53].

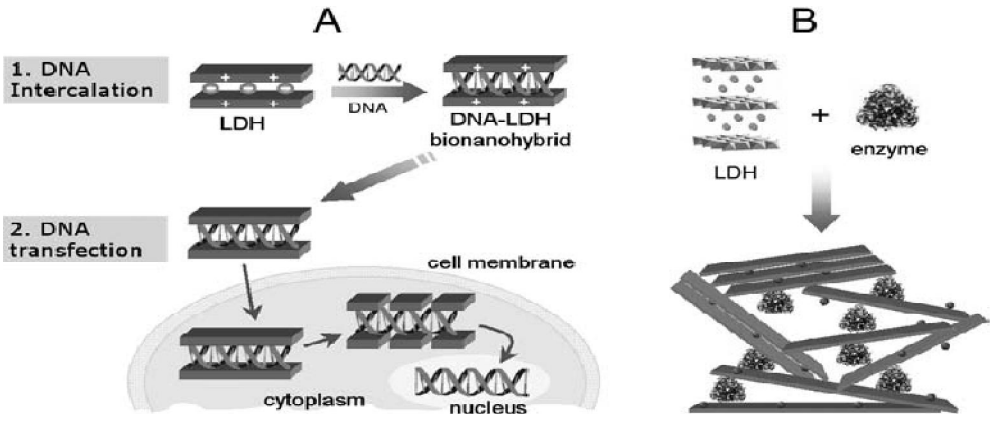

Figure 10: Uses of LDHs as (A) non-viral vector in gene therapy for transfection of DNA to the cell nucleus, and (B) as background for enzymes immobilization in the enlargement of biosensors [Adapted from Ref. 49].

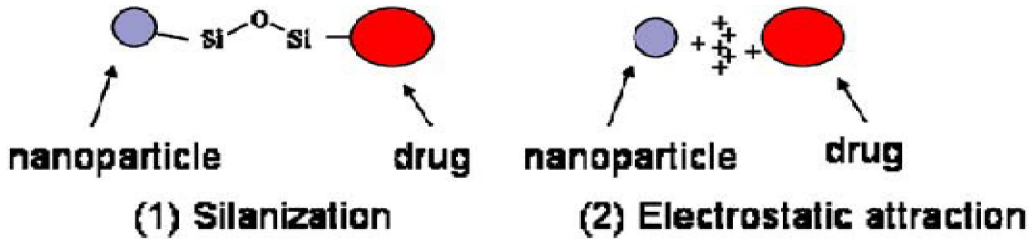

Figure 11. Nanoparticle bioconjugation methods: (1) silanization, and (2) electrostatic attraction[Adapted from Ref. 6].

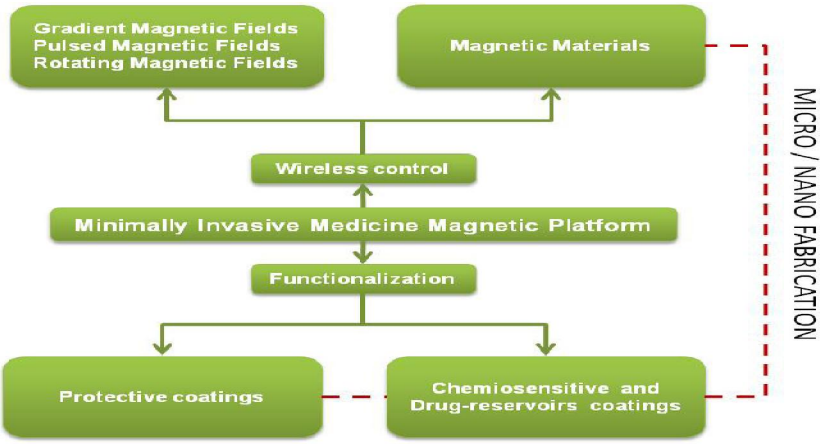

Figure 12: Aspects to be considered when designing a MIM Magnetic Platform

luminescence composite is accomplish wireless chemiosensing of oxygen condensation in the eye. The second centers on targeted drug delivery using biocompatible directing polymers whose possessions can be adjusted to integrate a higher amount of a model drug. Electrosynthesized polypyrrole (Ppy) coverings incapacitated with sodium dodecylbenzenesulphonate (SDBS) are talented applicants for drug-delivery requests.

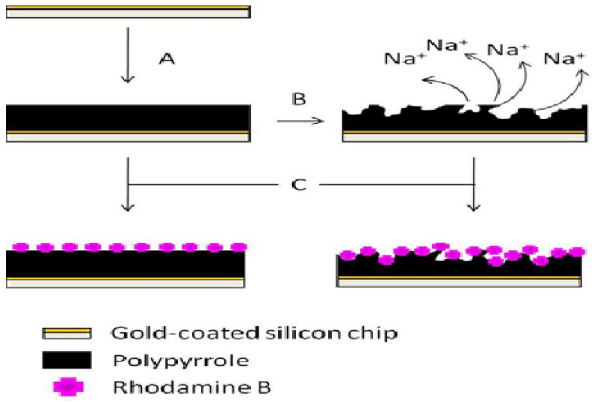

Figure 13: Illustration showing the steps of fabrication of the Ppy coatings: (A)Electrodeposition; (B) Anodic undoping; (C) Adsorption of Rh-B[Adapted from Ref. 72].

In this procedure, the sodium ions are emitted from the polymer producing the creation of microcracks. The rise of undoping rounds encourages the propagation of cracks, thus increasing the surface area and shifting the surface wettability. Such transformation of the material can be helpful for attractive drug adsorption. The additional undoped the Ppy coating is; the more Rh-B is unrestricted. Such growth in release might be because of the mixture of a rise in surface area and a variation in surface chemistry persuaded by the undoping procedure. For drug-delivery requests, both the surface area and the hydrophobicity of the efficient polypyrrole films can be adjusted with the purpose of increasing the quantity of model drug that can be adsorbed [72].

Conclusion

Nanotechnology in overall and as it relates to drug delivery in humans has been reviewed in this paper. The interdisciplinary nature of nanotechnology permits diversification and improvement in order to develop quality of life. Scientists in numerous fields such as engineering, material science, food, biomedical sciences, environmental sciences, agriculture, and energy and information technology should be abreast with and use nanotechnology, as suitable, for the development of research. Additionally, nanotechnology is a technology that every government should invest in to bring about development in areas such as healthcare, water, agriculture, energy and environment. If the whole thing runs efficiently, nanotechnology will one day turn out to be part of our ordinary life and will support save many lives. Nanostructured delivery architectures are encouraging applicants that will permit effectual and targeted delivery of novel drug compounds. Continued drug release and intracellular entry capability are properties of nanoscale drug delivery mechanisms that will minimize side effects and permit for the straight cure of the cause of the disease rather than the symptoms of the disease. The drug release requests of inorganic nanoporous materials are at their embryonic stage, particularly compared to polymeric coatings. Although the scientific applications of these materials are getting closer, still many more studies and tests are required before their full potential is recognized. The examples specified in this article denote only some of the materials and techniques presently studied. Nanophase ceramics have excellent occasions to help targeted drug delivery efforts due to their unique capability to modulate drug release kinetics, include multifunctional molecules and target specific focus sites. Developments in bio adhesive-based drug delivery and, specifically, the delivery of novel, highly-effective and mucosacompatible polymer, are producing novel commercial and medical opportunities for arrival of a large number of new drug molecules from drug discovery. Mucoadhesive drug delivery will play an even more significant role in delivering these molecules. Certain polymer properties such as

charge, hydrophilicity, molecular weight among other factors can affect the achievement and strength of adhesive bond. Moreover, environmental aspects such as the tonicity and mucus turnover rate must also be considered prior to formulation. Taking such considerations into account, polymers can be chemically organized and engineered to fit an individual pharmaceutical application..

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