

MODERN IMPROVEMENTS OF NANOSCIENCE IN TRANSPORTATION OF DRUGS, BONE TISSUE ENGINEERING AND FOOD PROCESSING

S. Bagyalakshmi*¹ and M. Priya²

¹Department of Physics, Sri Ramakrishna Institute of Technology, Coimbatore, Tamilnadu, India.

²Department of Chemistry, Sri Ramakrishna Institute of Technology, Coimbatore, Tamilnadu, India.

Corresponding Author: S. Bagyalakshmi

Department of Physics, Sri Ramakrishna Institute of Technology, Coimbatore, Tamilnadu, India.

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ABSTRACT

Nanotechnology refers to the interplays of cellular and molecular components and created material typically, clusters of atoms, molecules, and molecular parts into implausibly little particles between one and a hundred nm. Nanometer-sized particles present different structural, optical, and electronic properties. Nanoparticles had an enormous application in delivery systems of various production domains. In recent years, nanotechnology has increased credit to defeat the effects of genes and drug delivery. It is necessary to identify the reactions of nanomaterials on various administration and environmental factors to perform the economic and efficient way drug delivery. Nanotechnology conjointly plays a significant role in "Nanomedicines". Nanotechnology has supported the possibility of fabricating nanophase magnetic particles with functions suitable for targeting and treating varied bone diseases. There are also several benefits of nanotechnology in the field of food production and processing industry. This article evaluates the modern developments in nanotechnology for drug delivery, bone tissue engineering, and the food processing industry. Nanomedicine, the significant field in new world delivery systems are that the micromillimeter sized particles ideally starting from one to a hundred metric straight unit containing encapsulated, dispersed, adsorbed, or conjugated medication and imaging agents.

KEYWORDS: Food Processing, Imaging, Nano medicine, Nanotechnology, Orthopedics, Targeted drug delivery.

I. INTRODUCTION

Nanotechnology is that the understanding and manipulation of matter at dimensions of roughly one to one hundred nanometers, wherever distinctive phenomena alter novel applications. The benefits of nanotechnology have been recognized by many industries such as, in the microelectronics, aerospace, and pharmaceutical industries. Developments in these industries were driven by basic and applied analysis in physics, chemistry, biology, engineering, and materials science. Nanotechnology has the potential to impact many aspects of food and agricultural systems. Food security, health problem treatment delivery ways, new tools for molecular and cellular biology, new materials for agent detection, and protection of the atmosphere were samples of the very important applications of the field of study to the engineering, science of agriculture and food industry. Nanotechnology has wide applications in different fields. In health and biomedical areas, it can be used in drug delivery and therapeutics. Nano carriers are used in nanotechnology for targeted, triggered, and controlled the delivery of drugs or other therapeutic molecules. This review describes the existing nanoparticles used to deliver

therapeutic molecules and discusses their potential in the treatment of several diseases. Different targeting strategies (active or passive) are overviewed.

II. Influence of nanoparticles in drug transportation methods

Nanoparticles comprised solid, mixture particles consisting of molecule substances that shift in size from ten nm to one hundred nm.^[1,2] The drug of concern is dissolved, entrapped, adsorbed, fastened up or encapsulated into the nanoparticle pattern. Nano capsules were cyst arrangements among that the drug is restricted to a cavity surrounded by a different compound membrane, whereas nanospheres were pattern systems during which the drug is physically and uniformly dispersed. Counting on the approach of preparation, nanoparticles, nanospheres or Nano capsules is concerned with totally distinct properties and unfastens properties for the encapsulated therapeutic agent. The advantages of exploitation nanoparticles for drug delivery result from their 2 main basic properties. Nanoparticles, recognition to their little size, will penetrate through smaller capillaries and were inhabited by cells, which permit

efficient drug collection at the target sites. The employment of biodegradable materials for nanoparticle preparation allows the continued drug to unharness among the target place over a few days or even weeks. Targeted delivery is accomplished by either active or passive targeting. Active targeting of a therapeutic agent is obtained by conjugating the therapeutic agent or the transport system to a tissue or cell-specific matter. Passive targeting is accomplished by coupling the therapeutic agent to an organic compound that indifferently reaches the organ.^[3] Localized delivery of nanoparticles in restenosis is additionally a useful approach because of it'd provide sustained drug influence inside the target artery. The medicine encapsulated in nanoparticles or medicine linked to macromolecules like high mass polymers quietly targets the growth tissue through the improved penetration and reservation (EPR) impact. The alternative method includes the immersion of nanoparticle suspension to the available organ or tissue victimization infusion catheters. Nanoparticles are necessary for the delivery of pharmaceutical agents when binding to focus on cellular epitopes by a mechanism referred to as 'contact expedited drug delivery'.

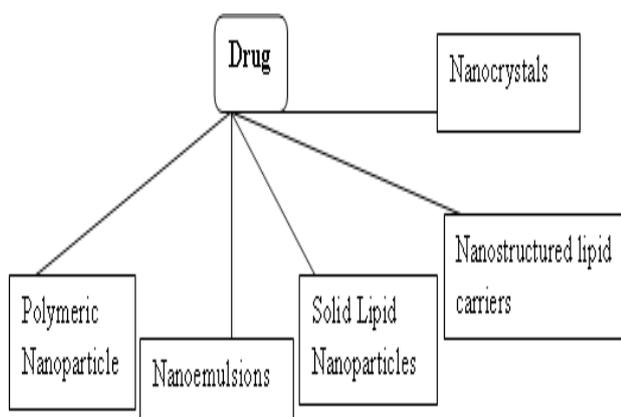


Fig. 1: Application of nanoparticles in drug delivery.

III. Varieties of Nanoparticles In Drug Delivery Systems

A. Liposomes based Nanoparticles

Liposomes may be a little artificial cyst of a globular class which can be created from natural non-toxic phospholipids. Liposomes were normally expected to stay to cellular membranes to deliver a drug or simply transfer drugs following endocytosis. Because of their size and deliquescent nature, hydrophobic, as biocompatibility, liposomes are promising ways for drug delivery. They were coaxial bilayer vesicles with a circled by a lipid membrane. It relates to micelles that are usually composed of a monolayer of lipids.^[4] The amphiphilic nature of liposomes, their simple surface modification, and proper biocompatibility profile makes them an appealing explanation for increasing the half-life of proteins and peptides. They'll contain deliquescent compounds that keep encapsulated among the liquid interior or hydrophobic compounds, which may escape encapsulation through diffusion out of the fat membrane.

These vesicle properties vary considerably with lipids composition, size, surface charge and therefore the technique of preparation. They classified into 3 categories maintained their size and variety of bilayers. The small uni-flagellar vesicles (SUV) are encircled by one lipid layer and were 25–50 nm in diameter. The giant uni-flagellar vesicles (GUV) are a heterogeneous group of vesicles almost like SUVs were encircled by a lipid membrane. Multilamellar vesicles (MLV), however, bring with it many lipid layers separated from each other by a layer of solution. Moreover, the choice of bilayer elements determines the 'rigidity' (or fluidity) and hence the charge of the bilayer. The introduction of utterly or charged lipids contributes to the liposomes a surface charge. The medication-related to liposomes have considerably changed pharmacokinetic properties compared to medication in the analysis.^[5,6] They are effective in reducing specific toxicity and preventing early degradation of the encapsulated drug once introduction to the target the vesicular surfaces are quickly changed by joining polyethylene glycol (PEG)-units to the bilayer (producing what is mentioned as stealing liposomes) to spice up their circulation time among the blood of the encapsulated drug once introduction to the target organism. Furthermore, liposomes are often conjugated to antibodies or ligands to strengthen target-specific drug pharmaceutical care.

B. Inorganic Nanoparticles

Ceramic nanoparticles were usually composed of inorganic compounds like silicon dioxide or aluminum oxide. However, the nanoparticle core is not limited only with these materials whereas it can also be produced with various metals, metal oxides and sulfides with varied dimensions and porosity.

C. Dendrimers based Nanoparticles

Dendrimers were enticing systems for drug delivery due to their nanometer size vary, easy preparation and functionalization, and their ability to show multiple representations of surface teams for biological restructuring processes. Dendrimers molecules are monodispersing symmetric macromolecules built around a small molecule or in a linear polymer core using connectors and branching units.^[7] Communication of dendrimers macromolecules with the molecular atmosphere is preponderantly controlled by their end teams. Dendrimers possess some individual properties related to their globular shape and the appearance of internal cavities.^[8,9] The several significant ones are the chance of encapsulation of curative agents within the macromolecule depths. Drug molecules are filled each within the interior of the dendrimers also as associated with covering teams. Water-soluble dendrimers are capable of binding and solubilizing little molecules and might be used as covering agents to shield or deliver medication to specific sites within the body or as time-release carriers for biologically active agents. 5-Fluorouracil (5FU) is known to have extraordinary

anti-tumor activity, but it has great deadly side effects. PAMAM dendrimers subsequent acetylation can form dendrimer-5FU conjugates which upon hydrolysis delivers free 5FU, thus decreasing toxicity.^[10,11] Dendrimers are constructed from monomeric or oligomeric units and it is a polymer-based macromolecule, such as each layer of branching units' twins or triplets the number of peripheral groups. The void space inside a Dendrimers, the range of its branching, its comfort of modification and preparation, and size control offer great potential for drug delivery. Dendrimers generally have a symmetrical structure, with the potential to build a separate 'active site' core area through chemical functionalization.^[12,13] Modification of the degree of branching might allow encapsulation of a particle among this structure.

D. Polymeric based nanoparticles

Most polymeric nanoparticles are biodegradable and biocompatible have been adopted as a favored method for nanomaterial drug delivery.^[14,15] In addition, they exhibit a fair potential for surface modification via chemical transformations, give magnificent pharmacokinetics management and relevant for the defense and delivery of a large variety of therapeutic agents. Relevant nanoparticle formulations encompass those made up of gelatins, chitosan, poly (lactic-co-glycolic acid) copolymer, polylactic acid, polyglycolic acid, poly (alkyl cyanoacrylate), poly (methyl methacrylate), and poly (butyl) cyanoacrylate. Furthermore, polymer-based layers may be functionalized onto another type of nanoparticles to modify and improve their biodistribution properties. The biologically inert compound poly (ethylene glycol) (PEG) has been covalently linked onto the surface of nanoparticles. This compound coating is considered to cut back immunogenicity, and restrict the motion of nanoparticles by the RES, gravitate to stored blood levels of a drug in organs like the brain, intestines, and kidneys.

E. Polymeric micelles-based nanoparticles

Polymeric micelles possess numerous advantages above standard surface-active agent micelles into they need great thermodynamically stable in physiological determination, being designated by their low important micellar concentration that makes composite micelles firm and stops their accelerated separation. Micelles have a fairly narrow size distribution in the nanometer range and are characterized by their unique core-shell architecture, in which hydrophobic segments are isolated from the aqueous surface. Micellar systems are useful for the systemic delivery of water-insoluble drugs.^[16,17] Drugs can be partitioned in the hydrophobic core of micelles and the outer hydrophilic layer creates a stable distribution in aqueous media, which can be applied intravenously. The delivery of drug-loaded compound micelles within the body is decided primarily by size and surface properties. Polymeric micelle included drugs may expand to a greater extent than free drug into tumors and demonstrate a reduced distribution in non-targeted areas. Gathering of

polymeric micelles in malignant tissue is because of increased vascular permeability and impaired lymphatic drainage. Tumor vessels are more broken and less perm selective than normal vessels and hence there is the perivascular accumulation of macromolecules and colloidal drug carriers in tumor tissue.^[18,19]

F. Nanotubes

Nanotubes are self-assembling films of atoms arranged in tubes. They may be organic or inorganic in composition and can be manufactured as single- or multi-walled structures.^[20,22] A modern version of a carbon nanotube comprises the utilization of soluble carbon derivatives, such as C60. Nanotubes have colossal intrinsic volumes and therefore the exteriors are often simply functionalized. It has been shown that nanotubes are acutely toxic and may generate cell death via an oxidative-stress pathway.

G. Nanocrystals

Nanocrystals are sums of molecules that can be merged into a crystalline form of the drug surrounded by a skinny covering of chemical agents. They have widely used in materials analysis, chemical engineering, and quantum dots for biological imaging, but few so in nanomedicine for drug delivery. A nanocrystalline species may be made from a hydrophobic mixture and coated with a thin hydrophilic layer. The biological reaction to nanocrystals depends vigorously on the chemical characteristics of this deliquescent coating. The deliquescent layer supports the biological distribution and bioavailability and inhibits the collection of the crystalline drug material. These portions mix to enlarge the strength of overall drug delivery. Huge dosages can be accomplished with this formulation, and poorly soluble drugs can be formed to increase bioavailability via treatment with a proper coating layer. Both oral and parenteral transfers are possible, and the restricted carrier, consisting of primarily the thin coating of surfactant, may reduce potential toxicity.

IV Nanotechnologies toward Imaging Purposes

A. Magnetic Nanoparticles

Magnetic nanoparticles are a great and talented diagnostic agent in biology. Bound to proper antibody, they are applied to name specific molecules, cell populations, structures or microorganisms.^[23,24] Magnetic immunochemical assay techniques are acquired within which the flux created by the magnetically marked targets is detected directly with a sensitive gaussmeter. Binding of antibody to target molecules or disease-causing organism is the source of several tests. Superparamagnetic nanoparticles are employed as contrast agents in magnetic resonance imaging. They consist of an inorganic core of iron oxide (magnetite Fe₂O₃, magnetite or other insoluble ferrites) capped with a polymer such as dextran. Lumen (silicon-coated iron oxide particles with diameter 300 nm) and Endorem (magnetite nanoparticles of 150 nm in diameter coated with dextran) are the marketing names of superparamagnetic nanoparticles. These Nano-particulate

contrast agents are being applied for imaging of tissue for diagnostic applications.^[25]

B. Ferrofluids

Ferrofluids are colloidal suspensions of iron oxide magnetic nanoparticles circled by a polymeric layer coated with bond molecules, such as antibodies, for capturing cells and other biological targets from blood or other fluid and tissue samples.^[26] Ferrofluid particles are so tiny (25–100 nm in radius) that they act in liquids as a solvent preferably than suspension. When the coated Ferrofluid particles are combined with a sample containing cells or other analytes, they communicate confidentially and effectively. These properties enable the development of specialized reagents and systems with extremely high sensitivity and efficiency and capture.^[27]

V Purpose of Bone Materials in Nanotechnology

In the body, bones serve the following three functions: provide mechanical support, as it is the site of muscle attachment for movement; protect various organs, including bone marrow filled with nutrients; and provide a metabolic function (storing calcium, phosphorus, and other essential ions to be used by the body when needed). Specifically, bone is a natural nanostructured (that is, a material with constituent features less than 100 nm in at least one dimension) composite composed of organic compounds (mainly collagen) reinforced with inorganic ones (hydroxyapatite).^[28,29] It is this natural nanostructure that nanotechnology aims to emulate for orthopedic applications. Merging of nanotechnology and orthopedics is the realization that bone is a natural nanostructured composite material composed of intertwined inorganic (bone apatite) and organic compounds (mainly collagen).

VI Effect of Nano materials in Orthopedics

Nanotechnology has provided for the opportunity of building nanophase magnetic particles with functions suitable for targeting and treating various bone diseases.

A. Metals

Metals are used as bone replacement materials in hip prostheses, dental implants, and so on. The most generally used elements in orthopedics are stainless steel, cobalt chrome alloys, titanium, and titanium alloys. After 10–15 years of implantation into the human body, metals lastingly separated from the bone. Additional problems of metallic orthopedic materials include the requirement for an additional operation to eliminate temporary implants such as plates, pins, and screws and negative tissue responses to the ions liberated from metallic implant materials.^[30] It has been stated that increased osteoblast functions such as adhesion, proliferation, and deposition of calcium-containing mineral on the nanophase show great growth for the compared to traditional metals: Ti, Ti₆Al₄V, and CoCrMo₂₀. Nanometer-sized powders of Ti, Ti₆Al₄V, and CoCrMo have been individually pressed into model implant surfaces, and osteoblast adhesion has been inspected.^[30] The results exhibited that osteoblast

adhesion was significantly more prominent on nanophase Ti, Ti₆Al₄V, and CoCrMo, when analyzed the results, shows that enhanced osteoblast adhesion might be due to the larger number of defect boundaries at the surface of nanophase materials, creating unique surface energy attracting the adsorption of certain proteins necessary for osteoblast adhesion.

B. Ceramics

Ceramics have been used widely in orthopedics owing to their popular biocompatibility properties with bone cells and tissues. Metallic oxides (e.g., alumina, zirconia, Titania), calcium phosphates (e.g. Hydroxyapatite (HA), tricalcium phosphate (TCP), calcium tetraphosphate (Ca₄P₂O₉)), 32 and glass ceramics (e.g., Biogas and Cervical) 33 are generally used in orthopedic tissue engineering applications. These ceramics are analyzed bioactive because of their surface properties that encourage bone cell adhesion, proliferation, and differentiation. Specific ceramics (such as HA and TCP) have similar properties related to the mineral phase of natural bone. Ceramics (such as alumina, Titania, and HA with grain sizes greater than 100 nm) maintain good biocompatibility properties. Unique ceramic elements can promote and sustain Osseointegration with the surrounding bone is important for enhanced orthopedic implant treatments. This research indicated that the improved Osteoblast adhesion was independent of surface chemistry and was dependent only on the surface topography and consequent roughness of ceramics for nanostructured corresponded to conventional metals.

C. Polymers

Polymers are simply built into programmed shapes and structures. Besides, polymers can be altered chemically or functionalized via chemical and biochemical reactions. Synthetic polymers have brought increasing awareness in tissue engineering applications. Polymeric material should meet the needs of special orthopedic applications. The most familiar natural polymer for tissue engineering is collagen. Collagen is a fibrous, nanoscale protein and a major element of natural extracellular matrices. Due to its engaging biological properties (such as biocompatibility), collagen has been practiced for building fabrication. However, there are yet various issues over the application of collagen for orthopedic applications because of bad handling and poor mechanical properties. Most of the synthetic degradable polymers considered for orthopedic applications belong to the poly (α -hydroxyl acid) family, including poly (lactic acid) (PLA) (also known as polylactide), poly (glycolic acid) (PGA) (also known as polyglycolide), and their copolymers such as poly (lactic-co-glycolic acid) (PLGA) (also known as polylactide-co-glycolide). The degradation rate of these polymers can be managed via variations in the ratio of polylactic acid to PGA, molecular weight, crystallinity, and hydrophilicity, pH of the surrounding environment, as well as specimen size, geometry, porosity, surface properties, and the sterilization process. New investigation

results have confirmed that the adsorption and conformation of proteins (such as fibronectin and vitronectin), which control osteoblast adhesion and other functions, are intensified on nanophase compared to conventional polymers.

VII Nanotechnology in Food Processing Industry

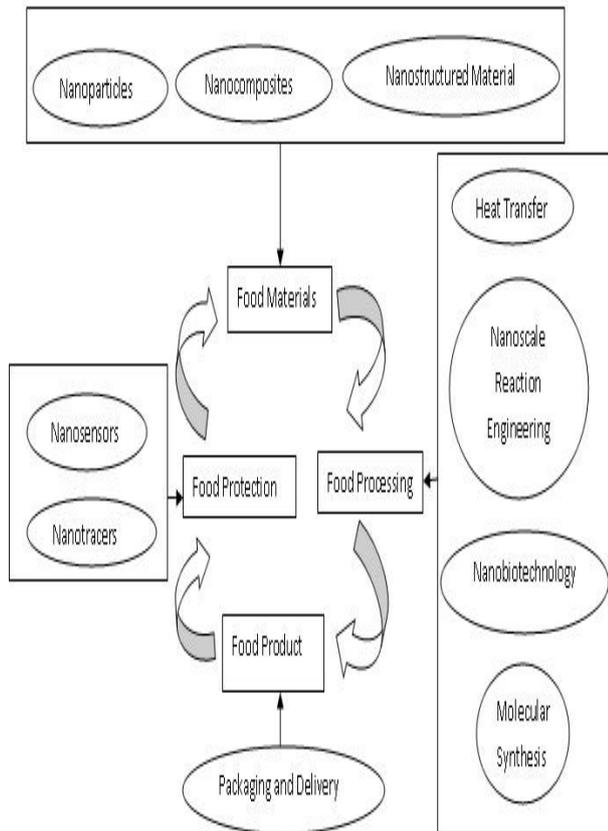


Fig. 2: Role of Nanotechnology in the Food Industry.

A. Food Processing using Nanotechnology

Food processing is a multi-technological fabrication industry requiring a wide type of raw materials, high biosafety requirements, and well-regulated technological methods. Four important fields in food products might have the advantage of nanotechnology: the advancement of the latest practical materials, small scale and nanoscale process, development, and strategies and instrumentation style for developed food protection with food safety and biosecurity. The functional ingredients area unit rarely utilized straight in their true kind. Alternatively, they're typically included in a variety of delivery systems. A delivery system must perform several diverse roles. It is a carrier for carrying the practical component to the required area of action. Next, it should require supporting the helpful ingredient from chemical or biological degradation (for example, oxidation) throughout the process, storage, and utilization; this keeps the useful component in its active state. It may require to be capable of prevailing the discharge of the functional ingredient, like unfasten the discharge rate or the precise environmental conditions that trigger discharge (for example, pH, ionic strength, or

temperature). The delivery system should be fit with the opposite parts within the system, besides, as being compatible with the chemical science and qualitative characteristics (that is, appearance, texture, taste, and shelf-life) of the final product. The features of the delivery system were one of the leading important factors determining the effectivity of practical components in several industrial products. A wide variety of delivery system has been extended to encapsulate sensible ingredients, likewise as sincere solutions, association colloids, emulsions, biopolymer matrices, and so on. A delivery system has its distinct advantages and drawbacks for encapsulation, protection, and delivery of useful ingredients, as well as cost, regulatory status, comfort of use, biodegradability, and biocompatibility. Fig.2 depicts the role of nanotechnology in the food industry.

B. Nano-emulsions

Through the means of Nano emulsions, Functional food components can be combined within the droplets, the interfacial region, or the continuous phase. Encapsulating working parts inside the droplets normally allows the hindrance of chemical degradation methods by managing the characteristics of the surface layer near to them. While it's hard to superintend the interfaces to be entirely water-resistant to compounds within the bulk division which will operate with the encapsulated compounds, the speed of permeation can usually be considerably decreased, thus enhancing the dynamic stability of the bioactive.

C. Nano laminates

A nanolaminate consists of a couple or a cluster of layers of fabric with micromillimeter dimensions that are actually or with chemicals empowered to every distinct. One of the leading great ways relies on the LbL deposition technique, in which the charged surfaces are coated with interfacial films consisting of multiple nanolayers of different materials. Nanolaminates will give food scientists some advantages for the construction of edible coatings and films over standard technologies and order so have a variety of essential applications inside the food trade. Edible coatings and films are shortly used on a good form of foods, including fruits, vegetables, meats, chocolate, candies, bakery products, and French fries. These coatings or films might function wet, lipid, and gas barriers. The essential functional properties of edible coatings and films depend upon the characteristics of the film-forming materials applied for his or her preparation. Today, the first film-forming materials accustomed to create these edible coatings and films are polysaccharides, proteins, and lipids. Commonly, lipid-based films are active wet barriers, nevertheless, they offer very limited resistance to gas transfer and have poor mechanical strength. In distinction, biopolymer-based films are frequently good oxygen and carbon dioxide barriers, but they contribute little protection against moisture migration.

VIII. CONCLUSION

The multidisciplinary field of engineering science survives the encouragement of addressing technological discovery and is going in no time from thought to reality. The versatility to change or accommodate nanotechnology to satisfy the requirements of pathologic conditions both for therapeutic applications and as a diagnostic instrument is an essential component of the technology. Nano delivery systems include the specific potential to overcome a number of the restrictions to expeditiously target a diversity of various cell varieties. This represents an associate interesting risk to overcome problems of drug resistance in target cells and to promote the movement of medicine across boundaries. Targeted drug delivery may be accustomed to managing several diseases, like vas diseases and polygenic disease. Nevertheless, the leading necessary application of targeted drug delivery is to treat cancerous tumors. Nanoparticles have proved themselves to be energetic aspirants for targeted drug delivery; they're wide out there, easily functionalized, biocompatible, and well-built. These features give focused doses of hepatotoxic medication to be encapsulated and delivered on to the tumor area. This review focused on the applications of nanoparticles in drug delivery, bone tissue engineering, and food processing industry.

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X. REFERENCES

1. Wilkinson J.M. *Med. Device Technol*, 2003; 14(5): 29–31.
2. Roco M.C. *Curr. Opin. Biotechnol*, 2003; 14: 337–346.
3. Bangham A.D. *J. Mol. Biol*, 1965; 13: 238–252.
4. Dagar S, Krishnadas A, Rubinstein I, Blend MJ, Onyuksel H. *J Control Release*, 2003; 91: 123 - 33.
5. Park JW, Hong K, Kirpotin DB, Colbern G, Shalaby R, Baselga J. *Clin Cancer Res*, 2002; 81: 172 - 81.
6. Tripathi PK. *Pharmazie*, 2002; 57: 261–264.
7. Mainardes RM, Silva LP. *Curr Drug Targets*, 2004; 5: 449 - 55
8. Boas U, Heegaard PM. *ChemSoc Rev.*, 2004; 33: 43 - 63.
9. Quintana A, Raczka E, Piehler L, Lee I, Myc A, Majoros I. *Pharm Res*, 2002; 19: 1310 - 6.
10. Cloninger MJ. *Curr OpinChem Biol*, 2002; 6: 742 - 8.
11. Gessner A, Waicz R, Lieske A, PaulkeMader BK, Muller R.H. *Int J Pharm*, 2000; 13: 245 - 9.
12. Zweers ML, Engbers GH, Grijpma DW, Feijen J. *J Control Release*, 2004; 100: 347 - 56.
13. Radwan MA, Zaghoul I.Y, Aly ZH. *Eur J Pharm Sci*, 1999; 8: 95 - 8.
14. Mainardes RM, Silva LP. *Curr Drug Targets*, 2004; 5: 449 - 55.
15. Nishiyama N. *Adv. Exp. Med. Biol*, 2003; 519: 155–177.
16. Kataoka K. *Adv. Drug Deliv. Rev*, 2001, 47: 113–131.
17. Rosler A. *Adv. Drug Deliv. Rev*, 2001; 53: 95–108.
18. Kagan VE, Tyurina YY, Tyurin VA, Konduru NV, Potapovich AI, Osipov AN, Kisin ER, Schwegler-Berry D, Mercer R, Castranova V, Shvedova AA, *Toxicol. Lett*, 2006; 88: 165-168.
19. Porter AE, Gass M, Muller K, Skepper JN, Midgley PA, Welland M. *Nat. Nanotechnol*, 2007; 2: 713.
20. Manna SK, Sarkar S, Barr J, Wise K, Barrera EV, Jejelowo O, Rice-Ficht AC, Ramesh GT. *Nano. Lett*, 2005; 5: 1676.
21. Pereira E. J. *Drug Target*, 2003; 11: 19–24
22. Ito A. *Cancer Sci*, 2003; 94: 308–313.
23. Lubbe AS. *Cancer Res*, 1996; 56: 4694–4701.
24. Babincova M. *Z. Naturforsch. (Sect. C)*, 2001; 56: 909–911.
25. Tsavellas G. *Clin. Exp. Metastasis*, 2002; 19: 495–502.
26. Liu Q. *Verlag Berlin Heidenberg: Springer*, 2004; 219.
27. Smith R. *Public Health Service, Office of the Surgeon General*, 2004; 68–70.
28. Small IA, Misiek D. *J Oral Maxillofac Surg*, 1986; 44: 60–66.
29. McKee GK. *Biomaterials*, 1982; 3: 130–135.
30. Steflik DE, Sisk AL, Parr GR, Gardner LK, Hanes PJ, Lake FT, Berkery DJ, Brewer P. *J Biomed Mater Res*, 1993; 27: 791.