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Review Article

Nanotechnology in gastrointestinal endoscopy: A primer

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Abstract

Nanotechnology is the understanding, control of matter and development of engineered devices in nanometer range (1-100 nm). Nanoparticles have different physicochemical properties (small size, large surface area to volume ratio, and high reactivity) in comparison to bulk materials of the same composition. The nanotechnology has proved its usefulness in early diagnosis, proteonomics, imaging diagnostics and multifunctional therapeutics. Recent studies have shown its role in early diagnosis and targeted therapy of various gastrointestinal disorders such as hepatitis B virus and hepatitis C virus related liver disease, inflammatory bowel disease, gastric ulcer, and malignancy. Application of this technology appears promising in diagnostic and therapeutic endoscopy such as the endoscopic hemostasis of peptic ulcer bleeding, prevention of clogging of plastic stent and advance capsule endoscopy. This article will highlight the basic concepts of nanotechnology and its potential application in gastrointestinal endoscopy.

Key words Nanotechnology, nanoparticles, nanomaterials, nanopowder, hemospray, nano-based capsule-endoscopy

Introduction

Nanotechnology is defined as the "intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1 to 100 nm).[1] Nanotechnology uses the properties and physical characteristics of nanomaterials for the diagnosis and treatment of diseases at the subcellular and molecular level. It aims to develop and combine new materials by precisely engineering atoms and molecules to yield new molecular assemblies on the scale of individual cells, organelles or even smaller components, providing a personalized medicine.[2] It is being used to refine discovery of biomarkers, molecular diagnostics, drug discovery, drug delivery and therapeutics. It is a multidisciplinary field.

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Various nanomaterials and their properties

Nanotechnology manipulates the chemical and physical properties of a substance on molecular level leading to development of various nanomaterials with novel properties. Nanoparticles (NPs) have greater surface area per volume of smaller particle and therefore they are more reactive and can be coated with many molecules.[3] These are stronger and lighter than macroparticles. The inorganic nanomaterials have unique electronic, magnetic and optical properties. All electrons in iron oxide magnetic NPs spin in the same direction and produce larger, localized magnetic field as compared with that of larger particles. This larger magnetic field can increase the contrast on magnetic resonance imaging.[4] In metal NPs, the electrons can move between two energy levels: A ground state and an excited state. The difference between these two energy levels determines the fluorescence emission and color property of any metal NPs. The cadmium selenide semiconductor NP (known as CdSe quantum dots, or Qdots) has fluorescence emission far better than that of organic fluorescent dye molecules.[5] Quantum Dot of a specific colour offers a cheap and easy way to screen a blood sample for variety of proteins, viruses and other desired substances at the same time.

Unlike microparticles, NPs can cross blood brain barrier.[6] It

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has ability to evade the interception by immune system, and therefore have longer half-life and can be used as drug delivery vehicle.[7] NPs is acceptable to tumor cells and therefore, useful in cancer treatment.[8] It can specifically interact with biomolecules both on the cell surface and within the cell and can deliver diagnostic and therapeutic agents to specific cells and organelles. Because of these unique properties of NPs and the inherent nanoscale functions of the biological components of living cells, nanotechnology can be applied to medical fields.

The various classes of nanomaterials are being developed for use in medical sciences and includes liposome's, stealth liposome's, emulsions, micelle, polymer-drug conjugates, biocompatible ceramic NPs with porous characteristics (silica, titania, and alumina), metallic particles (iron-oxide NPs, gold shell NPs, nanocrystalline silver and aluminosilicate NPs), quantum Dots, calcium phosphate NPs, carbon NPs (fullerenes and nanotubes), nanocapsules, nanogels, dendrimer, nanoshell, nanopores, nanodevices and nanomachines (nanobots, nanotweezers, smart scalpels and intelligent pill).[9-27] Few of these have been approved by the Food and Drug Administration (FDA) for use in humans such as iron oxide (Feridex and Resovist for MRI contrast in liver), gold (Verigene for *in vitro* diagnostics in genetics), protein (Abraxane for breast cancer therapy), liposome (Doxil/Caelyx for various cancer therapy), and polymer (Oncaspar for acute lymphoblastic leukemia therapy). Some of these nonmaterial's are currently undergoing clinical trials such as iron oxide (Combidex for MRI contrast and Nano Therm for cancer therapy), gold (Aurimmune for cancer therapy), nanoshells (Auroshell for cancer therapy), quantum dot (Qdots, EviTags and semiconductor nanocrystals for fluorescent contrast *in vitro* diagnostic), polymer (CALAA-01 for cancer therapy), dendrimer (VivaGel for microbicide) and micelle (Genexol-PM for cancer therapy).[28]

Nanotechnology and gastrointestinal tract

Gastrointestinal tract is one of the portals for environmental NPs to enter the human body. Once ingested it readily traverse through mucus layer and comes into contact with enterocytes. They are scavenged by M-cells overlying the intestinal mucosa and therefore escape from active uptake by enterocytes. After cellular trafficking it can reach the blood stream and distribute all over the body. Faster diffusion through mucus layer is explained by smaller diameter of NPs.[29]

Each part of gastrointestinal tract has distinct feature and application of diagnostics and therapeutics is not always easy, as the targeted delivery of drugs or endoscopy in distal small intestine is still far from perfection. Knowing the properties of NPs, application of nanotechnology in gastrointestinal tract appears promising. It has been tried in many gastrointestinal conditions with varied success, such as; (a) targeted delivery of therapeutic agents in terminal ileum and colon (e.g. inflammatory bowel disease) and stomach (e.g. gastric ulcer), (b) theragnostic use in cancer (e.g. pancreatic, gastric and colonic cancer), (c) gene therapy in gastric and colonic cancers, (d) hepatoproteonomics [gene expression (genomics) and protein production (Proteomics)] and (e) gastrointestinal endoscopy.[30-38]

Nanotechnology and gastrointestinal endoscopy

Nanopowder as hemostatic agent in gastric ulcer bleed

Endoscopic hemostasis by electrocautery, injection tamponade and hemoclips has been established as the treatment of choice for peptic ulcer bleeding. However, endoscopic hemostasis can be difficult and unsuccessful in situation of severe active bleeding and difficult anatomy. *Giday et al*. used a novel nanopowder (TC-325) application in spurting arterial bleed in stomach in an animal model at endoscopy and showed its safety and high effectiveness in achieving hemostasis in an anticoagulated severe arterial gastrointestinal bleeding.[34] In another prospective pilot clinical study, 20 patients of peptic ulcer bleeding (Forrest score Ia or Ib) underwent endoscopic application of hemospray within 24 hours of hospital admission. Hemostasis was achieved in 95% of patients. The one patient in whom acute hemostasis was not successful had a Forrest Ia ulcer. Bleeding recurred in 2 patients within 72 hours. No major complications were reported during 30-day follow-up. Limitation of study was that the only spurter of this study did not respond to therapy.[35] Hemospray if revalidated appears simple, easy to use and effective method of endoscopic treatment of active gastrointestinal bleeding.

Prevention of clogging of plastic stents

Endoscopic placement of biliary plastic stents is widely applied in the management of malignant and benign biliary disorders. However, the major limitation of plastic stents for biliary drainage is their occlusion by sludge. The biliary plastic stents are occluded by sludge because stents surface allows adherence of protein, glycoproteins or bacteria. Nanotechnology provides new possibilities for the modification of surface by soil-release phenomenon (the lotus effect- lotus leaves stay clean because easily flowing water takes any particle from surface). Sol-gel technology allows for systematic design of abrasion-stable nanometer-thin coating with determined physical and chemical characteristics. An *in vitro* study has shown, sludge deposition to be reduced on biliary plastic stent made of teflon with sol-gel coating consisting of organic epoxide of 190 g/mol, or 500 g/mol and propylaminosilane as comparison to uncoated teflon and clear coating. The nanocoating of plastic stents may therefore, prevent biliary plastic stents from clogging.[36]

Nano-based capsule-endoscopy

Capsule endoscopy is a widely accepted new tool in the diagnosis of small-bowel and colonic diseases. The procedure is easy to perform and is well accepted by patients. Major limitations of capsule endoscopy are inability to detect deep tissue disorders and absence of therapeutic capability.

The concept of merging two technological platforms: nanotechnology for targeting and marking the affected organ and capsule-endoscopy to detect the marked disorder has recently been addressed. Nano-based capsule-Endoscopy with Molecular Imaging and Optical biopsy, (NEMO) project, supported by European Union is trying to integrate optical technology with nano-technology, bio-sensing and maneuvering technology to create a capsule endoscope capable of secretion analysis and the detection of marked and deep tissue disorders.[37] This may be useful especially in highlighting cancerous and precancerous lesions in the gastrointestinal tract.

Nanorobots are innovative nanometric robots potentially capable of endoscopic procedures. The ultra-sound transducers, bioanalytical and mechanical sensors and robotic arms could be combined in capsule endoscopy system (called as "robotic beetle") to obtain tissue samples and provide treatment such as targeted drug releasing and thermal tissue destruction.[31]

The investigators have planned to develop intelligent endoscopic capsules (miniaturised robotic pill) with diagnostic and therapeutic capability. Concept is based on advancement in micro- and nanotechnology. The functional units of the VECTOR capsule consists of the basic capsule functions, locomotion systems, diagnostic systems and therapeutic/biopsy systems.[38]

Toxicity of nanoparticles

The properties, which make NPs so useful in medical science, may contribute to the potential toxicity in human being. The respiratory system, blood, central nervous system, gastrointestinal tract and skin have been shown to be targeted by NPs. Because of easy of entry, gastrointestinal tract is easily exposed to environmental NPs. Environmental factors of nanosize are putative risk factor for inflammatory bowel disease.[39] Recent *in vivo* and *in vitro* studies have shown that liver injury can be caused by nanomaterials.[40] Therefore, the potential toxicity in human being cannot be denied. The nanomaterials which are either approved for clinical use or under clinical trials have been shown to have adverse effects such as back pain, vasodilatation and acute urinary retention (Iron oxide), fever (Gold), cytopenia (Protein), hand–foot syndrome and stomatitis (Liposome), mild renal toxicity, urticaria and rash (Polymer), abdominal pain and dysuria (Dendrimer) and peripheral sensory neuropathy and neutropenia (Micelle).[28]

Summary

Nanotechnology is the understanding, control of matter and development of engineered devices in nanometer range. NPs have different physicochemical properties (small size, large surface area to volume ratio, and high reactivity) in comparison to bulk materials of the same composition. The nanotechnology has proved its usefulness in early diagnosis, proteonomics, imaging diagnostics and multifunctional therapeutics. Recent studies have shown its role in early diagnosis and targeted therapy of various gastrointestinal disorders such as hepatitis B virus and hepatitis C virus related liver disease, inflammatory bowel disease, gastric ulcer, and malignancy. Application of this technology appears promising in diagnostic and therapeutic endoscopy such as the endoscopic hemostasis of peptic ulcer bleeding, prevention of clogging of plastic stent and advance capsule endoscopy. The diversity of NPs, technical difficulties and potential adverse effects however, represent the major challenges.

In conclusion, the nanotechnology has emerged as a technical tool that enables us to keep the pace of advancement in diagnostics and therapeutics with the rapid progress of science and technology. We can hope that some of our unachieved dreams in diagnostics and therapeutic field of gastrointestinal sciences will be fulfilled by use of this technology.

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