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Novel Approach: of Nanotechnology

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Review Article

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Abstract

Nanotechnology has created a new horizon in diagnostic as well as therapeutic areas extending itself to even molecular levels because of its adaptability for success at atomic scale. Several delivery systems are being proposed and published worldwide over the last several years. Nanosystems include Dendrimers, Ceramic nanoparticles, Magnetic nanoparticles, Thiamine-targeted nanoparticles, Nanoparticle-aptamer bioconjugate, Multifunctional micelle, Carbon nanotubes, Quantum dots, Gold nanoshells etc. for purposes like targeting cancer cells, tissue imaging, thermal ablative cancer therapy, virus detection , noninvasive vaccine delivery etc. We continue with advanced uses like nanoburrs here, which are coated by hydrophilic polymers like PEG capable of travelling through bloodstream and avoids RES scavenging with increased residence time in systemic circulation. Advantages over other products like stents are given and can be utilized in treating those with complicated problems.

Keywords: *Nanotechnology, Dendrimers, Quantum dots, Nanoparticle-aptamer bioconjugate, Nanoburr.*

Introduction

Heart disease is one of the most common causes of death in our society, approximately a third of all deaths in males are due to cardiovascular disease. This figure has decreased since 1961, where almost 50 % of all male deaths were due to cardiovascular disease. Despite this, cardiovascular disease is one of the largest causes of death in males, equal only to cancer [1]. Amongst the possible causes of the high death rate due to cardiovascular disease is the fact that, on average, a male has a blood cholesterol level of 5.5 millimoles per litre – 0.5 mmol/l more than the government's recommendation [2]. High cholesterol levels are especially influential as a cause of atherosclerosis, the condition caused by a buildup of cholesterol, fibres and dead muscle cells as plaques (atheromas) on the lining of artery walls. Atherosclerosis causes the arteries to become narrower, thus leading to such other cardiovascular diseases as thrombosis and myocardial infarction.

Nanotechnology is a multidisciplinary scientific field that deals with formulation, preparation, characterization and application of structures, devices and system at nanometric scale [3].Nanotechnology can be extended for creation of specialized structures with added properties which can be used for controlling / manipulating biological structures because of their size advantage. Novel methods of diagnosis and medical treatment at molecular level can be performed as they possess the capability to work at atomic levels.

Table: 1 Nanoparticles with Medical uses

Systems	Uses
Dendrimers [4,5]	Targeting of cancer cells, drug delivery, imaging.
Ceramic nanoparticles [6]	Passive targeting of cancer cells
Lipid-encapsulated perfluorocarbon nanoemulsions [7]	Passive targeting of cancer cells
Magnetic nanoparticles [8, 9]	Specific targeting of cancer cells, tissue imaging
LH-RH-targeted silica-coated lipid micelles [8]	Specific targeting of cancer cells
Thiamine-targeted nanoparticles[10]	Directed transfer across Caco-2 cells
Liposome [11,12,13]	Specific targeting of cancer cells, gene therapy, drug delivery
Nanoparticle-aptamer bioconjugate [14]	Targeting of prostate cancer cells
Anti-Flk antibody-coated ^{90}Y nanoparticles [15]	Anti-angiogenesis therapy
Gold nanoshells [16, 17]	Tissue imaging, thermal ablative cancer therapy
Anti-HER2 antibody-targeted gold/silicon nanoparticles [18]	Breast cancer therapy
CLIO paramagnetic nanoparticles [19]	Imaging of migrating cells

Quantum dots [20]	Tissue imaging
Silicon-based nanowires [21]	Real-time detection and titration of antibodies, virus detection, chip-based biosensors
CNTs(carbon nanotubes) [22]	Electronic biosensors
Transfersomes [23]	Noninvasive vaccine delivery, drug delivery
Nanoburrs [32]	Targeting solid tumors and for diseases where vascular damage and permeability is observed.

Multifunctional Micelles

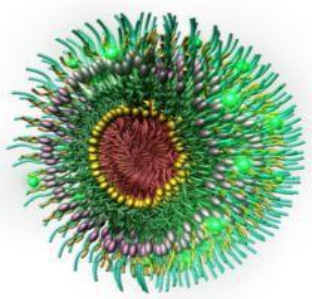


Figure 1: Multifunctional micelle.

Engineers at the University of California Santa Barbara have designed and tested a nanoparticle which they consider will target atherosclerotic plaques, specifically the "shoulder" region – the place where the plaque is most likely to rupture and causes in heart disease complication. This nanoparticle was a multifunctional micelle – a lipid based collection of molecules that form a sphere shape [22] (see Figure 1). The micelle has a peptide, a piece of protein [pentapeptide (cysteine-arginine-glutamic acid-lysine-alanine)], on its surface, and that peptide binds to the surface of the plaque. Fibrin has already been used widely as a target for drug delivery to specific sites and it is widely predictable as being deposited in atherosclerotic plaques.

They used these findings to test if their micelles could be used to deliver thrombin inhibiting drugs to the site of atherosclerotic plaques. Thrombin has been found to both induce clotting and increase the progression of atherosclerosis by causing smooth muscle cells to bind to Low Density Lipoproteins. If thrombin can be inhibited, then the progression of atherosclerosis can be halted and its adverse effects avoided. The production of thrombin 6 is induced when an atherosclerotic plaque ruptures – the specific place where the CREKA-targeting micelles were found to concentrate.
It is with this CREKA-targeting micelle that a treatment for atherosclerosis can be developed. By testing it on humans and approving it, we can advance the treatment for both atherosclerosis and thrombosis (and therefore myocardial infarction) through the use of the inhibitor drug Hirulog. The many benefits of micelles, outlined above, mean that they are excellent for progressing our medical treatment of atherosclerosis and, although not discussed here, tumours.

Research shows that there is great potential for CREKA-targeting micelles in the treatment of atherosclerosis and the prevention of its adverse effects. The problem faced now is that these findings are only reported in mice at present and therefore might not translate into the same positive effects in humans. However, if the same conclusions can be drawn for humans as for mice, then CREKA-targeting micelles would be an excellent solution to the current problem.[23]
Advantages

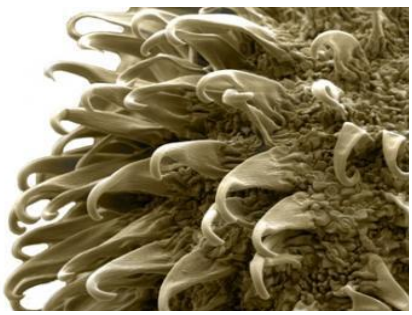
- Long circulation time.
- Designed to target the plaques that are most vulnerable to rupture
- Self-assembly and easy to be constructed.
- The targeted micelle can deliver an increased concentration of the anticoagulant drug Hirulog.

Applications
Vulnerable Plaque Diagnostics and Treatment

NANOBURRS

Nanoburrs or burrs are specialized spherical structure of 60 billionths of a meter (60 nanometers) in diameter, made of a lipid shell interface surrounding a polymer core. Thousands of them could be placed on the period placed at the end of this sentence. Each contains an inner core with a drug linked to a slowly degradable polymer [26]. Burrs have tiny hook like structures which can attach themselves to exposed surfaces of wounded arteries. They can also be used as a back-up for drug-eluting stents by delivering the drug to regions surrounding the stent struts [27]. These nanoburrs are made of a lipid shell interface surrounding a polymer core (see Figure 2). Initially nanoburrs will be limited to delivering medication to reduce the swelling of the damaged tissue, or to break down the atheroma. After this procedure further medication may be delivered by additional nanoparticles to repair the established damage to the intima, which would strengthen the lining of the coronary artery. The same method of drug delivery using nanoburrs can be used in the prevention of an ischemic stroke as the nanoburrs would act similarly in delivering a dose of a drug that could break down an atheroma in one of the arteries.

Structure:



Graphical image of a nanoburr

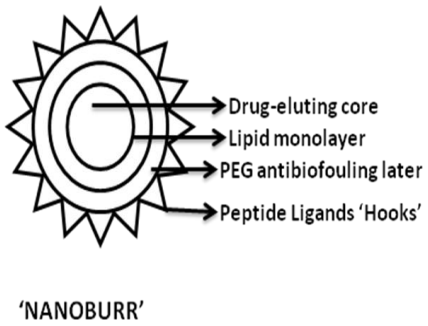


Fig.2. Structure of Nanoburr

It consists of 3 layers:

- Inner core: It contains the drug payload and a polymer chain Eg PLA (Polylactide).
- Middle core: It is made of fatty material Eg. soybean lecithin/lipid.
- Outer coating (PEG – Poly ethylene glycol, antibiofouling layer)

The outer coating is done by a polymer PEG which protects these burrs while traveling through the bloodstream. PEG is hydrophilic in nature and avoids RES scavenging resulting in burrs residing in the bloodstream for a long time. Burrs can be coated with a sticky protein making them cling to artery walls with simultaneous slow release of drugs loaded.

The inner core controls the drug release. It is decided by the length of the polymer chain present. Longer the chain, longer is the duration of action moderated by a reaction – ester hydrolysis. In this reaction, the drug detaches from the polymer for therapeutic activity.

Pam Baker reported Nanoburrs with 7 – amino peptides on the surface used for targeting the damaged vasculature of the basement membrane of which the working is shown as below in Figure 3 [28].

Schematic Diagram of working:

WORKING:

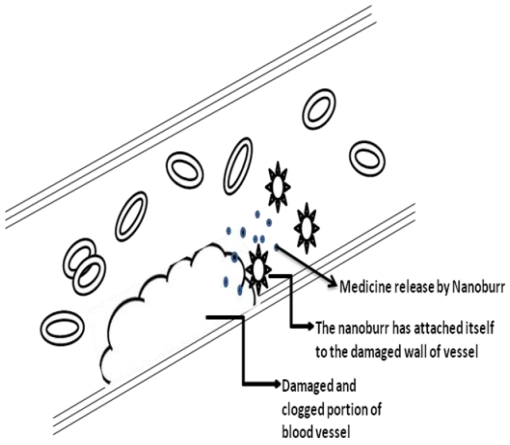


Fig.3. Diagram depicting how nanoburr would work

The particles (nanoburrs) have a "sticky" outer coating (peptide coating) which attaches to tissue basement membrane. Tissue membrane is only exposed in damaged portions of the arterial wall. When administered parenterally the burrs identify arteries needing treatment by the way of basement membrane. They attach themselves to this basement membrane and start releasing drug slowly reduces the damage of the arteries (Eg. Paclitaxel) and inhibits cell division and helps prevent growth of scar tissue that can clog arteries. But is only exposed when those walls are damaged.

This is a brand new technology which can be coupled with several other treatments more specifically with stents. An advantage of these burrs are that they can be used even in conditions where stents can't be used. Justin Borad [29] injected these into the rat tails and showed that they could travel upstream attaching themselves to the damaged rat left carotid artery. This is further undergoing further refinement and animal testing [29].

PREPARATION

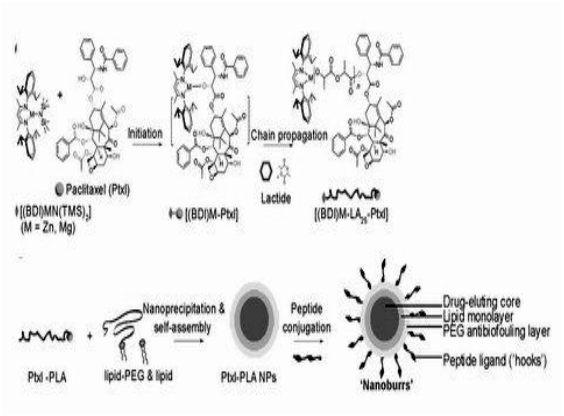


Fig.4. Nanoburr core-shell synthesis and characterization

(A) Schematic of Ptxl–PLA biomaterial synthesis. Ptxl was mixed with equimolar amounts of [(BDI)
ZnN (TMS) 2]; the (BDI) Zn–Ptxl complex formed in situ initiated and completed the polymerization of lactide. For the Nanoburr core, Ptxl–PLA25 drug conjugates is synthesized, which have approximately 25 D, L-lactide monomer units.

(B) Schematic of nanoburr synthesis by nanoprecipitation and self-assembly. Ptxl–PLA in acetone is added dropwise to a heated lipid solution, vortexed vigorously, and allowed to self-assemble for 2 h to form NPs. The NPs were peptide-functionalized using maleimide-thiol chemistry. Nanoburrs have a drug-eluting polymeric core, a lipid monolayer, a PEG antibiofouling layer, and

peptide ligands (hooks) to adhere to the exposed basement membrane during vascular injury.[31]

Some of the advantages can be listed as below:

1. Nanoburrs can stick to rupture arterial walls and can release drugs (such as paclitaxel) to teat damage area.
2. The drug release is controlled by PLA polymer chain and the duration depends on the length of the chain. Tests have revealed release of drug for over 12 days also [31].
3. Hydrolysis causes the release which is ideal as the body fluids comprise water mostly [31].
4. Normally, drug attachment requires chemical reaction making it more complicated. In burrs, this complication is simplified as the targeted moieties are attached to the outer shell and not even to the core [31].
5. In normal vesicular drug delivery systems, the common disadvantage is premature burst releasing drug in non required zone and quantities. This disadvantage can be overcome in burrs where the design eliminates bursting of the structures [31].
6. The most important advantage is the route of administration where the delivery can be from a very distant area other than the damaged zone [31]. This was corroborated by the study conducted by Justin Borad [29]. Here, burrs clung to damaged arteries at more than double that of non targeted nanoparticles [31].
7. Use of burrs can be extended with more precision for tumors involved with vascular damage altering the permeability of the arteries [28].

Uses of Nanoburrs:

- It can be used in various cardiovascular diseases.
- Nanoburrs can be used in various type of important disease like tumors and inflammatory disease where specially vascular rupture or permeability is occurs.

Nanoburrs Vs Stents

There is a lot of comparison done with available technology and novel technology like burrs. One of the most common comparisons done is with stents. Stents are no doubt good and used extensively as they keep the arteries open preventing sudden collapse. They can also deliver drugs loaded to the damaged artery walls. But, the disadvantage is that the stents are not mobile and are stationary in nature. They stick to one place and have to bear the load delivered by the collapsing artery which will increase over time. Compared to that, burrs are mobile in nature. They can spread themselves over wide areas along with capabilities of targeting damaged tissues. Stents may not be feasible for everyone as it is disadvantageous with patients suffering from renal failure, diabetes and hypertension. Along with this, stents may not be feasible to be placed in all the areas / locations like forks of the artery (bifurcation lesions), diffuse lesions, large arteries, already stented arteries having more than one lesion etc. [28]. Patients with narrowed arteries may not be suitable for stent placement. In all these conditions, burrs are useful making the treatment regimen more flexible and also adaptable

Conclusion

Although atherosclerosis is potentially mortal and a serious threat to our society, by using nanotechnology we may reach a reasonable cure and diagnosis's for it. Using both nanoburrs and micelles, as outlined above, atherosclerosis and damaged vascular tissue which precedes it may be diminished. Not only is this, but the use of nanoburrs in particular economically advantageous due to the decreased number of surgical treatments. As with most research, the research done to propose these ideas has raised a number of ethical issues, specifically that of animal testing. The possible advantages that lie ahead because of this research that the issues are far outweighed. In the not too distant future, it is probable that nanotechnology in the form of nanoburrs and micelles will provide the non-invasive cure for atherosclerosis that we desire.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.