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PRACTICAL IMPLICATIONS OF NANODOSIMETRY IN MEDICINE

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□ The grandiose promises made decades ago of cost reduction, miracle cures for cancers and universal availability of nanomedicine are still a far cry. Even we do not have any viable model to exploit nanotechnology in medicine. The most important arena of the nanotechnology is the development of nanoscale drugs for routine clinical practice. The current chemo protocols are based on maximum tolerable dose philosophy. Such a dose, when translated into active nanoscale clusters, quantitatively outnumbers the cells in an average human body. These nanoscale drug issues are discussed in this paper. A theoretical framework for commonly used drug aspirin has been considered as an example. The possible quantum physical effects have also been theoretically evaluated. Further, the amount of drug molecules in a standardized aspirin dose of 100 milligram has been computed into nanoclusters. The calculations show that the processing of nanoscale drug is a monumental task which requires new types of manufacturing facilities. Also there is a need to develop new protocols which will help realize the practical implementation of nanodosimetry in day to day drug administrations. These protocols will need to examine the implications of dose-responses such as necrosis, apoptosis and hormesis in medicine for routine clinical practice.

Keywords: nano, dosimetry, hormesis, apoptosis, cancer

INTRODUCTION

Nano scale material manipulation is an emerging field of science and technology. Its prospective impacts in medical industry are extensive. The expected applications range from surgical sutures to manipulating molecular machinery to treat the complex diseases. There are valid public concerns about severe toxicities associated with nanoparticles especially due to their translocations in a living system. There are also unknown consequences related to nanoparticles compared to their bulkscale counterparts consisting on same materials. However, there are other scientific and physical challenges related to nanoparticle manufacturing, dispensing and administration to patients in routine clinical practice. We will limit our discussion to quantum level behaviors, manufacturing issues and dispensing problems in nanodosimetry.

The United States in Americas, Liberia in Africa and Myanmar in Asia are the only countries in the world that still use an obsolete system of measurements in their daily lives. The rest of the world is using standard

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metric units known as MKS system. The MKS system of units is an abbreviation of Meter for length, Kilogram for weight and second for time. The second, as a time unit, is common to all systems. Liberia is too poor to change and Myanmar is too isolated to have any need or an impact in the international market. But the sole super power is too rich to afford the cost to change to standard metric system. Reasoning along the same lines the question arises: Will our current medical drug industry be ready to embrace the emerging nano drug manufacturing processes in near future? The drug manufacturing issue in the United States becomes extremely important because of its leadership in science and technology in the world. Unlike metric system, most of the world's drug industries and countries follow the USA pharmaceutical models for their healthcare needs. We need to evaluate the implications of nanotechnology in medical chemodosimetry to answer this question.

Generally it is claimed that everything in this universe is made of atoms. An atom of an element has neutrons, protons and electrons as its constituents plus binding energies that hold these ingredients together. Hydrogen atom is an exception which has only one proton and one electron. However, the objective of nano-scale technology is to exploit nano-size properties of materials. The alleged nanoscale is much smaller than our existing bulkscale material compositions but far larger than single atom of any element. Nanotechnology is popularly described as a method to assemble materials in an atom by atom or molecule by molecule fashion. The benefits of nano-scale properties are well documented in the research journals. In this article we will discuss the implications of nano technology in medical chemo-dosimetry. A length of 100 nanometer (nm) has been established as an upper metric to classify nano entities. One nanometer is one billionth of a meter in length i.e., 10^{-9}. The materials, in general, assume bulkscale properties beyond this length. (Poole and Owens 2003).

Historically physicians have adapted Maximum Tolerable Dose (MTD) therapy protocol to administer drugs to treat infectious diseases and malignancies. The objective of MTD protocol is to deliver maximum lethal dose to unwanted pathogens and malignant cells inside the body. The amount of such a lethal dose depends on many confounding factors including host's immunity status, age and the nature of a particular disease. Drugs are also administered in a cocktail fashion consisting on multiple prescriptions or in alternation with each other. The prescribed dose of a drug can range from microgram (μg) to gram (gm) per day for an individual. For instance the standard Arsenic Trioxide (As_2O_3) dose administered in Acute Promyelocytic Leukemia (APL) is about 10 milligram (mg) per day (Douer 2000). However, the dose of another drug, acetaminophen, may be up to 4 gm per day (Kuffner *et al.*, 2007).

The nanoparticles exhibit different characteristics in physical, chemical and biological domains compared to their bulkscale counterparts. The quantum uncertainties associated with smaller size particles may become pronounced at nanoscale. Their optical, vibrational, electrical, mechanical, rotational, magnetic and biological properties are different from their bulkscale siblings consisting on the same chemical compositions. The nanoparticle based reactions are amplified manifold because of their pronounced spread and expanded surface chemistry. For instance, a given amount of salt in nano formulation produces 10-30 times more chemical reaction than the same amount of salt in bulkscale form. Nanoparticles also trigger different biological reactions than bulkscale materials. This is mainly due to the translocation of nanoparticles inside a living system. A nanoparticle is highly vibrant and penetrates far deeper inside a living cell than aggregated molecules of the same material. Their biological reactions also change because of their translocations inside the cells. The physical and biological clearance of nanoparticles is yet another area of great concern regarding their side effects.

In this article, we would like to explain the implications of nanotechnology with respect to commonly used drug, aspirin, to elaborate its various aspects. Aspirin is the appropriate candidate for evaluation in terms of nanoscale implications because of its frequent uses as a common drug around the world. Aspirin is widely used as a standard drug therapy in the primary and secondary prevention of cardiovascular diseases (ATT 2009). Low dose aspirin saves cost significantly (Tsutani *et al.*, 2006, Elwood *et al.*, 1998). Some studies show that doses of 75 mg and 325 mg are equally effective in the prevention of cardiovascular diseases.

Malhotra *et al.* (2003) evaluated effects of 50, 80, 100, 162.5 and 325 mg aspirin doses which are widely used in clinical practice. However, they concluded that doses of aspirin less than 100 mg were not as effective in inhibiting platelet aggregation as doses greater than 100 mg Aspirin has been also credited as a promising chemoprevention agent in colorectal adenomas (Cole *et al.*, 2009, Grau *et al.*, 2009). The doses of aspirin in these studies ranged from 81 to 325 mg.

Historically, low dose aspirin is defined as 81-160 mg per day and higher-dose aspirin ranges between 300 – 325 mg per day. In another study the use of two standard tablets of aspirin consisting on a dose of 650 mg per week had significant reduction in the risk of colorectal cancer (Chan *et al.*, 2005).

NANOCLUSTERS PER DOSE

An aspirin molecule has a diameter of 1 nm. Its chemical formula is $C_9H_8O_4$ and molecular weight is 180. As described earlier the upper limit defined for nano-scale entities is 100 nm (Poole and Owens 2003). We

assume for simplicity that a dose consisting on 100 aspirin molecules constitute a single aspirin nanocluster. If the mass of a typical dose, m, is 100 mg then the number of aspirin molecules, N, in such a dose can be calculated by using the formula:

$$N = \frac{N_A * m}{A_w} \quad (1)$$

where N_A is Avogadro number, 6.02×10^{23}, and A_w is the molecular weight of an aspirin molecule. This assumption ignores all other correction factors such as effects of temperature, atmospheric pressure, humidity etc. on aspirin structure. The number of molecules in a 100 mg aspirin dose will be 3.34×10^{20}. If each aspirin nanocluster contains 100 molecules then a 100 mg aspirin dose consists on 3.34×10^{18} nanoclusters. The total length of clusters can be calculated by

$$L_n = d(2n+1) \quad (2)$$

where d is the diameter of a cluster and n is the total number of clusters in a dose. The value of n= 0,1,2,3,....N_o. We assume that each cluster can be placed at least 50 nm apart from other clusters to avoid aggregation. This assumption appears realistic due to the physical limits imposed by our current manufacturing technologies.

MANUFACTURING MOLECULE BY MOLECULE

Suppose if one nanosecond (nsec) is required to act on one molecule then the time required to act on 3.3×10^{20} molecules will be 3.3×10^{11} seconds or 10464.2 years.

Light Days Time: We assume that we have the capability to tackle each molecule with the speed of light. The total length formed by 100 mg aspirin molecules will be 3.3×10^{13} m. If we tackle each molecule with the speed of light then the total time required to account for all the molecules will be 1.1×10^{5} light sec or 1.27 light days.

Assembling Clusters into a Dose: Suppose the same timeline of 1 nsec is needed to assemble one nanocluster composed on 100 aspirin molecules then the total time required to assemble 100 mg aspirin into a nano dose will be 106 years.

QUANTUM MECHANICAL EFFECTS

Researchers often raised the question if quantum mechanical effects related to microscopic objects become pronounced at nano levels. Such effects are mainly due to the pronounced wave-particle duality of matter in quantum world. A precise positioning mechanism is needed to accurately place a drug cluster at a particular target position in a repetitive

fashion. If we ever develop the technology to handle individual molecule to be placed at a precise location then what type of uncertainty would be associated with such positioning mechanism? This can be estimated by calculating the associated positional probability due to the cluster size. Furthermore, such calculations are also needed to estimate the probability of misplacement of a drug cluster in an intended cell target in a research setup. These calculations are also needed to estimate the probable surface area of a drug vehicle. Drug vehicles are used to transport nanoclusters to a particular target inside the body.

The purpose of this section is to estimate the quantum-wave effects associated with an aspirin nanocluster. This will also help us determine how far off a drug nanocluster may land from its intended target due to its pronounced wave effects. Generally simulation program consisting on complex mathematical tools on computers are used to calculate these quantum effects. Such calculations are mainly based on models derived from Schrödinger wave equation. In this article we will use simple equations to determine the quantum wave associated with a nanocluster consisting on 100 aspirin molecules. The objective is to evaluate if this issue is worth exploring further in nanomedicine. To calculate the wavelength associated with a 100 nm cluster we use the equation:

$$\lambda = \frac{h}{mc} \tag{3}$$

where m is the mass of a nanocluster, c is the velocity of light and h is Plank's constant.

The density of aspirin is 1.40 g/cm^3. We can calculate the mass, m, by using formula:

$$m=\rho.v \tag{4}$$

where ρ is the density of aspirin and v is the volume. The volume of 100 nm diameter aspirin nanocluster can be calculated by using the formula:

$$\text{Volume} = \frac{4}{3}\pi r^3 \tag{5}$$

Volume = $4/3(\pi \times (5 \times 10^{-6})^3\ \text{cm}^3) = 523.6 \times 10^{-18}\ \text{cm}^3$.

Mass of an aspirin nanocluster is = density × volume = $1.40\ (\text{g/cm}^3) \times 523.6 \times 10^{-18}\ \text{cm}^3$ or mass = 733.04×10^{-21} Kg.

Now we can calculate the wavelength associated with an aspirin nanocluster by using the formula given in equation (3)

$$\lambda = \frac{6.6 \times 10^{-34}\ \text{J.sec}}{733.04 \times 10^{-21}\ \text{Kg} \times 3 \times 10^{8}\ \frac{\text{m}}{\text{sec}}}$$

$$\lambda = 0.003 \times 10^{-21} \frac{J \sec^2}{Kg.m}$$

$$\lambda = 00.03 \text{pÅ} .$$

as by definition J = m^2 Kg sec^{-2}.

The wavelength associated with a 100 nm aspirin nanocluster is extremely smaller than the nucleus of a Hydrogen atom. So the quantum probability of an aspirin cluster to fall outside of its intended target in a typical 10 micron living cell is almost zero.

INTERCLUSTER ATTRACTION

Given the mass of 733.04 × 10^{-21} Kg per nanocluster and inter-cluster distance of 150 nm, the attractive force between two aspirin nanoclusters is 159.3 × 10^{-35} N. Being other factors, such as Van der Wall forces, ignored these clusters are far apart from each other and will not aggregate to form bulkscale masses.

SURFACE AREA

We would like to estimate the surface area required to spread aspirin nanoclusters at a distance of 50 nm from each other. Using the formula L_n=d(2n+1) as defined in equation (2) the total length formed by 100 mg aspirin nanoclusters is

$L_{3.34x10^{18}}$ = 100(2 × 3.34 × 10^{18}+1) = 6.68 × 10^{20} nm. Area covered by these clusters will be 2.585 × 10^{10} nm^2 = 25.85 m^2.

If all the aspirin clusters are coated on the outer surface of a spherical shell then the diameter of such a pill will be:

$$d = \sqrt{\frac{A}{\pi}} \tag{6}$$

d = 2.87 m or 287 cm.

If an average height of an individual is 1.8 meter then the pill itself will be over 1.50 times taller than the average height of the user.

This volume may be reduced by producing pills in different geometrical configurations where nanoclusters can be spread on inner surfaces. However, this will complicate the manufacturing processes thus leading to higher prices and compromising the stability of the pill structures.

CELLULAR UPTAKE

In conventional bulkscale dosage extra drug amount is excreted in aggregate form from the system which pollutes our waterways. Furthermore, the aggregated drugs in bulkscale forms have limited penetrations inside the living organism due to their larger sizes and body's

resistance to further uptake after initial exposure. However, the scenario with nanocluster is different: Their damaging effects are mostly unknown in a living system as well as in the environment. In reality one needs a fraction of the existing MTD dose in nano formulation because of the optimal absorption and expanded chemical reactivity of the particles.

It has been estimated that there are 20 to 30 trillion cells in an average human body. Suppose we administer a 100 mg dose consisting on aspirin nanoclusters to an individual. Each nanocluster contains 100 aspirin molecules. The number of nanoculsters in a 100 mg aspirin dose far exceeds the number of cells in the body if each cell uptakes one nanocluster (i.e., 100 aspirin molecules per cell). If these extra aspirin nanoclusters pass through kidneys they can cause irreparable damage to them. Since there are only one million nephrons in each kidney, just few doses of nanocluster-based aspirin can completely wipe them out.

As described above, each 100 mg aspirin dose can be developed into 3.34 million trillion ($3.34x10^{18}$) nanoclusters. If there are 30 trillion cells in an average human body, then 100 mg aspirin nanoclusters is sufficient to saturate over 100,000 individuals and their pets. This claim is supported by mathematical calculations as the numbers do not lie.

CHALLENGES TO BE TACKLED

1. How to produce drugs composed on nanoclusters? Such nanoclusters-based drugs need not aggregate into bulkscale formulation over time.
2. How to assemble nano-drugs efficiently, economically and timely into manageable dispensing pills or suspensions for routine clinical practice?
3. How biocompatible vehicles be manufactured to transport nanoclusters for optimal therapeutic effects?
4. How to establish QA benchmarks for all the processes described in 1, 2 and 3.
5. How to achieve precision manufacturing technology at 50 nm scale?
6. Dose-response quantification to evaluate different biological effects such as necrosis, apoptosis, hormesis, etc. with different doses of drugs.
7. Studies of known and prospective additional new toxicities associated with common over the counter as well as prescription drugs due to their nanoscale effects. Such toxicities need evaluation in both quantitative and qualitative domains.
8. Nanodosimetry standardization based on Time-Dose-Response and Fractionation.

CONCLUSION

There are already numerous issues associated with MTD protocol. The foremost issue is the severe side effects produced by MTD with bulkscale formulations. Such side effects with nanoscale drugs will aggravate manifolds in addition to other unknown complications because of the translocations of nanoparticles deep inside tissues. There is an emerging evidence that smaller drug doses produce better results with minimum toxicity in chronic diseases especially in advance cancers (Satti 2009). Chemicals and radiation produce multiphase biological reactions with different doses. Stronger doses of drugs produce necrosis inside the host body. However, smaller doses produce hormesis and apoptosis. Apoptosis is a highly desirable biological process to heal a system without any significant adverse side effects. Hormesis can induce resistance in a biological system which can be administered as a prophylactic modality in preventive medicine. Yet further diluted doses produce bystander effects. Even a single charged particle can inflict lethal damage to a cell which in turn can produce bystander deaths in hundreds of other cells (Gaillard *et al.* 2009). We also know that energies less than 1 electron volt (eV) can produce symmetric, asymmetric and other vibrational effects in molecules (Anderson 1984). For comparison the photon energy from an incandescence light bulb ranges between 1 - 3 eV. There is an urgent need to revise our centuries old chemical dosimetery protocol, especially if we would like to avail the emerging nanotechnology in our daily practices. It is expected that such changes will come in big savings and better cure rates for chronic diseases in addition to other rewards such as environmental protections and ecological preservations. However to reap these rewards scientists need to overcome monumental task of nanomedicine from manufacturing, drug evaluation, dose specification, toxicological studies, clinical trials and QA maintenance in a clinical setup. The question remains to be seen if the rest of the world will wait for the USA to show leadership in nanomedicine dosimetry or they will take their own initiatives and set new standards in this emerging arena?

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