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Perspective

2D-Metal-NSs Based 'Smart Drug Delivery and Imaging Platforms' Treatment of Neglected Tropical Diseases (NTDs)

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Emerging Perspective

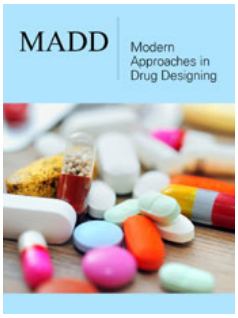
Recent publications have very often emphasized that the human population with unequal socioeconomic backgrounds do pollute the environment causing diverse human health problems in general. The study also recommended for linking these inequalities via the environment to the prevailing human health issues for finding out the pathways of effective interventions. The glaring example of the adverse effect of this inequality can be seen in human health care management und er the supervision of the WHO, in totality, before initiating various health related programs to run and to be monitored subsequently Cushing et al. [1].

Out of all human health related issues encountered globally, WHO could identify the area of 'Neglected Tropical Diseases (NTDs)' that put a burden of 47.9 million disability-adjusted life years throughout the World, particularly affecting the disadvantaged groups of people. Realizing the criticality of NTDs in jeopardizing the overall sustainable development goals, the WHO has been striving hard by making numerous positive efforts in this context as these diseases continue to attract lower priority at the global level. It requires more intensive efforts in implementing the well thought out action-plans by enhancing their priority first. This requires not only for sustaining the commitment of the current agencies, but also engaging the newer ones for paying more attention towards developing effective treatments of the prevalent tool-deficient diseases Pastrana et al. [2].

According to the WHO, a list of 20 diseases, classified under NTD-category, are found affecting >1 billion people in 149 countries. Most of the drugs used against these diseases are rather old having several undesired side-effects. Noting lack of interest from the pharmaceutical companies in developing more novel drugs or vaccines for NTDs manufactures, it is still worse as the target population belongs to those countries with a serious affordability problem. In this context of handling these deadly diseases, metal complexes have systematically been studied to offer better treatments shown by numerous clinical studies carried out using their unique physicochemical properties. It has also been noted that the metal complexes of arsenic, mercury, bismuth, platinum, antimony, gold, iron, gadolinium, samarium, technetium, and palladium, are certainly emerging as effective treatment strategies of these deadly diseases, as reviewed recently. Undoubtedly, there is a dire need of discovering newer drugs using simpler protocols scalable for commercial productions. Distributions of these drugs that are free from drug resistance to the affected populations at affordable costs would be a necessary giant step in this direction Ong et al. [3].

The success of metal-based complexes in treating these NTDs are now being presented as the future medicine for NTDs, as they act via more than one biochemical-interaction pathways to inhibit more than one target enzymes. For instance, a gold salt (e.g., 'Auranofin') is worth mentioning as it is noted to suppress the inflammations via stimulating cell-mediated immunity. WHO has authenticated this 'Auranofin' based treatment as it induces heme oxygenase 1 (HO-1) mRNA with anti-inflammatory properties? 'Auranofin' has been found effective in diseases like rheumatoid arthritis, leishmaniasis, and schistosomiasis Ong et al. [3].

ISSN: 2576-9170



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Submission: April 05, 2021
Published: May 20, 2021

Volume 3 - Issue 3

How to cite this article: Ahmad S. Global 2D-Metal-NSs Based 'Smart Drug Delivery and Imaging Platforms' Treatment of Neglected Tropical Diseases (NTDs). Mod Appro Drug Des. 3(2). MADD. 000562. 2021.
DOI: 10.31031/MADD.2021.03.000562

With the advances made in preparing nanomaterials for biomedical applications with much better efficacies in treating a large number of diseases during last few decades, the evolutions of nanomedicines are currently advanced using reduced dimension nanostructured material species of organic, inorganic, and biomaterials nature. The enhanced physico-chemico-biological features of these bio-medicinal nano formulations are finding growing applications in targeted drug delivery, imaging and theranostic applications in general. More recent developments of two-dimensional (2D) lamellar materials are showing even better promises in offering solutions appropriate for biomedicine. The current developments of monoelemental material nanosheets (NSs), called Xenes, are noted to offer smart features controlled by external stimuli that are highly effective in theranostic applications in nanomedicine. Theoretical and experimental investigations, made so far, in case of Xene-NSs of borophene, silicene, germanene, stanene, phosphorene, arsenene, antimonene, bismuthene, and tellurene have reached a stage where a number of highly sensitive and selective nano biosensors, and theranostic platforms are available for targeted drug delivery, including simultaneous tracking of the biochemical interaction pathways by advanced imaging techniques, along with the desired drug release and excretion profiles during their clinical trials. Xene-NSs are currently being investigated for their practical applications in biosensors, bioimaging, therapeutic delivery, and theranostics required in developing a smart platform Ahmad [4-7]; Kumar [8] and Tao et al. [9].

A number of precautions are found mandatory to take into account before developing such 'Smart Drug Delivery Platforms' involving significant advantages of better control of drug loading, targeting, release, and excretion related to 2D-NMs in comparison to traditional polymer-based drug delivery platforms. Possessing larger specific surface areas providing more effective loading of fluorescent dyes, targeting molecules and therapeutic drugs as discussed by Zhang et al., involve many 2D-NMs exhibiting capabilities of combined nano therapies. Such features were confirmed in case of graphene quantum dots (G-QDs) loaded with cisplatin (~ 50% at neutral conditions), exhibiting reduced toxicity along with pH-dependent slow release. Cell experiments confirmed their lower cytotoxicity, higher selective uptake rate and good targeting capability features. The toxicity of targeted cisplatin-loaded nanocarriers against MDA-MB-231 cells was found higher than non-targeted ones. Similarly, adding 2D-GO-nanopletlets in a thermosensitive matrix produce a hybrid photothermally sensitive nanogel exhibiting good stability Zhang et al. [10].

While exploring these advanced nanomedicines, one has to keep in view the negative features of 2D-NMs as their enhanced interactions with biological systems including tissues, organs, cells and biomolecules, might cause acute and chronic toxicity. The advantage of high drug-loading capacity of 2D-NMs could also result in precipitate formations with serum proteins or red blood cells after in vivo administration. Graphene nanosheets (G-NSs) are known to cause side-effects affecting growth factor-β-related signalling pathways and inducing apoptosis of mitogen-activated protein kinases. G-NSs increase the intracellular ROS generation and destroy the mitochondrial membrane, potential resulting in cytotoxicity and its derivatives showing dose-dependent haemolytic activity. Few layer thick graphene and high dose and long exposure of GO-NSs might lead to mitochondrial dysfunction. These observations do demand extra care in designing the smart drug delivery and imaging platforms by taking care of the additional side effects introduced along with their positive impacts Zhang et al. [10].

Based on the brief background information described here, it seems quite imperative to deploy 2D-NSs of metal species and their functionalized derivatives for fabricating 'Targeted Drug Delivery and Imaging Platforms' for treating a number of NTDs already listed. It is worth noting that the metallicity of these 2D-NSs can be engineered using their unique physicochemical properties derived from mono/multiple layered-NSs along with their surface functionalized derivatives in a controlled manner. Their colloidal suspensions in different liquid media as well as gel preparations are indicated to offer stable formulations necessary for Smart Drug Delivery and Imaging Platform. There are ample number of successfully reported experimental results that confirm the feasibility of this route in the near future. A somewhat similar indications are from age-old experience of using metal species based medicinal formulations in alternate system of 'Unani' and 'Ayurvedic' medicines of India to further corroborate these speculations. Deploying lamellar 2D-NSs of metal species based on improved formulations with significantly improved efficacies would also be made to contain they are *in-vivo* toxicity at acceptable level via several routes. Once, the physicochemical properties-based Structure-Activity-Relationship (SAR) data is compiled, in-silico models of drug-discovery would enable finding optimal formulations via artificial intelligence and machine learning techniques already in vogue for modern molecular medicines. Taking into account the quantum effects associated with the mono/multiple layered metal-NSs and their functionalized derivatives to incorporate stimuli-responsive smart features will not be complete without taking into account the spin-orbit coupling for realizing topological insulators along with highly conducting surface and edge states.

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