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RESEARCH ARTICLE

METALLIC NANO PARTICLES AS EMULSION STABILISERS

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ABSTRACT

Recently, the research focus is shifting towards replacing classic surfactants with colloidal particles in stabilizing emulsions. This review gives an overview of utility of metallic nanoparticles as emulsion stabilizers. The emphasis is on the use of metallic nanoparticle stabilized Pickering emulsions as carriers for antibiotics. It's an established fact that metallic nanoparticles possess antimicrobial properties themselves and can be a good choice for formulating drug delivery systems. Additionally, they have a capability to evade drug resistance mechanisms in bacteria. Metals like gold, silver, copper, iron, manganese etc are used extensively. So, combining plant based antimicrobials and a metallic nanoparticle into one drug delivery system, with an add-on of the recommended antibiotic seems a promising possibility.

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INTRODUCTION

Most of the medical interventions are dependent on antibiotics. The consistent development of multi-drug- resistant species of micro-organisms will render all this useless, if newer promising strategies for combating the same aren't developed. Increasing disease burden and a consumer demand for convenient yet efficient drug delivery systems has initiated a world- wide quest for varied newer formulations. There's going on a never ending search for new molecules, but help is required from efficacious drug delivery technologies to make them usable. Nanoemulsion technology in particular has gained momentum due to its multiple advantages and wide applications. According to a report by Zion Market Research, the global nanoemulsion market is expected to reach USD 15,290 Million By 2025 (Global Nanoemulsion Market, Zion Market Research, 2019). The advantages possessed by nanoemulsion based formulations are manifold, may it be the delivery of therapeutic or diagnostic agents, controlled drug release, high solubility of drug or improved bioavailability. Frequently surfactants are employed as emulsifiers, but off late, the harmful effects exhibited by them have gained notice. Studies show that surfactants may damage the enzyme activity and thus disrupt the body's normal physiological function. They also have some toxicity and may accumulate in the human body and are difficult to degrade.

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There have been reports that a few of them like SDBS (sodium dodecyl benzene sulfonate) is absorbed through the skin. A few of them may damage the liver and are carcinogenic and teratogenic as well (Yuan et al., 2014). Safiah Saah et al reported a study involving thirteen non-ionic surfactants that are frequently employed in drug delivery systems. Their toxicity on gastro-intestinal cell lines was studied and the highest was observed towards polysorbitan fatty esters, polyoxyethylene sorbitan fatty esters, polyoxyethylene castor oil derivatives and PEGylated glycerides (Saah et al., 2018). For the above mentioned and like reasons, recently, the research focus is shifting towards replacing classic surfactants with self- assembly of colloidal particles to satbilise emulsions. They can offer advantages, such as lack of irritancy in use (*e.g.*, on skin) biocompatibility and relative safety *in vivo (Calabrese et al.,2018)*. Such particle-stabilized emulsions are referred to as "Pickering emulsions" (Thompson et al., 2014). The self- assembly of fused colloidal particles at the interface of an emulsion forms Collidosomes. Particles self-assemble in order to minimize the total interfacial energy (Pratibharajan et al., 2011)[6]. Thus, colloidosomes have a core surrounded by a shell of colloidal particles and are generated from pickering emulsion templates (Thompson et al., 2014). In 2002, A.D Dinsmore reported efficient encapsulation of many active ingredients in colloidosomes (Dinsmore et al., 2020) [7]. Recently metallic nanoparticle stabilised emulsions are also being explored. Metallic nanoparticles, unlike conventional emulsifiers provide irreversible interfacial adsorption, stability

against coalescence, sedimentation, flocculation and creaming (Calabrese et al., 2018 and Koroleva et al., 2019).

Metallic nanoparticles as antimicrobials: Infectious diseases remain one of the primary reasons of morbidity and mortality. Amongst many reasons, Antimicrobial Resistance is of special concern as raised by world Health Organisation (WHO) AND Centre for Disease Control and Prevention (WHO, 2001).

This has triggered a worldwide hunt for newer effective, antimicrobial compounds. But developing equally efficient drug delivery systems is also needed simultaneously; efficacious in terms of safety or controlling the rate, time, and place of release of drugs in the body. This has led to extensive research activities throughout the globe. The ultimate motive is to develop and put to practice novel drug delivery and targeting systems. It's an established fact that metallic nanoparticles can be a good choice for formulating drug delivery systems and conveying antimicrobials at the desired sites and also many of them possess antimicrobial properties themselves (Baptista et al., 2018). Additionally, they have a capability to evade drug resistance mechanisms in bacteria. So, combining plant based antimicrobials and a metallic nanoparticle into one drug delivery system, with an add-on of the recommended antibiotic seems a promising possibility. Metallic nanoparticles exhibit antimicrobial activity via many mechanisms vis a vis structural changes in the cell wall, generation of reactive oxidative species, protein inactivation and destruction of DNA. Table 1 lists a few metals utilized as nanoparticles and their probable mechanism of action as antimicrobials.

Metallic Nanoparticles as Emulsion stabilizers: Pickering emulsions are surfactant- free emulsions, stabilised by the self-assembly of colloidal particles at the interface. Metallic nanoparticles can be used in lieu of conventional emulsifiers for the stabilization of Pickering emulsions. The selection can be made on the basis of wetting behaviour exhibited by them. Surface modification can be employed to have a control on the same and also on the emulsion stability (Chevalier et al., 2013). The initial self-assembled structures are known as Pickering emulsions. After the shell reinforcement at the interface using suitable techniques, the Pickering emulsion is now called as colloidosomes.

Thompson et al., 2014). Microencapsulation protects the active ingredient from the environment till its release, improves solubilisation and permeability. The materials used can also be tuned to offer stimuli-sensitive drug release (Verma et al., 2013). Many theories demonstrating the mechanism of stabilization in Pickering emulsions have been proposed, and the commonly accepted one is based on the formation of a steric barrier by solid particles adsorbing at the oil–water interface (Monégier du Sorbier et al., 2015)[19].That is, particles are able to irreversibly attach to the oil–water interface, leading to a more efficient stabilization than surfactant adsorption (Yang et al., 2013). A number of metallic nanoparticles can be been used to stabilise emulsions. Table 2 summarizes the selected studies carried out on stabilisation of emulsions using metallic nanoparticles.

Table 1. Metallic nanoparticles and mechanism for antimicrobial activity

Metallic nano- particle with antimicrobial activity	Mechanism of action	Citation
Ag	Silver Nanoparticles (NPs) are reported to hamper the cell wall synthesis by interacting with sulfur-containing constituents within the cell membrane.	(Gold et al., 2018)
Au	Gold results in decreased membrane integrity and a buildup of Reactive Oxygen Species within the cytosol of the cell.	(Gold et al., 2018)
Cu	Bacterial cells on coming in contact with the metallic copper surfaces were killed because of membrane and cell envelope damage.	(Akhidime et al., 2019)
Ni	The exact mechanism is yet to be ascertained and requires extensive research for safe use. A few reported mechanisms of antimicrobial activity are generation of Reactive Oxygen Species, release of metal ions, cell wall damage and dissemination of cell envelope.	(Behera et al., 2019 and Donaldson et al., 2012)
Al	An interaction of the nanoparticles with the cell surface is suggested as the possible mechanism for the toxicity.	(Mukherjee et al., 2011)
Zn	On the nanoscale, ZnO has shown antimicrobial effects. The exact mechanism of action is unknown, but reports claim it to be because of electrostatic interaction with the membrane, formation of Reactive Oxygen Species, and/or release of ions.	(Gold et al., 2018)
Ti	Titanium dioxide (TiO_2) NPs have been used as a broad-spectrum antimicrobial agent. They damage cell-membrane and release Reactive Oxygen Species. The antimicrobial properties of TiO_2 NPs can also be attributed to a photocatalytic reaction causing generation of free radicals from the TiO_2 NP.	(Gold et al., 2018)
Mg	The primary antibacterial mechanism of magnesium oxide (MgO) NPs is the production of Reactive Oxygen Species under light exposure. Once produced, the ROS lead to oxidative degradation of lipid molecules of cellular membranes, ultimately causing cytoplasm leakage.	(Gold et al., 2018)
Fe	A significant reduction in biofilm growth was observed in the presence of the high concentration of iron-oxide nanoparticles.	(Thukkaram et al., 2014)

Table 2. Summary of selected studies on Metallic NP stabilized emulsion

S.No	Metal coated colloidosome/pickering emulsion	Remarks	Reference
1	Kannamycin Au and Ag coated colloidosomes.	Investigation was carried out in E.coli. Ultrasound was used to trigger the drug release. The released antibiotic, the broken fragments, and the antibiotic loading on the capsule surface killed *E. coli*. Gold colloidosomes loaded a higher concentration of kanamycin than those of silver.	(Sun et al., 2018)
2	Doxorubicin Au coated and Au- functionalized colloidosomes	A new Au colloidosome functionalised using 4,4′-dithiodibutyric acid and crosslinked with proteins–rabbit immunoglobulin G (IgG) was reported. The aqueous core colloidosomes were prepared and ruptured using ultrasound. Au coated colloidosomes showed lower cytotoxicity. They showed non-permeability, ultrasound sensitivity and susceptibility to immunoassay targeting that can be applied to many medical applications.	(Sun et al., 2018)
3	Au particles functionalized with PEG-thiol and alkane thiol.	Amphiphilic gold nanoparticles were reportedly prepared to stabilize emulsions of hexadecane in water. The method was simple, scalable, and cost-effective, which made gold nanoparticle surfactants spontaneously self-assemble into clusters of controllable structure. Also, the subsequent functionalization of particle surfaces with thiol-terminated polyethylene glycol (PEG) chains and short alkane-thiol molecules resulted in nanoparticles, effectively serving as emulsifying agents than the original nonfunctionalized gold nanoparticles.	(Larson-Smith et al., 2012)
4	Pickering Emulsions stabilized by Mercaptocarboxylated Au NPs	Au nanoparticle stabilised Pickering emulsion was formulated without any surfactant, using mercaptocarboxylic acid as a stabilizing agent and preparation conditions were investigated. The emulsion size and size distribution depended on the rotation speed of the homogenizer, the NaCl and the Au nanoparticle concentration. Emulsions were found stable for a period of 12 months.	(Yamanaka et al., 2013)
5	Self-assembly of Au NPs at the interface of oil-in-water emulsion droplets.	A straightforward method for the preparation of submicron capsules with tailorable size and wall thickness. Tuning the wetting properties of the NPs controls the capsule size and the wall thickness. This was done by either changing the composition of ligand shell or the composition of oil phase. The NPs coated with two types of ligands stabilize much smaller capsules than those coated with one type of ligands. The obtained capsules, because of covalent cross-linking and hexagonal NP packing, are extremely robust and tight, even those composed. of the single NP monolayer. This feature makes the capsules suitable for storage and easy release of tiny cargoes.	(Sobczak et al., 2017)
6	Au spherical and non-spherical nano-particle at emulsion interface.	The method reports formation and accumulation of spherical and non-spherical gold nano particles at the emulsion interface. A reaction between decamethylferrocene (DmFc) in hexane and AuCl4 - within the aqueous phase, was used. The technique of microfluidics was used to prepare emulsion droplet. The prepared mico-capsules were robust and allowed easy release of tiny cargoes. Experimental variables studied were surfactants, solvents and droplets sizes. The formulator believes that this method, which requires small reaction times, may be useful for large scale production.	(Sachdev et al., 2017)
7	Pickering emulsions stabilised within microfluidics chip for the production of Fe3O4 Au particles.	Reported as the firstly prepared Pickering emulsions within a microfluidics chip for the production of Fe3O4-Au Nano- particles. Mercaptododecanoic acid stabilised Au nanoparticles were added to the aqueous continuous phase, in order to stabilise hexane emulsion droplets formed within a microfluidic chip. The diameters of Au Pickering emulsions could be controlled by varying the flow rates. The addition of a second nanoparticle, Fe3O4 (average diameter of 12 nm), into the organic phase produced core@shell particles. The technique has the advantages of not requiring long reaction times, surfactants or templates to produce the asymmetric materials.	(Sachdev, S. et al., 2017)
8	Au NPs at the interface of oil-in-water emulsion droplets.	Ultra-small colloidal capsules were generated by stabilising oil-in-water emulsions using Au nano particles. The wetting properties of nano-particles were modified by the formulator, which affected the size and thickness of the capsule walls. These capsules were stable in aqueous solutions, and their size didn't vary with time. This renders the colloidal particles suitable for storage and release of cargoes.	(Sobczak et al., 2017)
9	Iron oxide NPs as emulsion stabilizers.	The author has outlined the utility of iron oxide nanoparticles in stabilising emulsion systems. These nano-particles can be surface modified, which allows for tuning of HLB balance of emulsions. Experimental variables such as pH of the aqueous solution, oil/water volume ratio, polarity of the oil phase, ionic strength, nature of modification and concentration of the NPs affects the stability of Pickering emulsions.	(A. Udoetok et al., 2016)
10	Polychlorinated biphenyls (PCBs), stabilised by Bentonite, iron oxide and magnesium oxide	The study was carried to formulate polychlorinated biphenyls (PCBs), stabilised by Bentonite, iron oxide and magnesium oxide dispersions ex situ. The stability of generated emulsions was tested over time for the impact of varying the solid concentration, and the influence of the employed preparation techniques. Bentonite, iron oxide and magnesium oxide dispersions proved to be robust Pickering emulsion stabilizers, whereas manganese oxide dispersions were not.	(Roy-Perreault et al., 2005)
12	Tramadol W/O Pickering emulsion(PE) stabilized by MgO Particles.	This study envisaged the formulation of stable tramadol w/o pickering emulsion stabilised by magnesium oxide particles. Tramadol was incorporated in the internal phase. Parameters such as droplet size, pH and viscosity were affected by the amounts of Magnesium oxide particles and the active ingredient.	(Sy PM et al., 2018)
13	Dodecanethiol- capped silver nanoparticles at the liquid/liquid emulsion interface.	This report, offers the first work where by the investigation of nanoparticles in a liquid medium using the E-TEM was done. The dodecanethiol-capped silver nanoparticles of size range 1-5 nm were formed randomly and distributed as multilayers at the liquid/liquid interface	(Dai et al., 2005)

Conclusion

As antibiotics continue to be extensively used, the scenario of increase in resistant microorganisms is a persistent challenge. Where scientists are in continuous search for new and effective antibiotics, the lack of availability of novel drug delivery systems as carriers for them is a continuous halt. After reviewing literature, it is evident that both Pickering Emulsions and metallic Nanoparticles exhibit many potential benefits. It seems that using both in combination can be a promising possibility to cause higher bacterial toxicity, especially towards multiple drug resistant bacteria, as they might not be able to encounter multiple attacks at one time. But, before future application, more research is needed to gain a further understanding of how this new system will function on exposure.

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Conflict of Interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Keypoints

- Replacement of classic surfactants with metallic nanoparticles as emulsions stabilizers.
- These drug delivery systems can be used as carriers for antibiotics.
- Possibility of being effective against multi-drug resistant microorganisms.

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