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NANOTECHNOLOGY IN DRUG DELIVERY SYSTEM

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Abstract
A definition of nanotechnology is the science of designing, creating, characterizing, and using materials and technologies whose smallest functional organization in at least one dimension is on the nanoscale scale. Because of its high selectivity towards the target region, nanotechnology application is highly significant in the field of drug delivery. Drugs can also be shielded against deterioration by delivery methods based on nanotechnology. These characteristics have the potential to lower treatment costs, improve treatment outcomes, and minimize the number of doses needed. With the help of nanotechnology, we can also stop diseases before they even harm our bodies, such as with DNA vaccines. The creation of biodegradable polymeric nanoparticles has been a brilliant idea in the field of nanoparticles since they can transport medications. Over the past ten years, the research and supply of drugs has grown to be one of the manufacturing industries with the highest capital investments, demands, and growth. The issue of conventional drugs is reviewed, along with the importance of nanoparticles in medication delivery and their potential for toxicity. Differently synthesised nanoparticles have demonstrated improved therapeutic efficacy, stabilized drug delivery, and demonstrated the ability to selectively target cells and release drug within them under regulated conditions.
Keywords: Nanotechnology, health care, side effects, revolutionizing concentration.

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Introduction

Additionally, nanotechnology is giving us the means to stop diseases before they even affect our bodies, such as DNA vaccines. In terms of nanoparticles, the creation of biodegradable polymeric nanoparticles has been a brilliant idea as they can transport proteins, medicines, and DNA to a target region and release pharmaceuticals in a controlled way regardless of the mode of administration. The science of nanotechnology, which has emerged recently, allows for the creation of engineering useful materials, systems, and devices at the nanoscale. Nanomaterials are unique materials with a wide range of applications, from basic material research to personal care. These applications include mechanical, optical, magnetic, electrical, and biological features. The production and conversion of energy storage, increased agricultural productivity, water treatment and remediation, disease diagnosis and screening, drug delivery systems, food processing and storage, air pollution and remediation, construction, health monitoring using nanotubes and NPs, production of materials for space science, chemical industry, information technology, textile industry, manufacturer of electronic consumers, vector and pest detection and control, and automobile industry are some of the more recent applications of nanotechnology. New materials of atomic, supermolecular, and nanoscale sizes are created by nanotechnology. This molecular size, or one billionth of a meter, is often less than 100 nm. Although it is a relatively new discipline that is essential to the science and technology fields, nanotechnology is not yet at a mature state. There is a lot of promise for nanobiotechnology in the biological sciences. The prospective uses of nanobiotechnology in a range of nanotechnology fields, such as nanomedicine and nanobiopharmaceuticals, are emphasized in this paper. Recently, there has been a growing interest in nanotechnology as a solution to medicine delivery issues. For the purpose of drug delivery, nanosystems with various biological characteristics and compositions have been thoroughly studied. Nanoparticles made using a variety of methods have improved therapeutic efficacy, stabilized medications, and demonstrated the capacity to target cells and release pharmaceuticals in a regulated manner within them. In recent decades, polymeric nanoparticles have seen considerable development and usage in both medication delivery and diagnostics [1].

Drug delivery system

The idea of a drug delivery system was presented in order to address these concerns and problems associated with the formulation of drugs. A drug delivery system is the formulation process and mechanism used to deliver a pharmaceutical chemical to the body as needed to safely produce the intended therapeutic effect. It is a technique for giving a patient medicine in a way that makes some areas of the body more concentrated with the drug than others [2].

Nanotechnology in drug delivery system

Nanotechnology is the science and technology of developing materials specially engineered materials at nanoscale. It is manipulation of materials at nanoscale. The word "nano" is a Greekwhich means dwarf. One nanometer is equal to one billionth [10-9] of a meter. One nano meteris also equal to the combined diameter of three atoms. The Most considerable nanotechnology to be technology at sub-micron scale: 100's of nanometers. Nanotechnology as defined by size is naturally very broad, including fields of science as diverse as surface science, organic chemistry, molecular biology, semiconductor physics, micro fabrication, etc. Nanotechnology has been exploited by researchers in the development of novel nanocarriers/nano drug deliverysystems for the successful delivery drug molecules to the site of action [3]. This system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body therefore, avoiding any damage to the healthy tissue via the drug.

Drug development and delivery

In convention or traditional drug development and delivery system process includes oral ingestion or intravascular injection. The systemic blood circulation is responsible for distribution of drug inside the body. Thus, only a small portion of active drug ingredients reaches the organ. Sometimes drug also affects non-target organs which results in adverse effect. Also, the development of new drug molecule is high expensive and time-consuming process [4]. The current problems and challenges with a drug development and delivery which pharmaceutical companies are facing.

Low Solubility

Low aqueous solubility is the major problems encountered while the development of a specific formulation of the drug. Poor solubility affects the bioavailability of the drug [5]. Hence, it is the major challenge for new chemical entity discovered by the scientists and industries.

Low Bioavailability

Bioavailability is the fraction of drug dose available for systemic circulation.It is one of the major pharmacokinetic properties of the drug [6]. A drug has 100%bioavailability when administered intravenously, while its bioavailability decreases when it is administered through other routes (such as orally) due to incomplete absorption. Hence, bioavailability must be considered while administrating the drug other than intravenous.

Low Efficacy

Efficacy is the maximum response achieved from an applied dose of the drug. To be high efficient drug, the drug must have high-affinity results in tight binding with the target. This is known as affinity of the drug molecule [7]. The maximum response will be reduced if the affinity of the drug for target molecule is low. Low efficacy is the one of the major problem associated with drug molecules that leads to time taking in treatment of severe diseases.

Fast Excretion

Excretion or elimination is the removal of drug from the body by excretoryorgans like kidneys. Fast excretion of drug molecules makes the drug very effective as desired amount of drug molecule is not reached to the target organs.

First generation

This era basic mechanism of controlled drug release was established and most drug delivery formulations were oral and transdermal administration. The effectiveness and stability was low in these drug systems More than 150 years ago, Michael Faraday prepared gold particles in nanometer scale These colloidal gold particles were conjugated with antibodies for target specific staining known as immune-gold staining.This application of gold particle considered as a precursor of recent application of gold particles in nanotechnology. In 1960s, Liposomes and polymer micelles were first prepared, however it was never referred as nano-particles until 2000. In 1970s, NPs and dendrimers were first prepared without the knowledge of nanotechnological application.In 1980s, the period reported to be the successful development of micellesas drug delivery system. And in 1990s, Block co-polymers of polyethylene glycol (PEG), PEG-Polylysine have been invented by Kataoka Prior to nanotechnology revolution, in past liposomes, polymeric micelles, nanoparticles, dendrimers, and nano- crystals used for drug delivery, but in the era nanotechnology, the terms were unknown.

Second Generation

The modern nanotechnology uses as drug delivery began when United States launched the national nanotechnology initiatives, the world first program in the field of nanotechnology [7,8]. There were various new methods introduced for drug delivery among them nanotechnology method became more efficiency and cut down drawbacks in ordinary DDS Current immature nanotechnology use microchips, carbon nanomaterials, micro needles based transdermal therapeutic systems, layer by layer assembled system and various microparicles produced by inject technology as well as previous nanocarriers were developed using co-polymers such as polyethylene glycol(PEG) and ligands..

a. Nanoparticles

There are mainly 2 types of nanoparticles as, Organic nanoparticles {Polymers in DDS (polymeric miscalls, polymeric NPs, polymeric drug conjugates dendrimers, nano crystals and lipidbased NPs like liposomes, solid lipids} and Inorganic nanoparticles {Metal NPs (gold, silver, iron, platinum, quantum dots, Silica NPs mesoporous, Xerogels

b. Liposomes

The shape, surface charge, size and functional groups in liposomes can easily change according to the drug and target site. Liposomes have high efficiency and low toxicity, so it can use to deliver DNA, RNA, proteins, antisense oligonucleotides both hydrophobic and hydrophilic chemotherapeutic agents. Liposomes can be prepared by methods such as mechanical agitation, solvent evaporation, solvent injection,surface solubilization method [8].

Drugs are incorporated in to the liposomes by encapsulation method and it provides various size ranges, various physiochemical properties and prevents subsequent leakage from liposomes. pH liposome composition, osmotic gradient, surrounding environment, magnetic field and radio frequency regulates the drug release to the target site Adsorption, fusion, lipid transfer and endocytosis are the various methods which can be use to interaction of liposomes with cells. Liposomes are encapsulated with various drugs such as anticancer drugs, neurotransmitters, antibiotics and anti-inflammatory drugs. For instance doxorubicin is highly toxic compound, when treated to the cancer patients it have the ability to affecting tumor cellsas well as heart and kidney, finally using liposomes it delivered directly to the tumor cells instead of accumulate in the heart and kidney.

The drawbacks include with liposomes as low encapsulation efficiency, quickly releasing of drugs, poor storage ability, lack of tunable triggers for drug release and it release drug in to the extracellular fluids. To overcome these problems scientists modified surface of liposomes usingPEG and it is act as protection layer on the surface of liposomes and it can slowdown liposome recognition by macrophages. The liposomes attached to specific proteins, antigens, antibodies, ligands or other biological substances which helps to target cell recognition for target specificdrug delivery [9].

Interaction of nanoparticles with cells

Cells Inhalation, ingestion or dermal invasions are the route through which nanoparticles can enter into the human body. After entering into the living body, it interacts with a number of biomolecules such as sugars, proteins and lipids. They are dissolved in the body fluids like interstitial fluid between cells, lymph or blood. There is immediate coating of nanoparticles takes place and thus the newly formed structure is called "protein corona" that determines the biological fate of nanoparticles. Its composition is dynamic and depends on therelative concentrations of the individual components and on their affinities toward the nanoparticle surface. In fact, nanoparticles have to be viewed as evolving systems that adapt to varying concentrations of the biomolecules present in the fluid It has been suggested that the final corona reflects its own prior history. The size of nanoparticles has a strong effect on their interactions with living cells, influencing uptake efficiency, internalization pathway selection, intracellular localization and cytotoxicity. Still, we believe that there are a few general trends that can be trusted; (a) For an efficient endocytosis there must be an optimal size of nanoparticles which is independent of particle composition, (b) Such a small size can alter with surface properties and type of the cell (c) There is a higher probability of internalization by passive uptake than bigger once Receptor mediated endocytosis is initiated by membrane wrapping process as nanoparticles interacts with cell membrane. It requires the concerted formation of multiple NP receptor interactions. There is a less receptors are available for small nanoparticles as compared to larger ones [10]. Several small nanoparticles needed to be interacting with receptors simultaneously to trigger membrane wrapping. While an individual, large nanoparticle can act as a crosslinking agent to cluster receptors and induce uptake. But as per mathematical modelling analysis receptor mediated endocytosis is optimal due to no unavailability of ligand on nanoparticles and no shortage of ligand on the surface of the c. As the size matters, a 50-60 nm nanoparticle is highly efficient in capable for activating enough receptors to initiate successful internalization in respect of thermodynamics. Cellular responses can be modified by protein corona which is controlled by the ligand present on the surface on the nanoparticles(11). Two factors, size and coating have own influence on the distribution of internalized nanoparticles. The positively charged 5.2nm CdTe QDs (Quantum Dots) nanoparticles were distributed throughout the cytoplasm of N9 cells but did not enter the nucleus, whereas positively charged 2.2nm QDs were localized predominantly in the nuclear compartment in contrast, intracellular distribution was not influenced by the size of QDs whichwas functionalized by with thiols, amines or mercaptopropionic acid. The ultimate intracellular destination of Au nanoparticles coated with cell penetrating peptide was controlled by its diameter(8). Smallest one with a size of 2.4 nm Au nanoparticles was capable to localize nucleus while nanoparticles with a size of 5.5 nm and 8.2 nm remain sequestered in Endo lysosomal zone. Accordingly, understanding the underlying mechanism of cellular uptake is an important step toward understanding the biological fate of nanoparticles, both the favorable and adverse aspects. Physio-chemical features of nanoparticles/cell interactions are influential factors in determining the particle-cell interactions and consequently influence the behaviour of the cell. It has been reported that preferential cellular uptake of positively charged nanoparticles over negatively charged nanoparticles due to electrostatic interactions seems simplistic and reductive and considers only surface potential despite of involvement of many other parametersin the equation.

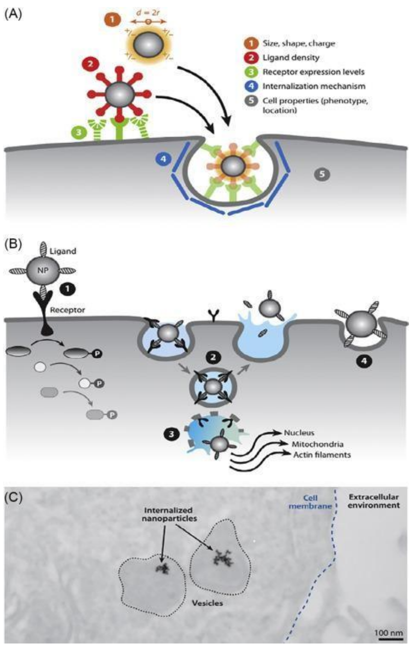

Fig1: interaction of nanoparticles -cells

In the extracellular fluid, NPs are coated by proteins and other biomolecules. The so-called protein corona determines how the NP interacts with a cell. Cellular internalizations may Involve active receptor-mediated or passive transport across the cell membrane. NPs have to surmount the cell membrane to intrude on cells.

Interaction of nanoparticles with living cells and the key role of the protein corona

When nanoparticles enter into the biological system it comes under the influence of a number of biomolecules, rapidly absorbs at its surface and covers it entirely. This so called "protein corona" that manipulates the properties of nanoparticles and thus a new 'biological identity' is introduced. Such a new biological identity creates an additional complexity in respect of complex formation. The protein corona formation is a dynamic process consists of competitive molecular binding at the surface of the nanoparticle. Protein which is highly abundant absorbed on the surface and their replacement is followed by high affinity proteins. Because of high complexity as well as its dynamic nature, the existence of protein corona is always doubtful. Also, it has been recognized that it induces the change I hydrodynamic diameter and zeta potential of nanoparticle. Even if it is true that the initial charge of the nanoparticle actually influences the nature of the proteins that adsorb and consequently has an indirect impact on nanoparticle/cell interactions.

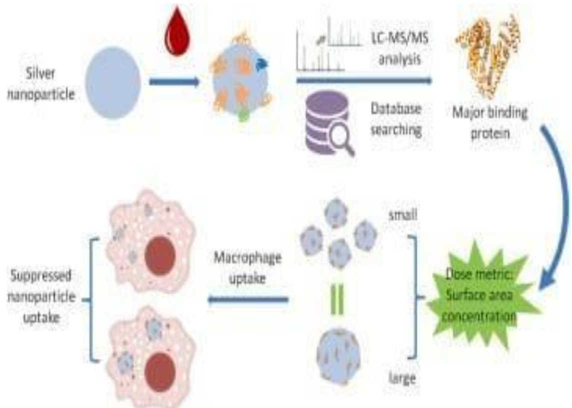

Fig2: Nanoparticles of protein corona

Mechanism of toxicity caused by nanoparticles

Physicochemical reactivity of nanoparticles leads to the formation of free radicals or ROS including superoxide radical anions and hydroxyl radicals direct or indirect through activation of oxidative enzymatic pathways result in oxidative stress. In general, there are several sources for oxidative stress:

a) Oxidant-generating properties of particles themselves as well as their ability to stimulate generation of ROS as a part of cellular response to nanoparticles,
b) Transition metal-based nanoparticles or transition metal contaminants used as catalysts during the production of non-metal nanoparticles,
c) Relatively stable free radical intermediates present on reactive surfaces of particles,
d) Redox active groups resulting from functionalization of nanoparticles,
e) Small NPs have a higher probability to be internalized by passive uptake than large ones,
f) Under otherwise identical conditions, small NPs are more Likely to cause toxic cellularresponses

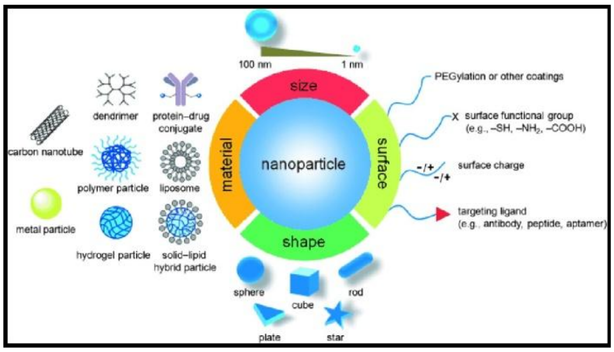

Fig3. Mechanism of toxicity caused by nanoparticles

Generation of ROS induced by nanomaterials, directly or indirectly, plays a vital role in genotoxicity. Oxidative DNA damage is associated with biological mechanisms involving mutagenesis, carcinogenesis, and aging-related diseases in humans. internalizations processes such as endocytocis and phagocytocis and depend on the shapes of nanoparticles. Spherical nanoparticles show faster endocytosis than tubular nanoparticles . Non-spherical nanoparticles show more toxicity as they are vastly more exposed to blood flow Formulation materials and methods for nanotechnology based drug delivery system:

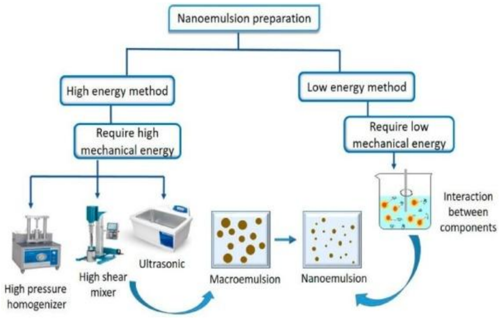

Fig4.formulation materials and methods for nanotechnology

Targeted delivery of nano drug can be obtained via intercellular transport, intracellular transport, controlling particle size, enhanced permeability and retention, coating with hydrophilic component (unhygenic) and conjugating with other materials such as peptide.

1) **Nano-precipitation*:*** It is easy and quick method performed by adding an organic solution which containing polymer and lipophilic drug in to the aqueous solution in drop-wise manner Under constant stirring. Co-polymer particles are highly flexible while it has both hydrophilic and hydrophobic surfaces. Inside water hydrophobic parts goes inside and hydrophilic parts come outside and forms globular structure while hydrophilic drug attach to polymer outer surface and hydrophobic drugs penetrated in to core hydrophobic area. Antibodies to targeting. The Size of NP can control by rate of polymer addition and by stirring speed.

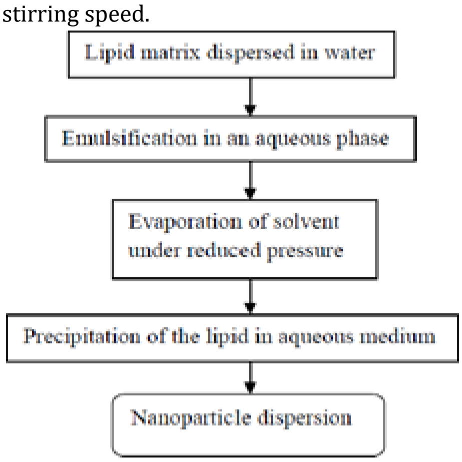

Fig 5.Nano-precipitation

2) **Emulsification based methods*:*** The organic phase contain drug and polymer are agitated/ sonicated in aqueous phase to form emulsified droplets. Emulsification-solvent evaporatio*n:* Polymer dissolved in volatile solvent like chloroform and emulsified in aqueous phase. Formation NP achieve by evaporation of solvent under reduced pressure. Adjusting solvent evaporation conditions such as temperature and pressure would improve quality but slower the process Emulsification solvent diffusion*:* Polymer dissolved in pre-saturated partially water dissolving solvents like benzyl alcohol. It produces oil-water emulsion droplets. The dispersed droplets diluted by large amount of water containing stabilizers. Diffusion of organic solvents out from droplets lead to condensation and nanoparticles.

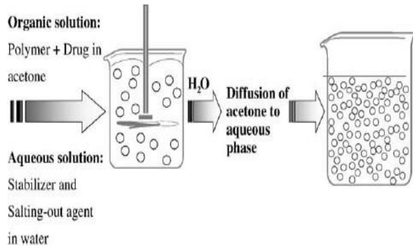

Fig 6.Emulsification based methods

3) **Emulsification salting out*:*** Organic solvent use is totally dissolved in water. (Ex; acetone) Polymer containing organic solvent is emulsified in aqueous phase with high salt concentration. The saturated aqueous solution prevents acetone from mixing water Diffusion of emulsion droplets in large amount of water result in an abrupt drop of salt conc.
4) **Layer by layer synthesis*:*** It makes electrostatic interaction between oppositely charged polyelectrolytes such as Polylysine, chitosan, gelatine-B complex with sodium alginate, dextran sulphate, hyaluronic acid, and heparin or contrition sulphate. Solid form of bioactive agentsis often use as core to grow the vesicular structure a polymer layer is first absorbed on to the colloidal template by incubation in polymer solution, washed and transferred to opposite charged polymer solution. Repeat the cycle to multiple coating that can control the release kinetics. This method is used to manipulate bioactive agents such as vitamins, peptides, insulinand nucleic acid.
5) **Genetic engineering method (GEM*):*** It can control structural, functional properties of recombinant protein-based drug carriers such as elastomer like proteins and silk like proteins. GEM can control molecular weight, hydrophobicity, drug conjugate site and secondary structure as well as provide higher transfection efficiency.

Fig 7: Genetic Engineering

Appilications of nano technology in drug delivery and design a sight: The importance of nanotechnology in therapeutics and the role played by it in combating some of the chronic diseases, such as cancer. Areas in drug delivery where nanotechnology can make a difference include. Drug loading and release the size and surface properties of nanoparticles have been explored to optimize bioavailability decrease clearance and increase stability by controlling these characteristics it is possible to get the drug to tissuesin the body that may have been inaccessible before. The technology enables the delivery of drugs that are poorly water soluble and can provide means of by passing the liver, thereby preventing the first pass metabolism. Nanotechnology is used to conduct sensitive medical procedures nanotechnology is showing successful and beneficial uses in the fielids of diagnostics ,diseases treatment, regenerative medicine gene therapy, dentistry, oncology, anaesthetics industry, drug delivery, and therapeutics.

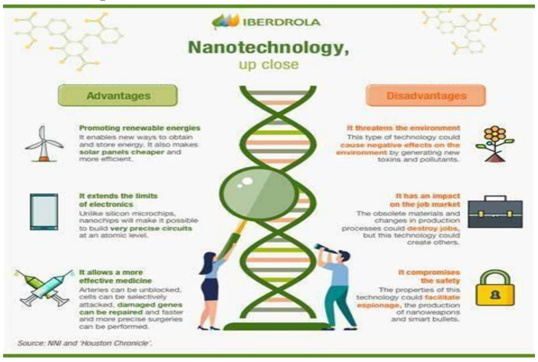

Fig 8 Genetic Engineering

Conclusion

Biochemistry and medicine meet at one of their most significant interfaces: drug discovery and delivery. We have covered the benefits and issues with the present medication delivery systems in this review, as well as the potential for nanotechnology to solve all of these issues. Nanomaterials are always favored as the best drug delivery vehicle because of their biodegradable, biocompatible, targeted, and sustained release drug profiles. However, because they are not entirely safe, these nanomaterials can be harmful to healthy cells. Therefore, in biomedical applications, particularly in innovative drug delivery systems, gene delivery, and therapeutic applications, assessment of nanoparticle toxicity is required. Using nanotechnology, several things that are extraordinarily potent by today's standards can be created. Both opportunity and risk are created by this possibility. The potential advantages of nanotechnology are undeniable, and as it has already started to permeate many other research sectors, it would be impossible to stop the advancement of related research. Nonetheless, rules can be used in the development of nanotechnology to guarantee that the technology circulates medications.

- Cutting down on or eliminating toxicity.
- Raising the level of precision.
- Improving vaccine adjuvants and administration;
- Targeting medications to specific cells or tissues.

creating innovative nanostructures for usage in particular fields, such as neurology, orthopedics, cancer treatment, and ophthalmology. Successful introduction of nanoscale items has the potential to occur in the fields of gene delivery, repair, and replacement of faulty genes.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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