IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On : Nanotechnology And Green Chemistry: Green Nanomedicine

Mr. Pavan M. Raut[1] , Mr. Abhijit K. Banait[2] , Prof. Ruchika V. Gawande[3], Mr. Harshal K. Marshetwar[4], Miss. Komal P. Chirange[5]

Jagadambha Institute Of Pharmacy & Research, Kalamb, Maharastra 445401, India.

Abstract:

This paper explores the effects of ecologically safe and green chemistry on the field of medication delivery powered by nanotechnology, a relatively new topic known as "green nanomedicine." Research have revealed that while there are many examples of green nanotechnology-driven medicine delivery systems, nanometal particles are the ones attracting the most interest.

In this Review Composition, we bandy seminal approaches that led to the development of successful the rapeutic products involving small molecules and macro motes, identify three medicine delivery paradigms that form the base of contemporary medicine delivery and bandy how they've backed the original clinical successes of each class of remedial. We also outline how the paradigms will contribute to the delivery of live- cell the rapies.

KEYWORDS: *Nano Drug delivery, Nanoparticle, Green chemistry, Green technology,*

Introductions :

Perfecting mortal health is presently witnessing an explosion of attention led by the use of nano particles (nanoparticle) to deliver medicines to cells. similar nanoparticle are finagled so that they're attracted specifically to diseased cells, which allows for the direct treatment of those cells, perfecting efficacy, dwindling side goods, and overall perfecting human health. This technique reduces the side effects of drug sin the body. However, despite the pledge of nano drug across all diseases, there area number of disadvantages for using these nano drug delivery vehicles, which should not be ignored. medicines delivered from nano scale realities may bear else from when delivered in normal or conventional form. As an example, the capture of intravenously fitted poly(- lactide-co-glycolide)(PLGA) nanoparticle for medicine delivery in rats was shown to be vastly dropped by liver Kupffer cells as compared tothe free medicine.[1]

Coating glamorous nanoparticle with natural polymers(similar as carbohydrate sand proteins) is also common. In addition, numerous natural polymers are biocompatible and are thus suitable for sheeting nanoparticle for biomedical operations similar as cancer treatment.[2,3] Despite the wide spread development of nano technology and nano materials through out the last 10 – 20 times, only lately has their implicit toxicological effect on humans, creatures,and the environment received some attention.Moreover, although the original intended use of nano medicine was to ameliorate mortal health, nanoparticle can be deliberately misused for other intentions as numerous experimenters have beenreporting due to smirching or maximizing the toxicity of the nanoparticle.[4,5]

Using green technology is one of the newest and most creative ways to produce better nanopharmaceuticals that can address the issues mentioned previously. All areas of chemistry are included in "green chemistry," but the creation of chemical compounds and chemical engineering techniques for use in natural resource-based industrial applications are given special attention. On the other hand, in order to create a safer atmosphere, laboratory research must adhere to the fundamental principles of green chemistry. Green chemistry, also known as sustainable chemistry, aims to reduce the use and production of hazardous compounds in reactions and synthesis. Green chemistry also encompasses processes for creating renewable materials.

The main goals of green chemistry are as follows:

- The utilisation of renewable materials and energy sources.
- The use of safe solvents or reactants,
- The avoidance of waste formation are the primary objectives of green chemistry.

Too frequently, as well, nanoparticle or nanomaterial(similar as carbon nano tubes(CNTs)) conflation ways involve toxic accoutrements . In order to drop the cost of nanodrug delivery vehicles, makethemmore effective in the body, promote a healthy environment, and reduce unintended use, new approaches and design principles are easily demanded for this field.

Production Of nanoparticle By Green Chemical Reactions Nono Metal Compounds :

In recent times, green chemistry has been introduced for the conflation of essence nanodrugs in numerous fields. Traditional processes for the conflation of essence nanoparticle occasionally produce large amounts of poisonous as well as gratuitous and dangerous substances.[1] still, similar metallic nanoparticle have shown great pledge in drug. For illustration, maghemite nanoparticle(γ- Fe2O3nanoparticle) and magnetite nanoparticle(Fe3O4- nanoparticle) have been extremely helpful in medicine delivery, treatment, and imaging of integrins on excrescence cells as well as remedial issues. [2,3,4]

The use of iron oxide glamorous nanoparticle for inductive hyperthermia, chemotherapy, gene carriers for gene remedy, glamorous seeing examinations for in vitro diagnostics, vaccines, antibody agents, and remedial agents for hyperthermia- grounded cancer treatments has formerly been studied. still, through similar studies, particularly in vivo, the field has learned of some of the dangerous consequences of using glamorous nanoparticle. For illustration, the effective treatment of brain diseases needs careful consideration due to medicines and nanoparticle crossing the blood – brain hedge(BBB). The medicinal parcels of iron oxide nanoparticle anions and the adequacy of lysophosphatidic acid(LPA) to temporarily disrupt tight junctions and allow iron oxide nanoparticle anions to enter brain cells have created excitement for the treatment of neural conditions as well as caution for the unintended iron accumulation in the brain. Under normal conditions, iron oxide nanoparticle anions have a tube half- life of 6 twinkles, with the liver and spleen being the major organs of deposit. Treatment with LPA modified with iron oxide nanoparticle anions in the brain and spleen in mice revealed no signs of supplemental vulnerable cell infiltration in the brain and no significant activation of microglia or astrocytes. The study showed bettered delivery effectiveness of iron oxide nanoparticle anions following LPA administration. similar findings suggest a temporary dislocation of the BBB, which may be safe and effective for adding iron oxide nanoparticle anion delivery to the brain.[5]

lately, magnesium(Mg) nanoparticle have been shown to have extraordinary merit in terms of modifying remedy exclusivity and thermal ablation goods on excrescences. likewise, the low toxin and side goods of Mg-grounded chemistries that remain in the body after surgery are noteworthy.[6] Some of the main advantages of glamorous nanocompounds for hyperthermia- grounded remedy and controlled medicine delivery are given in **Figure 1.**

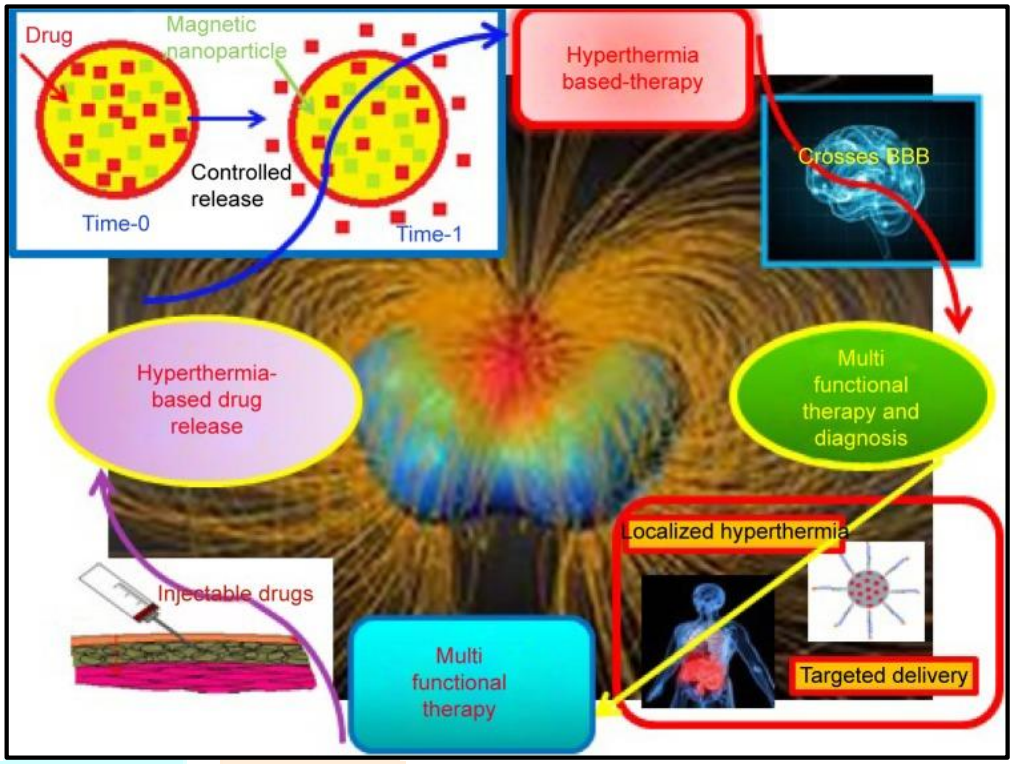

Figure 1. A schematic representation of some of the unique advantages of magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery.[7]

Biocompatible and monodispersed iron oxide superparamagnetic nanoparticle were modified using folic acid(FA), which was chosen as the targeting agent combined with poly(ethylene glycol)(cut) by Zhang . The natural study showed that modifying nanoparticle with cut – FA significantly bettered the intracellular uptake of nanoparticle by target cells.[8] medicine- delivery vehicles grounded on two ring- type soft attractions, and a simple plastic hinge is another illustration for active locomotive intestinal capsules. The present medicine delivery vehicle has good medicine- lading capability and can conquer inimical distribution throughout the body, which is common for other medicine delivery vehicles of much larger size.[9]

In vivo results verified that the medicine- loaded HMSNs averted excrescence growth vastly with minimum poisonous side goods. This system introduced new perceptivity into the extension of the new product of green chemistry- deduced medicine delivery carriers by the excrescence medium.[10] Other favorable green polymers have been prepared grounded on polyacrylate/ nanosilica. still, polyacrylate coatings have promoted pleural effusion, pericardial effusion, and pulmonary fibrosis and granuloma, which are allowed to be due to the high disposal of the nanoparticle in the lading process.[11]

Nanoparticle have decreasingly been used for multitudinous artificial purposes. still, enterprises about their poisonous and dangerous goods on humans and the terrain have been raised. Some exploration has determined the presence of nanoparticle in patient necropsies and has reported the implicit pernicious goods to mortal lungs. Using electron microscopy and energy- dispersiveX-ray analysis, as an illustration, silica nanoparticle were linked in macrophages, pulmonary microvessels, vascular endothelial cells, microlymphatic vessels, and pleural effusions and a many in alveolar epithelial cells and pulmonary interstitial apkins(with no microscale patches present) and have been shown to damage alveolar epithelial cells, macrophages, vascular endothelial cells, and the blood – gas walls. Grounded on the well- proved toxin of the silica nanocompound, it's possible that these silica nanoparticle may be related to some of the illness reported by experimenters.[12]

Some nanopolymer matrices prepared by the chemical reduction of essence ions in an waterless medium have been used as medicine carriers. These new hydrophilic healthy nanocomposites containing tableware nanoparticle(Agnanoparticle) have been composed of a functional polymer matrix of poly(1- vinyl--co-N-vinylpyrrolidone)(poly(VT- co- VP)) prepared by free radicalinitiated polymerization. Due to their sufficient stabilization by functional groups, Agnanoparticle don't precipitate and/ or change in size indeed after storehouse in waterless medium. The toxin of the original poly(VT-co-VP) copolymer and nanocomposite containing Agnanoparticle was linked on white mice, its value being> 5,000 mg/ kg. The nanocomposite had a

pronounced antimicrobial exertion toward different strains of Gram-negative and positive bacteria. The minimal inhibitory attention(MIC) dropped the growth of the microorganisms at attention ranging from0.5 to 8 µg/ mL, and the minimal bactericidal attention(MBC) ranged from0.5 to 16 µg/ mL. So, these new tableware(Ag) nanocomposites in a poly(VTco- VP) matrix are promising carriers for hydrophilic antiseptics and antimicrobial medicines for medical operations to treat numerous contagious conditions, including surgically acquired bones.[13]

A molybdenum disulfide(MoS2) nanosheet was developed as a photothermal agent for excrescence ther revision of cut has been fulfilled during a facile approach to prepare soybean p reprised MoS2(SP- MoS2) nanosheets with excellent colloidal stability. By not observing clear in vivo hemolysis, coagulation, and cyto/ histo- toxin, the SP- MoS2 nanosheets illustrate good p conversion performance and photothermal stability during bone excrescence photothermal remedy. The pMoS2 nanosheets showed low cost, simple fabrication, and good in vivo hemo/ histo- comity, promising capacity for the treatment of cancer.[14]

Figure 2 shows a schematic illustration of the syn MoS2. occasionally, bovine serum albumin(BSA) has been used to modify NaGdY4- grounded upconversion nanoparticle(UCnanoparticle).

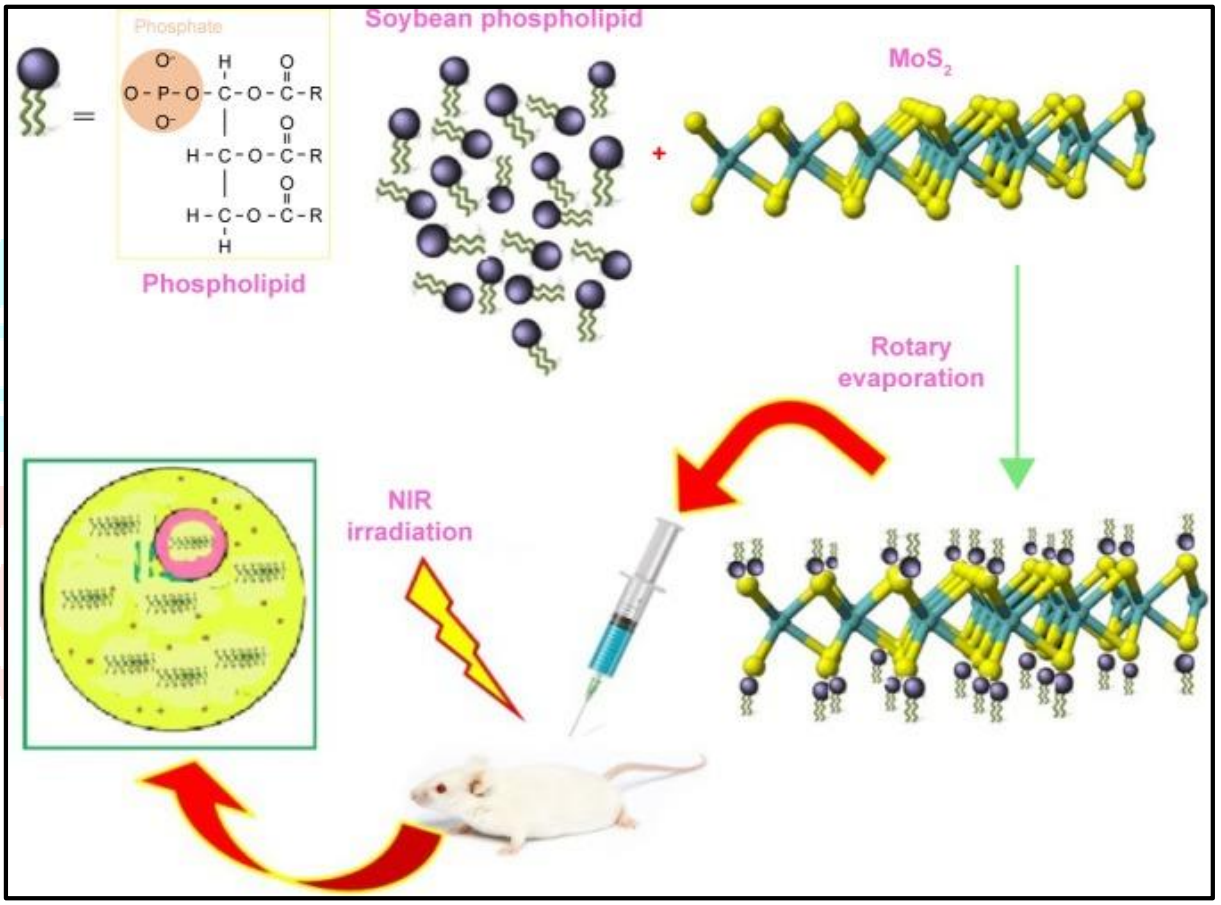

Figure 2 : Schematic illustration of the synthesis of soybean phospholipid-encapsulated MoS2.[7]

Polymer Nanocomposite (Pnc) :

A PNC containing a polymer or copolymer with nanoparticle dispersed in the polymer matrix is one way to drop toxin and increase safety. These nanocomposites of course can have different shapes(eg, platelets, filaments, and squares) but should have at least one dimension in the range of nanometers. Polymeric nanoparticle have been prepared for decades for use in a variety of high- performance accoutrements similar as nanodrug delivery or functionalized with medicines, showing their safety if the proper chemistry is used. To introduce a novel and healthy medicine seeker for treating endometriosis, a new polymeric nanogene delivery vehicle conforming of polyethylenimine grafted chitosan oligosaccharide(CSO- PEI) with hyaluronic acid(HA) and small snooping RNA(siRNA) was prepared.

There was no clear difference in size observed between(CSO- PEI/ siRNA) HA and CSO PEI/ siRNA, but the luminescence accumulation in the endometriotic lesion was more important for(CSO- PEI/ siRNA) HA than for CSO- PEI/ siRNA due to the specific list of HA to CD44. In addition, the(CSO PEI/ siRNA) HA

nanoparticle gene remedy significantly reduced the endometriotic lesion size with atrophy and degeneration of the ectopic endometrium. After receiving CSO-PEI/siRNA HA therapy, the epithelial cells of the ectopic endometrium in rat models of endometriosis had a considerably decreased expression of CD44 compared to controls. likewise, compliances under an electron microscope showed no egregious poisonous goods on reproductive organs and verified that the(CSO- PEI/ siRNA) HA gene delivery system can be used as a safe and effective way for the treatment of endometriosis.[15]

Fresh exploration related to molybdenum nanoparticle includes phosphate spectacles incorporating vanadium and molybdenum oxides as 14 useful composites for the control of medicine dissolution and medicine release. The modified vancomycin motes demonstrate lesser hydrogen cling with vanadium- unravel spectacles and accordingly slower medicine release over 14 days showing an bettered face revision with medicine motes. This can be described by the strong consonance of medicine factors to the glass face compared to the free molybdenum. The strong attachment is due to hydrogen cling between the amino functional groups of vancomycin and the doused P – O – H groups in the glass network.[16]

Colorful types of medicine- delivering vehicles between noncross- linked micelle NCM) and folic acid-corecross-linked micelles are shown in **Figure 3**. Another synthesized nanodrug delivery vehicle grounded on green chemistry is pH-sensitive DOX reprised in the hydrophobic cores of the amphiphilic triblock copolymers. The copolymer micelles entered into lysosomes using a lysosome shamussystem. These safe and effective micelles can be used as a hopeful treatment for enhanced intracellular medicine delivery and real-time imaging.[17]

In total, it was set up that nano- TCP is a good seeker for curing hepatocarcinoma fully and presenting a new choice for cases to admit healthy, presto, and effective treatment.37 Another illustration of a green medical emulsion is nanoparticle phrasings with chitosan. Chitosan – graphene oxide(GO) green nanocomposite flicks were prepared by mixing waterless chitosan results and GO in dilute acetic acid as a detergent. The nanocomposite included quaternized chitosan QC)/ BSA/ rectories(REC- DOX was used to probe the ruse effectiveness and release pattern in nanoparticle). Results showed that using REC could increase medicine encapsulation capability and lading implicit.[18]

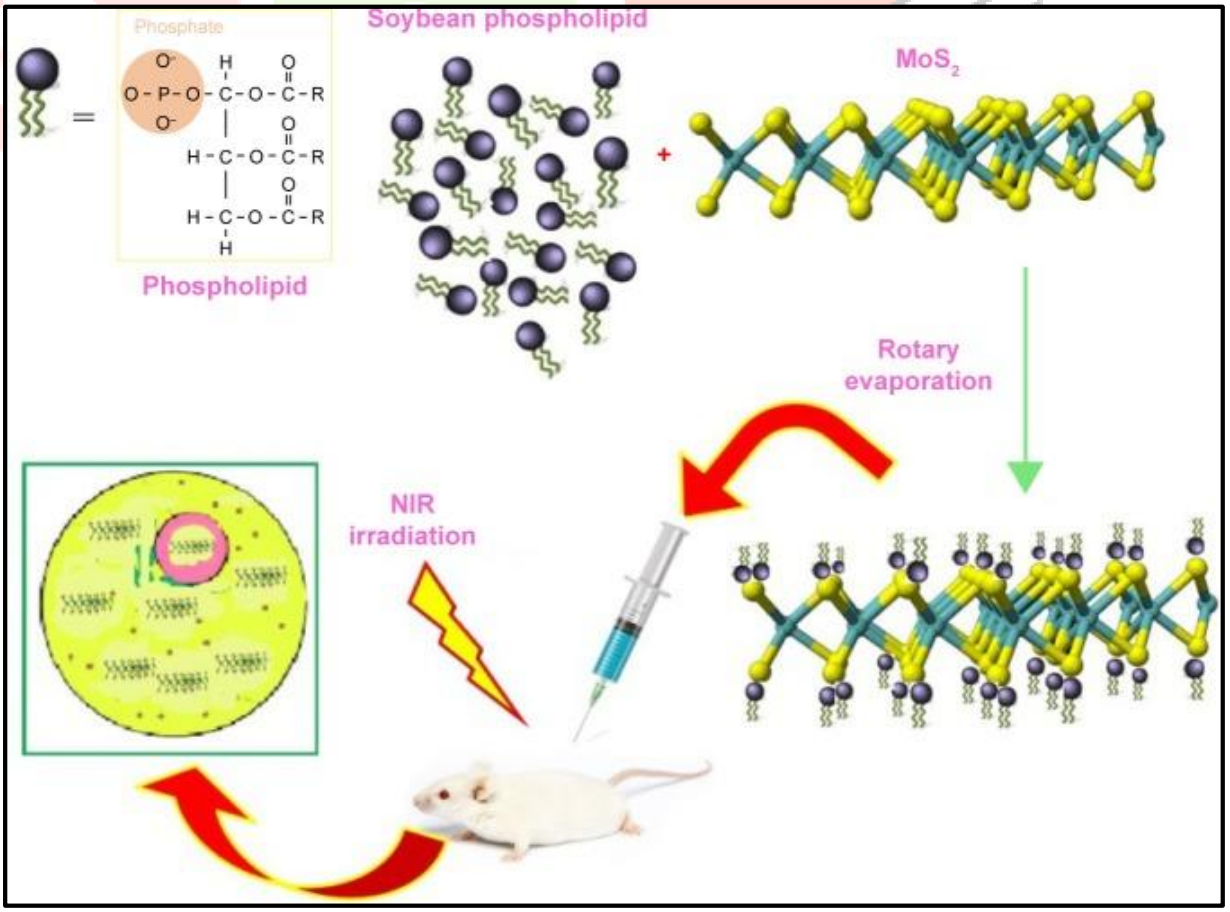

Figure 3 : Schematic image of different drug-delivering vehicles and releasing techniques between NCM and FA-CCM.[7]

The activation of the nervous micromedia by Nano- Cab nanoparticle significantly averted pancreatic excrescence progression, whereas the blockage of the neural niche by Nano- Ato nanoparticle generally destroys neurogenesis in excrescences and the development of pancreatic cancer. The Ft- grounded nanoparticle, therefore, include a successful and healthy way of carrying neural medicines for new anticancer curatives.39 Alginate also represents a green nanomedicine approach to drop nanoparticle toxin. For illustration, quinapyramine sulfate(QS)- supported sodium alginate nanoparticle have been prepared to drop unwelcome poisonous goods of QS against the sponger Trypanosoma evansi, a causative factor of trypanosomosis. To identify the toxin of the new nanoparticle, the biocompatibility of QS- nanoparticle was tested using Vero, HeLa cell lines, and steed erythrocytes in a cure dependent manner and displayed no toxin at effective trypanocidal boluses and indeed at boluses several times advanced than the effective cure.[19]

Green Quantum Dots (QDs) :

Grounded on special physical and chemical parcels, graphene and graphene composites have been effectively used for active and unresistant targeted medicine delivery. A water-answerable graphene outgrowth, specifically GO, is presently being largely delved by experimenters each around the world. For illustration, Gurunathan reported an environmentally friendly, cost-effective, and green system for the conflation of water-answerable graphene using bacteria biomass. Green nanomedicine is exemplified by this reduction conflation, which prevented the operation of toxic reactants such hydrazine and hydrazine hydrate composites.[20]

Recently, a graphene-gold (G-Au) nanocomposite was created via a sonochemical method. Through the sonochemical system, contemporaneous exfoliation of graphite and the reduction of gold chloride passed to produce a highlycrystalline G – Au nanocomposite. This G – Au nanocomposite was used to modify glassy carbon electrodes(GCE) to fabricate an electrochemical detector for the picky discovery of nitric oxide(NO), a critical cancer biomarker. G – Au- modified GCE displayed an enhanced electrocatalytic response toward the oxidation of NO as compared to other control electrodes. likewise, this enzyme-free G – Au/ GCE displayed an excellent selectivity toward NO in the presence of interferences. This G – Au nanocomposite introduced a new electrode material in the sensitive and picky discovery of NO, a prominent biomarker of cancer.[21]

Biosynthesis Of Nano Drug Delivery Vehicles :

The current development in the biosynthesis of nanocarriers, specifically the conflation of nanocompounds with specific sizes and shapes, is leading to the progression of new nanoparticle in cancer rectifiers and opinion(eg, medicine and gene delivery, imaging, phototherapy, and radiotherapy improvement treatments). likewise, some significant parcels, similar as high essential safety, high face area, and tunable stability, of nanoparticle are veritably precious in multitudinous medical and medicine delivery operations.[22,23,24]

Using a new detergent for the assay of medicine release from a polysaccharide grounded nanocompound for a colon-specific medicine delivery system is an eco friendly and cost-effective system for the medication of applicable nanomaterials using biomaterials. For this, probiotic culturesof Bacteroides, Bifidobacterium, Lactobacillus species, Eubacterium, and Streptococcus present in the colonic region were produced and placed in the solvent media and compared with those attained from rat cercal- and mortal fecal- grounded turmoil model. The attained results with the probiotic system indicated that a probiotic dissolution system can be used for the medicine release of any polysaccharide- grounded oral expression meant for colonic delivery.[25]

Classes Of Therapeutical Delivery Challenges :

For all medicines, the thing of delivery is to maximize remedial efficacity by transporting and releasing the medicine(passively or laboriously) to the target point in the body and by minimizing out- target accumulation of the medicine. This can be achieved by controlling medicine PKs, reducing medicine toxin, adding the accumulation of the medicine at the target point and perfecting patient acceptance and compliance.

Small molecules

Small- patch medicines(< 900 daltons) similar as chemotherapeutics, antibiotics and steroids have been linked, developed and used as medicinals since the late 1800s7. By virtue of their size, small patch medicines can

fleetly diffuse through natural fluids, across numerous natural walls and through cell membranes[26]. These advantages enable 28 small motes to navigate the complex vasculature and to interact with nearly all apkins and cell types in the body. still, for rapid-fire prolixity and access to the systemic vasculature, small motes must be freely answerable in natural fluids; hence, this limits(or hampers) the remedial mileage of inadequately answerable molecules[27]. About 90 of preclinical medicine campaigners are low- solubility compounds[28], so this remains a challenge. Strategies to overcome low bioavailability concentrated on perfecting medicine solubility by modulating the original medium(in particular, via the use of pH modifiers for small motes with considerable pH-dependent solubility). This enabled clinical successes similar as intravenous ciprofloxacin, which is formulated with lactic acid to ameliorate its solubility via pH modulation[29].

Other strategies concentrated on altering the small motes themselves to modulate their physicochemical parcels for bettered solubilization, prolixity or immersion. For illustration, the angiotensin- converting- enzyme impediments benazepril brand name, Lotensin) and enalapril(Vasotec) are commercially formulated with alkyl ester prodrugs that mask ionizable groups, thereby perfecting the immersion and bioavailability of the drug[30]. Meanwhile, the marketable expression of the critical protease asset for HIV treatment ritonavir(Norvir) is thiazole- modified to ameliorate its metabolic stability and waterless solubility.[31]

Protein Peptides :

By virtue of their large size, peptides and proteins parade size grounded limitations in the penetration of natural barriers. This inspired the development of penetration enhancers(similar as sodium N-(8-(2-hydroxybenzoyl) amino caprylate); SNAC) that modulate the medium to buffer original gastric pH or to laboriously ameliorate transcellular immersion of the peptide or protein. This strategy contributed to the recent clinical blessing of semaglutide(Rybelsus), the first oral glucagon- suchlike peptide(GLP- 1) [32]. fresh sweats towards perfecting the stability of peptides and proteins in physiological fluids, as well as their transport across natural walls, led to the development ofnon-invasive delivery systems for bettered patient compliance and convenience. [33,34]

The focus onnon-invasive delivery and the challenges associated withnon-invasive routes of administration(oral, transdermal, inhalation and mucosal delivery, in particular) has played a crucial part in driving invention in medicine delivery strategies for peptides and larger rectifiers. Notablenon-invasive druthers include the following exemplifications the oral delivery of cyclosporine in a tone- emulsifying expression that bettered its solubility for increased bioavailability(Neoral); the use of saturation enhancers and pH modulators to increase the immersion of an oral GLP- 1 analogue Rybelsus); and the expression of insulin with the small- patch excipient fumaryl diketopiperazine to form microparticles suitable for gobbled delivery(Afrezza) [35,36]

Antibodies

The structure of antibodies(which differs mainly from that of other classes of birth) allows for specific relations between remedial targets and the vulnerable system(antibodies give signals to the vulnerable system by binding to cellulartargets[37]. By binding to a target antigen, antibodies can neutralize it, precluding signalling motes from binding to it and initiating(undesirable) cell processes[38]. also, antibodies can interact directly with host vulnerable cells to initiate phagocytosis, antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, driving the death of undesirable cell populations[39].

still, the unique features of antibodies that enable these specific relations can also lead to the development ofanti-antibodies, which can beget adverse events similar as rashes at the injection point, influenza- suchlike symptoms and the development of autoimmune conditions. [40,4142]This is instanced by muromonab- CD3(Orthoclone OKT3), the first clinically approved(in 1986) murine- deduced mAb, which caused adverse events associated with both its medium of action and its recognition as a foreign antigen by the vulnerable system[43].

Conclusion :

Utilising plant extracts and biomaterials like proteins and lipids, the majority of green process advancements have produced materials with low toxicity and great biocompatibility. One of the main issues with the nanoparticle drug delivery systems used today—toxicity—has been mitigated with the aid of green chemical techniques. Nevertheless, it is evident that much more effort is required to develop safe nanoparticle for medicine, both in the finished product and the manufacturing process, even with the studies highlighted here.

The development of more effective green chemistry techniques for the synthesis of nanodrug delivery vehicles may benefit from the use of low molecular weight compounds, biomacromolecules, and nanosized polymers. Plant extracts and biomaterials such as proteins and lipids are used in green processes to produce products with minimal toxicity and high biocompatibility. One major issue with the present nanoparticle drug delivery systems is their toxicity, which is recognised to be addressed by integrating green chemical technologies. The paragraph concludes that further study is required to assure the creation of safe nanoparticles for medical applications, both in terms of the final product and the manufacturing methods involved in developing effective nanoparticle, not with standing the advances described.

References :

1. Ravichandran S. Green chemistry- a potential tool for chemical synthesis. *Int J Chem Tech Res.* 2010;**2**(4):2188–2191.

2. White MA, Johnson JA, Koberstein JT, Turro NJ. Toward the syntheses of universal ligands for metal oxide surfaces: controlling surface functionality through click chemistry. *J Am Chem Soc.* 2006;**128**(35):11356–11357.

3. Arruebo M, Fernandez-Pacheco R, Ibarra MR, Santamaria J. Magnetic nanoparticles for drug delivery. *Nano Today.* 2007;**2**(3):22–32.

4. Mornet S, Vasseur S, Grasset F, Duguet E. Magnetic nanoparticle design for medical diagnosis and therapy. *J Mater Chem.* 2004;**14**(21):61–75.

5. Sun Z, Worden M, Thliveris JA, et al. Biodistribution of negatively charged iron oxide nanoparticles (IOnanoparticle) in mice and enhanced brain delivery using lysophosphatidic acid (LPA) *Nanomedicine.* 2016;**12**(7):1775–1784.

6. Kumar CSSR, Mohammad F. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. *Adv Drug Deliv Rev.* 2011;**63**(9):789–808.

7. Jahangirian H, Lemraski EG, Webster TJ, Rafiee-Moghaddam R, Abdollahi Y. A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. Int J Nanomedicine. 2017 Apr 12;12:2957-2978. doi: 10.2147/IJN.S127683. PMID: 28442906; PMCID: PMC5396976.

8. Zhang Y, Sun C, Kohler N, Zhang M. Self-assembled coatings on individual monodispersed magnetite nanoparticles for efficient intracellular uptake. *Biomed Microdevices.* 2004;**6**(1):33–40.

9. Le VH, Rodriguez HL, Lee C, et al. A soft-magnet-based drug-delivery module for active locomotive intestinal capsule endoscopy using an electromagnetic actuation system. *Sens Actuat A Phys.* 2016;**243**:81–89.

10. Liu J, Luo Z, Zhang J, et al. Hollow mesoporous silica nanoparticles facilitated drug delivery via cascade pH stimuli in tumor microenvironment for tumor therapy. *Biomaterials.* 2016;**83**:51–65.

11. Zhu X, Cao W, Chang B, et al. Polyacrylate/nanosilica causes pleural and pericardial effusion, and pulmonary fibrosis and granuloma in rats similar to those observed in exposed workers. *Int J Nanomedicine.* 2016;**11**:1593–1605.

12. Song Y, Li X, Wang L, et al. Nanomaterials in humans: identification, characteristics, and potential damage. *Toxicol Pathol.* 2011;**39**(5):841–849.

13. Pozdnyakov AS, Emelyanov AI, Kuznetsova nanoparticle, et al. Nontoxic hydrophilic polymeric nanocomposites containing silver nanoparticles with strong antimicrobial activity. *Int J Nanomedicine.* 2016;**11**:1295–1304.

14. Li X, Gong Y, Zhou X, et al. Facile synthesis of soybean phospholipid-encapsulated MoS2 nanosheets for efficient in vitro and in vivo photothermal regression of breast tumor. *Int J Nanomedicine.* 2016;**11**:1819–1833.

15. Zhao MD, Cheng JL, Yan JJ, et al. Hyaluronic acid reagent functional chitosan-PEI conjugate with AQP2-siRNA suppressed endometriotic lesion formation. *Int J Nanomedicine.* 2016;**11**:1323–1336.

16. El-Meliegy E, Farag MM, Knowles JC. Dissolution and drug release profiles of phosphate glasses doped with high valency oxides. *J Mater Sci Mater Med.* 2016;**27**(6):108.

17. Hao W, Liu D, Shang Y, Zhang J, Xu S, Liup H. pH-triggered copolymer micelles as drug nanocarriers for intracellular delivery. *RSC Adv.* 2016;**6**(35):29149–29158.

18. Tu H, Lu Y, Wu Y, et al. Fabrication of rectorite-contained nanoparticles for drug delivery with a green and one-step synthesis method. *Int J Pharm.* 2015;**493**(1–2):426–433.

19. Manuja A, Kumar B, Chopra M, et al. Cytotoxicity and genotoxicity of a trypanocidal drug quinapyramine sulfate loaded-sodium alginate nanoparticles in mammalian cells. *Int J Biol Macromol.* 2016;**88**:146–155.

20. Gurunathan S, Han JW, Eppakayala V, Kim JH. Green synthesis of graphene and its cytotoxic effects in human breast cancer cells. *Int J Nanomedicine.* 2013;**8**(1):1015–1027.

21. Renu GB, Kasturi M, Meifang Z, Muthupandian A, Nay MH, Sivakumar M. Sonochemical and sustainable synthesis of graphene–gold (G–Au) nanocomposites for enzymeless and selective electrochemical detection of nitric oxide. *Biosen Bioelectron.* 2017;**87**:622–629.

22. Bolu BS, Gecici EM, Sanyal R. Combretastatin A-4 conjugated anti-angiogenic micellar drug delivery systems using dendron–polymer conjugates. *Mol Pharm.* 2016;**13**(5):1482–1490.

23. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation.* 2000;**102**(4):399–404.

24. Kommareddy S, Amiji M. Poly(ethylene glycol)-modified thiolated gelatin nanoparticles for glutathione-responsive intracellular DNA delivery. *Nanomedicine.* 2007;**3**(1):32–42.

25. Carlyle WC, McClain JB, Tzafriri AR, et al. Enhanced drug delivery capabilities from stents coated with absorbable polymer and crystalline drug. *J Control Release.* 2012;**162**(3):561–567.

26. Washington, N., Washington, C. & Wilson, C. *Physiological Pharmaceutics: Barriers to Drug Absorption* (CRC Press, 2000).

27. Savjani, K. T., Gajjar, A. K. & Savjani, J. K. Drug solubility: importance and enhancement techniques. *ISRN Pharm.* **2012**, 195727 (2012).

28. Kalepu, S. & Nekkanti, V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm. Sinica B* **5**, 442–453 (2015).

29. Sharma, P. C., Jain, A., Jain, S., Pahwa, R. & Yar, M. S. Ciprofloxacin: review on developments in synthetic, analytical, and medicinal aspects. *J. Enzym. Inhib. Med. Chem.* **25**, 577–589 (2010).

30. Beaumont, K., Webster, R., Gardner, I. & Dack, K. Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. *Curr. Drug Metab.* **4**, 461–485 (2003).

31. Kempf, D. J. et al. Discovery of ritonavir, a potent inhibitor of HIV protease with high oral bioavailability and clinical efficacy. *J. Med. Chem.* **41**, 602–617 (1998).

32. Suzuki, R., Brown, G. A., Christopher, J. A., Scully, C. C. G. & Congreve, M. Recent developments in therapeutic peptides for the glucagon-like peptide 1 and 2 receptors. *J. Med. Chem.* **63**, 905–927 (2020).

33. Anselmo, A. C., Gokarn, Y. & Mitragotri, S. Non-invasive delivery strategies for biologics. *Nat. Rev. Drug Discov.* **18**, 19–40 (2019).

34. Morales, J. O. et al. Challenges and future prospects for the delivery of biologics: oral mucosal, pulmonary, and transdermal routes. *AAPS J.* **19**, 652–668 (2017).

35. Ritschel, W. Microemulsion technology in the reformulation of cyclosporine: the reason behind the pharmacokinetic properties of Neoral. *Clin. Transplant.* **10**, 364–373 (1996).

36. Pfutzner, A., Mann, A. E. & Steiner, S. S. Technosphere/insulin—a new approach for effective delivery of human insulin via the pulmonary route. *Diabetes Technol. Ther.* **4**, 589–594 (2002).

37. Chames, P., Van Regenmortel, M., Weiss, E. & Baty, D. Therapeutic antibodies: successes, limitations and hopes for the future. *Br. J. Pharmacol.* **157**, 220–233 (2009).

38. Shih, T. & Lindley, C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin. Ther.* **28**, 1779–1802 (2006).

39. Smith, M. R. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene* **22**, 7359–7368 (2003).

40. Aarden, L., Ruuls, S. R. & Wolbink, G. Immunogenicity of anti-tumor necrosis factor antibodies—toward improved methods of anti-antibody measurement. *Curr. Opin. Immunol.* **20**, 431–435 (2008).

41. Baert, F. et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N. Engl. J. Med.* **348**, 601–608 (2003).

42. Atzeni, F. et al. Immunogenicity and autoimmunity during anti-TNF therapy. *Autoimmun. Rev.* **12**, 703–708 (2013).

43. Sgro, C. Side-effects of a monoclonal antibody, muromonab CD3/orthoclone OKT3: bibliographic review. *Toxicology* **105**, 23–29 (1995).