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Research Publications 2021-22

Sr.	Title of the Publication	Author/s	Name of the Journal
1	Purification and modification of neem gum for enhancement of its suspending property	MG Kalaskar, RE Mutha, AU Tatiya, SD Firke, SJ Surana, KA Dhoka, K Heda	Future Journal of Pharmaceutical Sciences
2	Electrostatic deposition assisted preparation, characterization and evaluation of chrysin liposomes for breast cancer treatment	PK Deshmukh, RE Mutha, SJ Surana	Drug Development and Industrial Pharmacy
3	Cissus quadrangularis L: A comprehensive multidisciplinary review	PS Bafna, PH Patil, SK Maru, RE Mutha	Journal of Ethnopharmacology
4	Surface architectured metal organic frameworks-based biosensor for ultrasensitive detection of uric acid: Recent advancement and future perspectives	SN Nangare, PM Sangale, AG Patil, SHS Boddu, PK Deshmukh, NR Jadhav, RS Tade, DR Patil, A Pandey, S Mutalik, JK Patel, AM Patil, SB Bari, PO Patil	Microchemical Journal
5	Emerging Approaches to Overcome Acquired Drug ResistanceObstacles to Osimertinib in Non-Small-Cell Lung Cancer	M Shaikh, Y Shinde, R Pawara, M Noolvi, S Surana, I Ahmad, H Patel	Journal of Medicinal Chemistry
6	Fabrication of polyethyleneimine surface-functionalized fluorescent carbon dots and its applications towards highly sensitive and selective detection of glutathione in aqueous medium and *in vitro* cell imaging of *HeLa* cells	ZG Khan, PO Patil,	Journal of Materials Science: Materials in Electronics
7	Green synthesis of Fe-doped Ag-loaded reduced graphene oxide ternary nanocomposite for efficient photocatalytic degradation of toxic dyes	SN Nangare, S Landge, AG Patil, RS Tade, PK Deshmukh, PO Patil	Advances in Natural Sciences: Nanoscience and Nanotechnology
8	Crystallinity modulated silk fibroin electrospun nanofibers based floating scaffold as a candidate for controlled release of felodipine	S Dugam, S Nangare, A Gore, S Wairkar, P Patil, L Choudary, N Jadhav	International Journal of Polymeric Materials and Polymeric Biomaterials
9	Structural design of nanosize-metal-organic	SB Bari SN	Journal of Nanostructures

	framework-based sensors for ultrasensitive detection of organophosphorus pesticides in food and water samples: Current challenges and future prospects	Nangare, SR Patil, AG Patil, ZG Khan, PK Deshmukh, RS Tade, MR Mahajan	in Chemistry
10	Design and Synthesis of Poly-L-Lysine-Functionalized Graphene Quantum Dots Sensor for Specific Detection of Cysteine and Homocysteine	ZG Khan, PO Patil	Materials Chemistry and Physics
11	Graphene quantum dots (GQDs) nanoarchitectonics for theranostic application in lung cancer	RS Tade, MP More, SN Nangare, PO Patil	Journal of Drug Targeting
12	Synthesis, molecular modeling study of the methaqualone analogues as anti-convulsant agent with improved cognition activity and minimized neurotoxicity	I Ahmad, SR Akand, M Shaikh, R Pawara, SN Manjula, HM Patel	Journal of Molecular Structure
13	Development and Evaluation of Lyophilized Methotrexate Nanosuspension using Quality by Design Approach	T Power, A Hajare, R Jarag, S Nangare	Acta Chimica Slovenica
14	Fabrication of Poly-l-lysine-Functionalized Graphene Quantum Dots for the Label-Free Fluorescent-Based Detection of Carcinoembryonic Antigen	RS Tade, PO Patil	ACS Biomaterials Science and Engineering
15	Comparative Phytochemical Investigation Antioxidant and Antimicrobial Activity of Leaves, Bark and Stem Extract of Muntingia calabura	RN Chaudhari, AK Jain, VK Chatap	Journal of the Maharaja Sayajirao University of Baroda
16	Pharmacognostic Studies on *Anisomeles Heyneana* Benth. (Labiatae)	RE Mutha, KJ Tiwari, DM Kokate, YV Ushir	Journal of the Maharaja Sayajirao University of Baroda
17	A 3 factorial design approach for formulation and optimization of azilsartan medoxomil nanosuspension for solubility enhancement	NR Shirsath, D Marathe, P Jaiswal, LR Zawar	Indian Journal of Pharmaceutical Education and Research
18	An insight into prodrug strategy for the treatment of Alzheimer's disease	NV Bhilare, VS Marulkar, D Kumar, VK Chatap, KS Patil, PJ Shirote	Medicinal Chemistry Research
19	Nanostructured metal-organic frameworks based luminescent sensor for chemical sensing: Current Challenges and future prospects	SN Nangare, AG Patil, SM Chandankar, PO Patil	Journal of Nanostructure in Chemistry
20	Formulation of silk fibroin-based single polymeric floating microspheres for sustained release of lafutidine	J Pantwalawalkar, S Nangare	Indian Journal of Pharmaceutical Education and Research
21	Neuroprotective properties of medicinal plants: a comprehensive review	A Mhaiskar, V Bagul, S Patil	Journal of the Maharaja Sayajirao University of Baroda
22	Surface nanoarchitectured metal-organic frameworks-based sensor for reduced glutathione sensing: A review	ZG Khan, MR Patil, SN Nangare, AG Patil, S HS Boddu, RS Tade,	Journal of Nanostructure in Chemistry

		PO Patil	
23	Formulation, optimization, and in vitro evaluation of anastrozole-loaded nanostructured lipid carrier for improved anticancer activity	D Ghadge, S Nangare, N Jadhav	Journal of Drug Delivery Science and Technology

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RESEARCH Open Access

Purification and modification of neem gum for enhancement of its suspending property

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Abstract

Background: The present study aimed to purify and modify the neem gum (NG) to evaluate its dispersing ability in a pharmaceutical suspension formulation. The modification was carried out to cross-link the sugars as carbamate in the presence of calcium chloride to improve the suspending property. Physiochemical properties such as pH, solubility, swelling index and ash value were performed before investigating the dispersing potential. The suspending potential of neem gum was studied in its different forms such as purified and modified gum in paracetamol suspension and was compared with sodium carboxymethylcellulose (CMC) being used as standard at a concentration range of 0.25–1% (w/v). The test suspensions were evaluated for the redispersibility, flowability, sedimentation volume (%) and stability study for 3 months.

Result: The redispersibility of modified neem gum (MNG) was found equal to CMC at a higher concentration. The flowability and apparent sedimentation of test suspending agents and CMC were found in the order of NG > MNG > CMC. It showed a positive correlation with the viscosity of suspension formulations. All the test paracetamol suspension formulations were found stable in the stability study.

Conclusion: The findings of the present study showed that as an alternate suspending agent, modified cross-linked neem gum could be used.

Keywords: Neem gum, Sedimentation volume, Redispersibility, Flowability

Background

Pharmaceutical excipients are additives with unique physicochemical properties that help to transform the drug substances into an effective type of dosage suitable for patient administration. Demand for new and updated excipients for drug delivery systems has been growing in order to meet the needs of new, better formulations. To be used as pharmaceutical excipients, natural polymers are readily available, biodegradable, non-toxic and cost-effective, to be used as an excipient for a range of pharmaceutical formulations [1].

Gums are ideal natural polymer for pharmaceutical emulsion and suspension formulations by increasing the viscosity of the continuous phase. Furthermore, it increases the tensile strength, by hydrogen bonding and molecular interactions, of the hydration layer formed around the suspended particles without minimizing the surface and interfacial tension.

Neem gum (*Azadirachta indica*) is a large evergreen tree that may grow up to 20 m in height. It occurs in tropical and semitropical regions of the world. The plant oozes plenty of gum throughout the year. Chemically, it contains mannose, glucosamine, arabinose, galactose,

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RESEARCH ARTICLE

Electrostatic deposition assisted preparation, characterization and evaluation of chrysin liposomes for breast cancer treatment

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ABSTRACT

Chrysin (CHR), a flavone found in multiple vegetables, fruits and mushrooms has been explored so far as a neurotropic, anti-inflammatory and anti-cancer biomolecule. Despite the stated therapeutic potential, low solubility and bioavailability limit its therapeutic benefit. To circumvent these drawbacks, development of chrysin liposomes (CLPs) is reported in the present investigation. The CLPs were developed by electrostatic deposition assisted film hydration method using chitosan/lecithin to protect chrysin in the nano-lipoidal shell. Developed CLPs were extensively characterized by DSC, XPRD, FE-SEM, TEM, particle size, polydispersity index, zeta potential, percent drug loading and encapsulation efficiency. These CLPs were further characterized by *in vitro* dissolution, *in vivo* bioavailability, *in vitro* anticancer and stability study. Suitable particle size, PDI and ZP implying stabilization of developed CLPs. The % DL and % EE was found to be 3.56 ± 0.13 and 90.5 ± 1.49 respectively. DSC and PXRD study revealed amorphous transition of CHR, which may help to increase its solubility and dissolution profile. *In vivo* pharmacokinetic study demonstrated more than 5-fold increase in relative bioavailability of CLPs. The in silico molecular docking study results demonstrated the electrostatic interaction between two polymers. The present study suggests that chitosan could protect and encapsulate chrysin which eventually enhances its cytotoxicity as well as bioavailability.

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Introduction

Encapsulation of bioactive drug using polymeric coating is beneficial due to its nontoxic, nonimmunogenic and biodegradable properties, along with protection of drug with improved biocompatibility [1–3]. In addition to this, issue of poor aqueous solubility and bioavailability of many bioactive compounds could be resolved using techniques like nanoencapsulation [4].

The electrostatic deposition method is based on the deposition of one polymer material on another in liquid form followed by evaporation of the solvent to form encapsulation of the subsequent polymer. This technique of encapsulation attracted researchers in recent years; herein it coats the active ingredient with the assistance of polymeric matrix [1]. The electrostatic deposition based microencapsulation approach has also been used for the preparation of hydrogels [5], microemulsion [6], liposomes [7] to name a few.

Out of the many approaches used for drug encapsulation, liposomes are widely used for both hydrophilic and hydrophobic drugs such as antioxidants, antimicrobials and other pharmacologically important compounds [8]. However, organic residual effect, leakages of active compounds and instability during storage of traditional liposomes may restrict their applications [9,10]. So as to conquer these limitations, polycationic polymer like chitosan could be used as a coating material which forms polyelectrolyte complex with oppositely charged polymeric r ial by intermolecular electrostatic deposition [11,12].

Chrysin (CHR), a flavone found in multiple vegetables, and mushrooms, has been suggested as neurotrophic for cells, anti-inflammatory, and anti-amyloidogenic [13]. The CH been known as an anti-cancer and wellbeing-promoting pound [14]. In several biological tests, it has demonstrated t may be effective against many disorders. The CHR may most cancer-related pathways and inhibits cancer by fost apoptosis and moderating cell death due to autophagy. H extensive research in this direction should be focused on i coming years to validate its possible clinical use in cancer.

The main objective of the present study was to encaps CHR in liposomal form using the electrostatic deposition nique for protection and further enhancement in bioavailal For the same, biocompatible and biodegradable biological m molecules viz. chitosan (CHN) and soya lecithin (SOL) were which form a polymeric nanoshell with the aim to shield against degradation and to enhance its biocompatibility [1 Being a polycationic macromolecule, chitosan, through inte lecular electrostatic deposition, form polyelectrolyte compl with oppositely charged macromolecules [17]. Developed ch liposomes (CLPs) were further characterized using different p cochemical parameters like particle size (PS), polydispersity i (PDI), zeta potential (ZP), entrapment efficiency (% EE), drug l ing (% DL), differential scanning calorimetry (DSC), transmis

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Cissus quadrangularis L: A comprehensive multidisciplinary review

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ABSTRACT

Ethnopharmacological relevance: Cissus quadrangularis L. is a perennial herb of the Vitaceae family and is utilized comprehensively as a medicinal herb in most tropical regions by various names. This herb is documented to possess a wide-ranging ethnomedicinal uses in malaria, fever, epilepsy, gout, piles, skin diseases, colic, etc.

Aim of the review: A organized summary of the botany, traditional uses, phytochemistry, pharmacology, toxicology, available marketed formulations and filed patents were presented to explore the future therapeutic potential and scientific potential of this herb.

Materials and methods: For a review of the literature, various databases were searched, including PubMed, EMBASE, and Scopus etc. From, total 408 records of this herb, we have screened 155 articles consist of desired information and available as full text. Present manuscript is structured from comprehensive information on this herb from screened 155 records. Plant taxonomy was confirmed to the database "The Plant List".

Results: Phytochemical assessment as a whole indicated the presence of flavonoids, triterpenoids, alkaloids, saponins, iridoids, stilbenes, vitamins, steroids, and glycosides. A toxicity study revealed that its LD_{50} value is above 3000 mg/kg in animals indicating its safety. A variety of pharmacological studies of aerial parts of this herb by different extracts have demonstrated analgesic, anti-inflammatory, anticonvulsant, antimicrobial, anticancer, anti-osteoporotic activity and other bone-related disorders to justify its name as *Hadjod*. Still, the herb has been utilized in clinical practice and several patents were filed in India and US for its antiosteoporotic property.

Conclusion: The studies on *Cissus quadrangularis* Linn. are extensive, but gaps still remain. The molecular mechanism, structure-activity relationship, potential synergistic and antagonistic effects of these components needs to be further elucidated. These findings suggest the need for further research on this herb for the management of several other chronic ailments.

1. Introduction

Natural substances are being used as a principal source of medicines directly or indirectly, for many decades and have proven to be extremely beneficial to human health. These substances are being investigated for biological activities in nearly every part of the world. Despite the fact that a large number of plant-derived chemicals are widely available, rigorous initiatives have been undertaken to isolate, identify and test molecular leads and develop novel chemicals with enhanced biological potential and low toxicity.

Natural products, notably those extracted from plants, tend to provide valuable leads in the drug development process (Balunas and Kinghorn, 2005). The initial process in drug research is to gather data on materials that have previously been used to cure a disease. Due to the custom of verbal transfer of the information regarding medicinal plants and their relevant techniques of use (Bhatia et al., 2014), there is concern that aboriginal herbal medicine knowledge is being endangered (Ssegawa and Kasenene, 2007). It is a need of time to conserve and document this traditional and advanced knowledge of plants proven through various experimentation and study protocols so that it will work as a lighthouse for the future researchers and give guideline with respect to safety, efficacy and specific uses (Bunalema et al., 2014).

Cissus is a genus of the Vitaceae family consisting of 800 species divided into 13 genera throughout the world, including Africa, Arabia, South Asia, Srilanka, India and other tropical regions. Out of these, 8 genera and 63 different species are found in India (Ansarali et al., 2016). *Cissus quadrangularis* L. (CQL), Vitaceae is a dicotyledonous flowering,

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Review Article

Surface architectured metal organic frameworks-based biosensor for ultrasensitive detection of uric acid: Recent advancement and future perspectives

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ABSTRACT

Gout is the world's most popular inflammatory arthritis and the prevalence of gout is rapidly rising worldwide. Typically, gout develops in a single joint as excessive swelling and intense pain wherein excessive deposition of uric acid (UA) crystals results in inflammation of the joint. Accordingly, UA is considered an effective biomarker to diagnose gout. Recently, the use of innovative sensors has attracted great attention, as it is effortless, responsive, quick, and powerful. While the traditional sensors for UA assessment are widely used, they pose many limitations and hurdles in terms of sensitivity, selectivity, and simplicity. In this vein, metal ions and organic ligand-based metal–organic framework (MOF) have gained much attention for the recognition of UA due to its larger surface area, porosity, high sensitivity, and defined selectivity. In this review, we provide details on the latest developments of MOF-centered biosensors for sensitive detection of UA. The status of gout, fundamentals of MOF, and MOF availed for detection of UA have been elaborated. Besides, we highlighted the nanoparticles and conjugates that rely on advanced strategies along with MOF that boost the sensitivity and selectivity towards the UA. Interestingly, different surface architectured MOFs biosensors showed a lower detection limit for UA from μM to nM. Finally, the threats and potential opportunities for MOF-based UA biosensors have been summarized. Therefore, based on ongoing research, the commercialization of this advanced platform for the biosensing of diverse biomarkers will open a new door for the *in vitro* diagnosis of assorted diseases.

1. Introduction

From its inception, arthritis is a severe health issue of a joint in almost all developed and developing nations. Arthritis is a term that derives from the Greek word "disease of the joint." Commonly, it can be stated as acute inflammation or chronic inflammation of the joint that is sometimes with the effect of pain and sometimes co-exists with structural damage [1]. As many as 100 classes of arthritis have been characterized according to the research. Generally, it can be classified into two type's namely non-inflammatory arthritis and inflammatory arthritis. In the first category, non-inflammatory arthritis is commonly known as osteoarthritis, while inflammatory arthritis is categorized

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Perspective

Emerging Approaches to Overcome Acquired Drug Resistance Obstacles to Osimertinib in Non-Small-Cell Lung Cancer

Matin Shaikh, Yashodeep Shinde, Rahul Pawara, Malleshappa Noolvi, Sanjay Surana, Iqrar Ahmad,* and Harun Patel*

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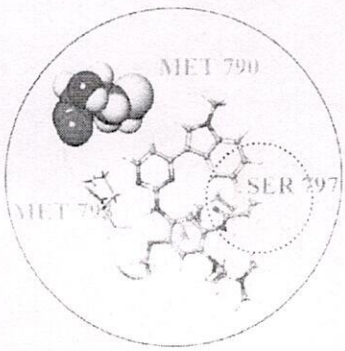
ABSTRACT: The pyrimidine core-containing compound Osimertinib is the only epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) from the third generation that has been approved by the U.S. Food and Drug Administration to target threonine 790 methionine (T790M) resistance while sparing the wild-type epidermal growth factor receptor (WT EGFR). It is nearly 200-fold more selective toward the mutant EGFR as compared to the WT EGFR. A tertiary cystein 797 to serine 797 (C797S) mutation in the EGFR kinase domain has hampered Osimertinib treatment in patients with advanced EGFR-mutated non-small-cell lung cancer (NSCLC). This C797S mutation is presumed to induce a tertiary-acquired resistance to all current reversible and irreversible EGFR TKIs. This review summarizes the molecular mechanisms of resistance to Osimertinib as well as different strategies for overcoming the EGFR-dependent and EGFR-independent mechanisms of resistance, new challenges, and a future direction.



1. INTRODUCTION

On March 30, 2017, the US Food and Drug Administration (FDA) conceded regular approval to Osimertinib (AZD9291) for the management of patients with metastatic "EGFR-T790M Non-Small Cell Lung Cancer (NSCLC)".[1,2] The FDA-approved drug Osimertinib is at the forefront for the treatment of NSCLC patients (Figure 1).[3−5] However, a significant proportion of Osimertinib-treated patients developed the EGFR kinase tertiary cystein 797 to serine 797 (C797S) mutation by the loss of covalent binding with the Cys797 residue, which renders a resistance to all the existing drugs.[6,7] Additional studies with mutant cell lines have shown that the allelic context of the activating gatekeeper and C797S mutations affects the sensitivity of three generations of EGFR inhibitors, with no epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKIs) alone or in combination able to suppress activity when the mutation is in the *cis*-form.[8−10] These data suggest that there is a pressing need for drugs that can overcome the ternary mutation (L858R/T790M/C797S EGFR) obstacle in NSCLC.[11] The crystallographic structure of C797S-EGFR revealed that the C797S mutation has no effect on the EGFR kinase's structure or function but does increase the degree of local hydrophilicity around residue 797 (Figure 2).[12−14]

The EGFR-independent pathway also contributes to the resistance to Osimertinib in addition to the acquired C797S mutation.[15,16] The EGFR-independent pathway (bypass pathway) is ascribed to the modification of other signaling molecules, such as MET amplification, MEK activation, ALK activation, FGFR amplification, HER2 amplification, AKT activation, BRAF activation, and AXL activation.[17,18] The tertiary undruggable C797S mutation in the EGFR kinase domain, which causes more than 20% of the incidence rate in clinical results, is the most difficult to deal with of all these potential mechanisms.[19−21] The focus of this review is to provide an exhaustive overview of Osimertinib resistance mechanisms and use the available information to develop potential strategies to overcome the associated resistance problem.

2. EGFR-MEDIATED SIGNALING PATHWAYS IN NSCLC

Different growth factors, cytokines, and hormones bind to the receptor tyrosine kinases (RTKs). Structurally, RTKs consist of the ligand-binding extracellular domain, the hydrophobic transmembrane domain, and the intracellular protein tyrosine kinase region.[22] Therefore, intracellular pathways that signal EGFR play a major role in various cancers, specifically NSCLC. The binding of a ligand (growth factor) to the EGFR extracellular domain causes dimerization, which subsequently activates the cytoplasmic tyrosine kinase domain

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Fabrication of polyethyleneimine surface-functionalized fluorescent carbon dots and its applications towards highly sensitive and selective detection of glutathione in aqueous medium and in vitro cell imaging of HeLa cells

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ABSTRACT

The present study aimed to synthesize polyethyleneimine (PEI) surface-functionalized fluorescent carbon dots (CDs)-based biosensor (GP-PEI-CDs) for highly sensitive and selective detection of glutathione (GSH). In brief, green pea (GP) shells were utilized for green synthesis of blue luminescent GP-CDs through hydrothermal method. The obtained GP-CDs were surface functionalized with PEI to improve surface defects and quantum confinement effects. The surface functionalization of GP-PEI-CDs was confirmed by different spectroscopic techniques, including FTIR, XPS, etc. Switch "on" of GP-PEI-CDs was quenched by Cu(II) ions (turn "off"), and the limit of detection (LOD) of Cu(II) was found to be 23 nM along with a linearity range as 0 μM to 50 μM. Then, turn "On" process enabled the restoration in fluorescence of surface-functionalized GP-PEI-CDs when different concentrations of GSH in phosphate buffer saline (PBS, pH 7.4) was added. This could be due to split up of Cu(II) from Cu(II)@GP-PEI-CDs complex by presenting selective affinity with thiol (–SH) group of GSH among the various biomolecules. The LOD of GSH was found to be 38 nM and linearity in the range of 0 to 25 μM. The cytotoxicity study confirmed the biocompatibility of surface-functionalized GP-PEI-CDs. Furthermore, a confocal analysis indicated exceptional penetrations of GP-PEI-CDs into the cell cytoplasm and nucleus, demonstrating the created probe's suitability for GSH sensing at the cellular level. The method was successfully applied to determine GSH in in human serum sample.

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Green synthesis of Fe-doped Ag-loaded reduced graphene oxide ternary nanocomposite for efficient photocatalytic degradation of toxic dyes

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Abstract

The green synthesis of iron nanoparticles (FeNPs) doped and silver nanoparticles (AgNPs) loaded reduced graphene oxide (rGO) (Fe-Ag@rGO) nanocomposite and its applications in methylene blue (MB), malachite green (MG), rhodamine B (RB) degradation were reported. Initially, AgNPs loaded rGO (Ag@rGO) nanocomposites were synthesised simultaneously by an ecological method using *Tamarindus indica* shell extract as a green reducing agent. Then, the doping of FeNPs into rGO@Ag nanocomposites afforded Fe-Ag@rGO nanocomposite. Interestingly, the finding of this study confirmed that the Fe-Ag@rGO nanocomposites exhibited countless stupendous features in terms of dye degradation. Briefly, the UV-visible spectroscopy and Fourier-transform infrared spectroscopy (FTIR) study confirmed the synthesis of Fe-Ag@rGO nanocomposite. The scanning electron microscopy (SEM) images showed the spherical shape with cross-linked network structures that confirmed the surface modification and synthesis of Fe-Ag@rGO nanocomposite. Finally, the dye degradation potential of the photocatalyst was found to be 97.20%, 98.43%, and 97.33%, for MB, MG, RB, respectively. Herein, the improved photocatalytic performance of the Fe-Ag@rGO was found due to the larger surface area, porous nature, high electron mobility, and synergistic effect of the Fe-Ag@rGO nanocomposite. Additionally, the effective interfacial hybridisation of 'Ag', and doping of 'Fe' on the rGO sheet extended the duration of the photogenerated electron (e^-) hole pairs that can also be contributing to dye degradation. Conclusively, the present experiment provides the new Fe-Ag@rGO nanocomposite to the dye degradation, which could be improved environmental remediation.

Keywords: dye degradation, nanocomposite, Fe-Ag@rGO, Tamarindus indica shells, graphene oxide, Green synthesisClassification numbers, 2.00, 5.00, 5.11

1. Introduction

Today is the era of accelerated industrialisation, which has seen rapid developments and has played an essential role in

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Crystallinity modulated silk fibroin electrospun nanofibers based floating scaffold as a candidate for controlled release of felodipine

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ABSTRACT

Floating gastro-retentive delivery approach provides a significant pathway for controlled release of drug with increase gastric residence. In this study, we report crystallinity modulated electrospun silk fibroin nanofibers (SF-NFs) floating scaffolds for the controlled release of felodipine (FD). The alteration in the crystallinity behavior due to changes in the structural conformation of SF helps to customize the release kinetics of FD-loaded SF-NFs scaffolds. Additionally, FD-loaded SF scaffolds system having a density less than the acidic gastric fluid explore as a new tactic for floating drug delivery system. The prepared FD-loaded SF nanofibers (FD-loaded SF-NFs) were characterized by spectral, thermal, and diffractometric techniques, scanning electron microscopy, floating profile, *in-vitro* degradation, mucoadhesion, and *in-vitro* dissolution studies, etc. The optimized batch had the least porosity and swelling, was annealed with ethanol and water for crystallinity modulation of SF-NFs to get controlled release of FD. Spectral, thermal, and diffractometric analyses could unveil the molecular dispersion of FD, coupled with amorphous form stabilization in NF. Excellent floating profile and satisfactory mucoadhesion of FD-SF-NFs also endorsed the formation of a novel floating drug delivery system. Temporal control over FD release was elucidated by *in-vitro* dissolution, demonstrating controlled release due to crystallinity modulation of SF-NFs. In conclusion, crystallinity-modulated electrospun NFs fabricated from SF waste could be used as a customizable carrier for drug delivery to the gastric region.

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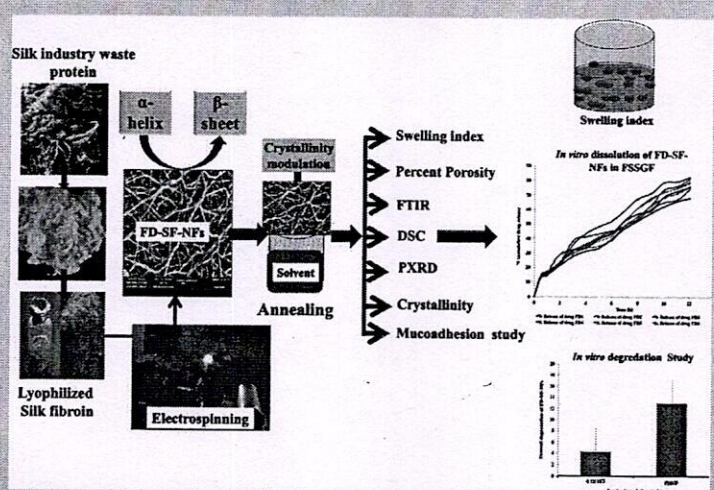
Silk fibroin; electrospun nanofibers; crystallinity modulation; felodipine; floating drug delivery; controlled release

GRAPHICAL ABSTRACT



Crystallinity modulated silk fibroin electrospun nanofibers based floating scaffold as a candidate for controlled release of felodipine

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REVIEW

Structural design of nanosize-metal–organic framework-based sensors for detection of organophosphorus pesticides in food and water samples: current challenges and future prospects

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Abstract
Organophosphorus pesticide (OPP) is regarded as an important food-chain and environmental contaminant that causes primary acute toxicity and numerous severe health issues. Therefore, the minute concentration of OPP present in food materials and environments needs to be identified before it causes any brutal harm to lives. Despite the plenty of merits of qualitative and quantitative sensing methods, the lower sensitivity, poor selectivity, detection speed, etc. towards the interest OPP are major drawbacks. Nanoparticles have attracted a lot of attention because of their unique and intriguing features, which have a variety of applications including sensor development as compared to their bulk counterparts. Recently, the structural design of nanosize-metal–organic framework (MOF) is gaining huge consideration from researchers for sensing applications owing to their versatile and tunable properties. Additionally, MOF-based sensors offer the rapid, simplistic, selective, and sensitive sensing of interest analyte. The present review provides brief information about OPPs and their toxicities. The emerging trends of structural design of nanosize-MOF including their properties have been summarized. Finally, nanosize-MOF-based fluorescent sensors, electrochemical sensors, and colorimetric sensors have been discussed with central focus on sensitivity and selectivity to OPPs. Due to the higher surface area, rich topology, ease of structural tunability and functionalization, tunable pore size, plenty of binding sites, good adsorption potential, excellent charge conductivity, and chemical stability, etc., MOF based sensors are endowed with the ability of OPPs detection upto aM. Hence, MOF as nanoporous sensors can be preferred as an excellent alternative for highly sensitive and selective recognition of OPPs in food and water samples.

Sopan N. Nangare and Sayali R. Patil contributed equally as a first author.

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Design and synthesis of poly-L-lysine-functionalized graphene quantum dots sensor for specific detection of cysteine and homocysteine

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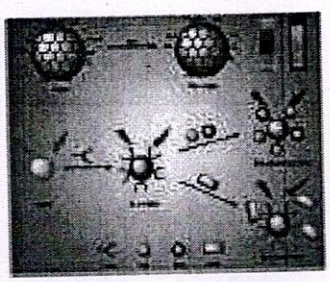
HIGHLIGHTS

- Waste material (pistachio shells) used for synthesis of graphene quantum dots (GQDs).
- Novel poly-L-lysine (PLL) surface functionalized GQDs (PLL-GQDs) based sensor was developed.
- The fabricated probe (PLL-GQDs) exhibited low cytotoxicity and excellent biocompatibility.
- The probe demonstrated highly sensitive and selective detection of cysteine (cys) and homocysteine (hcys) in real samples.

GRAPHICAL ABSTRACT



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ABSTRACT

In this paper, a novel poly-L-lysine (PLL) surface functionalized graphene quantum dots (GQDs) based sensor was developed for detection of cysteine (cys) and homo cysteine (hcys). A fluorescent probe (PLL-GQDs) was then fabricated by surface functionalizing GQDs with PLL, a biodegradable polycationic electrolyte to improve the sensitivity and selectivity towards cys and hcys. The detection was based on the specific binding of cys and hcys to PLL at the PLL-GQDs surfaces, which enabled dynamic quenching via electrostatic and hydrophobic interactions. This fluorescent probe provided good linearity for the tested biothiols, ranging from 0 to 150 nM for cys, from 0 to 100 nM for hcys, with limit of detections (LODs) of 2.38 and 1.94 nM, respectively in BPS (pH 7.4). Interestingly, fabricated probe was also able to display a significant selectivity towards cys and hcys against known interfering molecules. The cytotoxicity study confirmed the biocompatibility of PLL-GQDs, enabling its future scope for cell adhesion and other biomedical applications. Besides, confocal study revealed the excellent penetrations of PLL-GQDs into cell cytoplasm and nucleus that validate the practical application of developed probe to detect cys and hcys at cellular level. The method was successfully applied for detection of cys and hcys in human serum sample. We expect the design concept presented here would be broadly used for selective and sensitive estimation of cys and hcys.

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REVIEW ARTICLE

Graphene quantum dots (GQDs) nanoarchitectonics for theranostic application in lung cancer

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ABSTRACT

Lung cancer (LC) is heading up as a substantial cause of mortality worldwide. Despite enormous progress in cancer management, LC remains a crucial problem for oncologists due to the lack of early diagnosis and precise treatment. In this context, numerous early diagnosis and treatment approaches for LC at the cellular level have been developed using advanced nanomaterials in the last decades. Amongst this, graphene quantum dots (GQDs) as a novel fluorescent material overwhelmed the horizons of materials science and biomedical fields due to their multifunctional attributes. Considering the complex nature of LC, emerging diagnostic and therapeutic (Theranostics) strategies using GQDs proved to be an effective way for the current practice in LC. In this line, we have abridged various approaches used in the LC theranostics using GQDs and its surface-engineered motif. The admirable photophysical attributes of GQDs realised in photolytic therapy (PLT), hyperthermia therapy (HTT), and drug delivery have been discussed. Furthermore, we have engrossed the impasse and its effects on the use of GQDs in cancer treatments from cellular level (*in vivo-in vitro*) to clinical. Inclusively, this review will be an embodiment for the scientific fraternity to design and magnify their view for the theranostic application of GQDs in LC treatment.

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Lung cancer; graphene quantum dots; theranostics; photolytic/hyperthermia therapy; drug delivery

Introduction

Global cancer risk is elevating gradually and results in a greater mortality rate per year. As per the fresh report of GLOBOCAN 2020, about 19.3 million cases and nearly 10.0 million deaths by cancer were recorded in 2020. Epidemiologists suggested that there would be probable 28.4 million new cases of cancer to befall nearly in 2040. Amongst all cancers, lung cancer (LC) has positioned on second diagnostic occurrence followed by breast cancer (11.7%) and crossed about 11.4% mortality rate, led by 1.8 million deaths (18%) in 2018 [1]. Besides, LC mortality is probable to reach 2.45 million globally by 2030. Principally, LC is a complex form of (adenocarcinoma) which increasing worldwide as an utmost cause of mortality. Generally, adenocarcinoma is known as the cancer of glandular mucus-producing cells (especially lungs). As per literature, LC is classified into four types: invasive adenocarcinoma (IA), adenocarcinoma in-situ (AIS), and minimally invasive adenocarcinoma (MIA) and other variants (e.g. lipidic) (Figure 1(A)). Besides this, the World Health Organisation (WHO) gives a sub-classification of lung adenocarcinomas as per their cellular origin. It includes acinar cells, papillary cells, bronchoalveolar, and mucus-secreting [2]. Literature survey advocated that there is a scarcity in our current knowledge of cancer statistics due to changing epidemiological trends of LC amongst developing countries [3]. In this context, it is observed that there is a vital role of the Human Development Index (HDI) in cancer mortality and morbidity in several countries. Both developed and developing countries experiencing an evident rise in the augmented effects of cancer risk factors. Moreover, there is an alarming rise in LC incidents in non-smokers as well. Notably, some major risk factors associated with the LC are smoking, exposure to second-hand smoke, previous radiation therapy, exposure to radon gas, exposure to asbestos and other carcinogens, and hereditary history of LC. Besides, the world is evidenced by the residual burden of different respiratory infections associated with LC. For example, Coronavirus disease 2019 (COVID-19), its emergence in 2020, and recurrence in 2021 have been overwhelmed the global healthcare systems. At this juncture, COVID-19 is becoming a major risk factor for LC patient's treatment. However, an extensive survey regarding the precise impact of COVID-19 associated with a patient suffering from LC is not available to date [4,5].

Current diagnostics and management strategies for LC

Despite the significant development in cancer therapeutics, several risk factors escalating in front of the developed and developing nations. Recently, Sung et al. reviewed the global cancer prevalence, which suggested the frequent diagnostic appearance as well as morbidity of LC up to 2020 which raised significantly after 2018 (Figure 1(B)) [1,6].

The traditional methods including X-ray, magnetic resonance imaging (MRI), Computed tomography (CT), or positron-electron microscopy (PET) scanning are commonly used for the diagnosis of cancer. Primary screening of LC by traditional methods is dependent on the severity and phases of LC. Unfortunately, the lack of site-specific localisation or inability to detect micrometer-sized tumours becomes inconclusive in the early detection of LC. Apart from this, sputum cytology, biopsy, and bronchoscopy methods are commonly used for the diagnosis of LC.

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nthesis, molecular modelling study of the methaqualone analogues anti-convulsant agent with improved cognition activity and inimized neurotoxicity

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ABSTRACT

In the current research, methaqualone derivatives were synthesized and assessed for their anti-convulsant activity. Among them, compounds **3, 4, 6, 7** and **11** exhibited significant anti-convulsant activities with ED_{50} values of 132.23 mg/kg, 120.34 mg/kg, 100.78 mg/kg, 145.89 mg/kg, and 148.46 mg/kg, respectively. The toxicity profiling (TD_{50}) of these compounds (**3, 4, 6, 7** and **11**) demonstrated that these drugs caused only a minor neurological impairment. The PI scores of these compounds (**3, 4, 6, 7** and **11**) were higher than the reference drug (methaqualone PI: 1.99). The acetylcholinesterase enzyme level is significantly reduced in these compounds, indicating the enhancement of cognition activity. Pharmacophoric modelling and molecular docking studies against the human GABA-A receptor are in close agreement with each other. Molecular dynamic simulation of compound **6** indicates that it remains stable with the human GABA-A receptor for a 100 ns time span.

ntroduction

Epilepsy is among the oldest medical disorders recorded in his- [1]. Despite the wide and expanding range of antiepileptic gs (AEDs) available for treatment, around 30% of epileptic pa- nts have suboptimal seizure control, and another 25% have seri- s side effects [2]. Epilepsy is linked to a higher incidence of neu- sychological disorders, including emotional disturbance, cogni- e deficits, and psychiatric disorders, all of which have a severe pact on quality of life [3–7]. Therefore, there is an immense e to develop new AEDs that are both effective and have a her safety profile. Methaqualone has a tumultuous past as both nedicinal and a recreational substance [8,9]. In the early 1960s, thaqualone was sold under the trade names Parest, Quaalude, onal, Somnafac, and Mandrax, as a non-barbiturate hypnotic h a broad safety margin and limited abuse potential [1]. In er years, methaqualone became one of the world's best-selling iative-hypnotic agents with other structural analogues (collectively known as "quaaludes") [1]. Although the clinical characteristics of methaqualone are quite typical for a sedative-hypnotic medication, some of its *in vivo* effects differ from those produced by conventional central nervous system (CNS) depressants. [10,11]. As compared to benzodiazepines and barbiturates, methaqualone, purportedly facilitates a rapid induction of a more natural deep sleep, resulting in less severe dizziness/dullness, and headaches in insomnia patients [10,11].

Several quinazoline derivatives have been identified and reported to stimulate GABA-A receptors [12]. The GABA-A receptor is an ionotropic ligand-gated ion channel receptor, and γ-aminobutyric acid (GABA) is an endogenous ligand that is the primary inhibitory neurotransmitter in the CNS. Upon activation, the GABA-A receptor primarily flows Cl^-*via* its pore, causing the neuron to hyperpolarize. This inhibits neurotransmission by inhibiting the action potential [13–15]. Many quinazolinones with structural similarities to methaqualone have been discovered and investigated for anti-convulsant action (Fig. 1) [12].A continuous issue faced with these compounds emanates from the fact that nearly every analogue evaluated in combined neurotoxicity and anti-convulsant testing revealed neurotoxicity values (TD_{50}) that were less than or only slightly higher than the effective doses

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Scientific paper

Development and Evaluation of Lyophilized Methotrexate Nanosuspension using Quality by Design Approach

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Abstract

With the application of the quality by design (QbD) approach, a high-pressure homogenizer (HPH) methodology was employed to develop methotrexate nanosuspension (MTX-NS) to boost bioavailability. The Ishikawa diagram was used to analyze potential risk factors in formulation development. To screen and study the impact of various formulation and process factors on the critical quality attributes (CQA), the Placket–Burman design and central composite design were utilized. The number of HPH cycles, poloxamer 188 concentration, and tween 80 concentration were shown to be significant parameters ($P<0.05$), that were further optimized using Central Composite Design. The zeta potential of optimized lyophilized MTX-NS was determined to be −11.6 ± 7.52 mV and the average particle size was 260 ± 0.25 nm. In vitro cytotoxicity experiments revealed a greater than 80% inhibition, with apoptotic cells shrinking, fragmentation, and cell death. Furthermore, the C_{max} and AUC_{0-t} were increased by 2.53 and 8.83 folds, respectively. The relative bioavailability of MTX-NS was found to be 8.83 times higher than that of MTX-aqueous dispersion. As a result, the QbD method resulted in the development of a lyophilized MTX-NS with process understanding and control based on quality risk management.

Keywords: Nanosuspension; Lyophilized, QbD approach; Central Composite Design; Plackett– Burman Design; *In-vivo* study.

1. Introduction

Pharmaceutical experts have long struggled with the formulation and development of poorly water-soluble drugs, and these challenges are projected to worsen since more than 40% of new chemical entities discovered by drug discovery are poorly aqueous soluble.[1] Whereas, it is more problematic in the case of poorly soluble drugs with poor absorption profile, and bioavailability because it is dissolution rate-limited and can be affected by patient fed or fasted state condition[2]. Traditional approaches including solubilization by surfactant, surfactant dispersion, micronization, use of the oily solution, permeation enhancers, which evolved too earlier, that address the challenges of formulation and have limited use.[2,3] The major milestone has been achieved in the development of poorly water-soluble drugs using various newer technology, but to date, there is no universal thumb approach applicable to all active pharmaceutical ingredients.[3] Consequently, a new approach has been progressively required to deal with formulation issues that are associated with the delivery of poorly soluble drugs, to enhance their therapeutic efficacy and maximize their pharmacodynamics therapy.[2]

A drug delivery aims to deliver a sufficient amount of drug to a proper side in the body such that, the optimal concentration of the drug is reached rapidly and then sustained. The development of a proper dosage form is an essential element to achieve this objective.[4] From its inception, oral drug delivery is the most commonly used route of administering the drug in various dosage forms due to