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DEVELOPMENT AND CHARACTERIZATION OF SUBLINGUAL FILM CONTAINING ROPINIROLE HYDROCHLORIDE

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ABSTRACT

In the present work films of ropinirole hydrochloride were prepared by using polymers such as hydroxy propyl methyl cellulose (HPMC E-15) and polyethylene glycol (PEG-400) as plasticizers, by a solvent casting method, for treatment of Parkinson's disease. HPMC E-15 was used as film forming agent in the range of concentration 50 mg – 600 mg and PEG-400 was used as plasticizer in the range of concentration 0.3-1.0 mL for solvent casting method. The optimized concentration of film forming agent was 400 mg and plasticizer concentration was 0.7mL. By using optimized concentration, Ropinirole Hydrochloride mouth dissolving films (MDFs) were prepared by additionof other excipients. The formulated MDFs were evaluated for different physical characteristics like uniformity of weight, thickness, folding endurance, drug content uniformity, percentage elongation, and tensile strength, disintegration, *in vitro* drug release studies and provided agreeable results. The FTIR and DSC studies confirmed that no physicochemical interaction in between drug and excipients accured. Mouth dissolving film of Ropinirole Hydrochloride containing HPMC E-15 as polymer showed 97.66 % drug release at 30 min. Mouth dissolving films of ropinirole hydrochloride containing HPMC E-15 showed better tensile strength (70.56 ± 0.9 g/mm2), percentage elongation (33.33 ± 2.88 %), folding endurance (168± 2.081 numbers of folds), *in vitro* disintegration time (35± 3.511 sec.) and thickness (0.4± 0.17 mm).

Keywords: Ropinirole hydrochloride, Parkinson's disease, solvent casting method, tensile strength, mouth dissolving film

INTRODUCTION

Since time immemorial, oral drug administration is one of the most suitable and commonly accepted routes of delivery for most therapeutic agents. Conventionally, oral formulations refer to tablets, capsules and liquid preparations which are taken orally, swallowed and transit through the gastrointestinal tract (GIT) for post buccal absorption. For the last few years, investigators have been developing intraoral drug delivery systems (IODS) that can produce desirable drug exposure for optimum therapeutic effect. The intraoral formulations include fast dissolving dosage forms (tablets, films, wafers), sublingual tablets, buccal/ gingival patches, microparticles, Periodontal fibres, solutions and sprays, chewing gums, dry powders, topical gels, topical pastes, bioadhesive tablets, topical ointments, local injections, dissolvable lozenge etc and more[1].

New developments of orally fast dissolving dosage form such as the fast dissolving tablet or fast dissolving films have advantages of ease of dosing and convenience of dosing in the absence of any fluid and water. Most of the existing fast-dissolving drug delivery systems are in the form of tablets and designed to dissolve or disintegrate in to the mouth within a few seconds or minutes, without any need to swallow or chew. The films overcome the risk of choking and the development of a fast dissolving film also brings an opportunity for a line extension into the market place; an extensive range of drugs (e.g., neuroleptics, cardiovascular drugs, antiasthmatic, analgesics, antihistamines, and drugs for erectile dysfunction have been developed)[2].

Recently, mouth dissolving film (MDF) is one of the most extensively used marketable product because of its quick onset of action, fast dissolution, and fast disintegration in a few seconds'. Therefore Mouth dissolving film is also widely used as local anesthetics for toothaches, headache, body pain, migraine, hypertension, oral ulcers, cold sores and treatment of psychological

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Synthesis of mesoporous alumina: an impact of surface chemistry on release behavior

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ABSTRACT

The present investigation describes the successful synthesis of mesoporous alumina (MeAl) nanoparticles for controlled drug delivery *via* a soft template route have been adopted using hexadecyltrimethyl ammonium bromide as template and aluminum chloride as precursor. The obtained Langmuir type II isotherm for MeAl showed P/Po 0.1 at 10 cm^3/G STP. The Brunauer-Emmett-Teller study revealed the formation of uniform morphology and mesoporous structure. The fourier transform infrared spectroscopy study confirmed the presence of characteristic peaks of mesoporous alumina. Elemental analysis demonstrated the substantial Al and O peak supported with nanosized crumb with cluster by field emission scanning electron microscopy. The transmission electron microscopy indicates wormhole strikingly inter connected pore system assigned to functionalized MeAl. X-ray diffraction pattern suggests the formation of γ-Aluminum oxide. The particle size and surface charge of synthesized MeAl were successfully analyzed to assess the surface charge. The drug loading was confirmed by spectroscopic study with eloquent extension in drug release was found to be 74.44% attributed to release by control manner. In present study, synthesized MeAl holds an excellent compassionate impact on particle size and exterior chemistry for sustained release of model drug.

KEYWORDS

Mesoporous; FESEM; adsorption; functionalization; particle characteristics

1. Introduction

Mesoporous Alumina (MeAl), a novel member of molecular sieve family kindled worldwide resurgence in the field of inorganic solid mesoporous materials. Porous material plays fundamental role in a variety of scientific and industrial operations such as adsorption, separation, host-guest encapsulation and catalysis etc (Liu et al. 2013). The architecture and remarkable properties of unique mesoporous structure of MeAl have fascinated ample attention in the former decades due to promising biomedical applications and rapid expansion in an area such as tissue engineering, DNA sequencing, photonics etc (Zhang et al. 2009; Biumen, Cheng, and Ramos 2007). In consonance to International Union of Pure and Applied Chemistry (IUPAC), pores are categorized as micropore, mesopore and macropore depends on their varying particle sizes(<2 nm, between 2 nm and 50 nm,> 50 nm) (Zdravkov et al. 2007). The nature of porous material may be inorganic, organic or possesses both properties with technological significance. The porous material represents capability to link with atoms, molecule or ions to load the solid, liquid or gaseous chemical entities (Zhao 2006). Based on above dominance, mesoporous material emerged as talented host for extensive range of companion molecules like proteins (Vinu et al. 2004; Vinu, Murugesan and Hartmann 2004) drugs (Regi, Ramila and Del 2001) and smaller biological molecules(Anderson, Rosenholm and Areva 2004). Conventionally, High-surface-area transition alumina or activated alumina have been used as a porous alumina. However, the limited performance of MeAl identified may be due to deactivation during catalysis have been by pore plugging or coke formation in micropores. Therefore, the requirement was to synthesize alumina having ordered, uniform and tunable pore diameter. Thus, the successfully synthesized alumina showed remarkable properties such as controlled porosity, high thermal and mechanical stability, chemical inertness and tunable surface chemistry has made MeAl as excellent host for large drug loading and controlled release in an area of biomedicine (Kim et al. 2003; Ramli and Saleh 2008). The swift evaluation of sol-gel approach during former two decades has drive electric breakthrough in deliberate synthesis of porous materials. Sol-gel is an inexpensive method serves straightforward tailor substitute for traditional synthesis method. In comparison to traditional procedure, this lenient method provides outcome of mixed oxides with low cost and enhanced homogeneity. The sol-gel method produced

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Fabrication and characterization of colon specific eudragit coated graphene oxide microsphere for sustained delivery of tramadol hydrochloride

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ABSTRACT

Present investigation reports a straight forward method for synthesis of graphene oxide (GO) followed by fabrication of graphene oxide microsphere (GMS) using water in oil (w/o) emulsification technique. For colon specific drug delivery, enteric coating is desirable, which was done using Eudragit S100 and characterized by Fourier transform Infrared Spectroscopy (FTIR). The surface morphology of fabricated microsphere was confirmed using scanning electron microscopy (SEM). Drug loaded microspheres demonstrated a high payload capacity for model drug tramadol hydrochloride (TmH). The comparative *In-vitro* drug release showed around 72.37% release from uncoated microspheres, whereas eudragit coated microspheres retarded the drug release upto 10 h.

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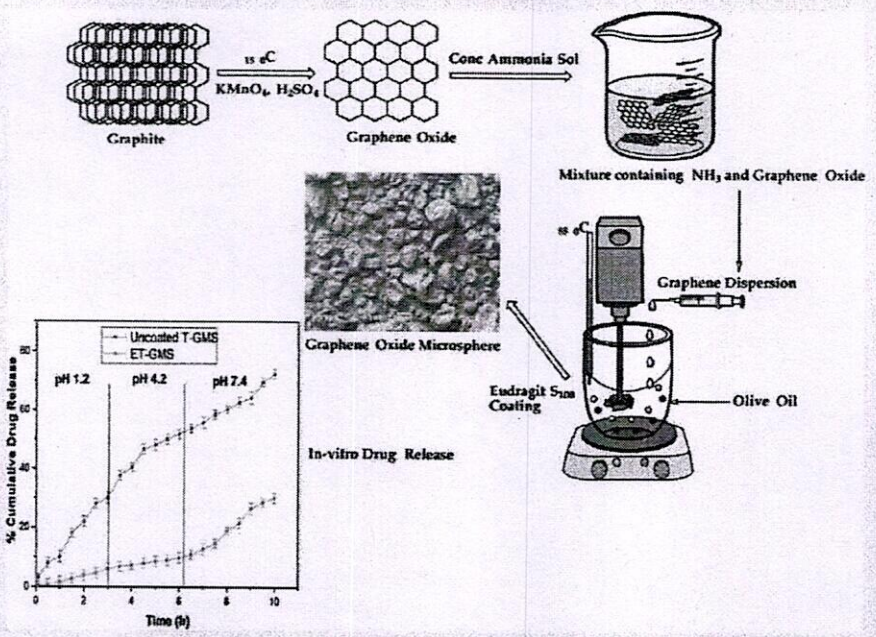
Graphene oxide; microsphere fabrication; colon targeted drug delivery system; irritable bowel disease



1. Introduction

An inflammatory Bowel disease (IBD) intensifies in many traumatic conditions such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, etc. Specifically, IBD is most common functional disorder in colon region.[1] Due to many transportation barriers such as acid reach environment in stomach, differential pH condition and larger micro flora in small intestine, therapeutic agent is unable to reach at the colon site.[2] It seems to be very difficult for

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lpte.

SYNTHESIS AND CHARACTERIZATION OF THIOLATED GUM KONDAGOGU AND EVALUATION AS MUCOADHESIVE POLYMER

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ABSTRACT

Present work focused on thiolation for enhancing the mucoadhesive potential of Gum kondagogu (GK). Thiolation of GK was done by esterification process with 80 % thioglycolic acid in presence of 7N HCl. Thiolated Gum kondagogu (ThioGK) was determined to possess 1.59 ±0.04 mmol of thiol groups/g of the polymer by Ellman's method. ThioGK was characterized by FTIR, NMR, DSC, XRD, and FE-SEM. The tablets were prepared by direct compression using 75 mg of ThioGK and GK. Tablets containing ThioGK (F1) and GK (F2) were subjected to evaluation of weight variation, hardness and friability and show enhanced disintegration time, swelling behavior, drug release and mucoadhesion. *In vitro* drug release of batch F1 exhibits complete release of drug in 24 hr with zero order release kinetics. Comparative mucoadhesive strength was studied using chicken ileum by texture analyzer and revealed higher mucoadhesion of tablet containing ThioGK. From the above study, ThioGK was suitability exploited as mucoadhesive sustained release matrix tablet.

Keywords: Thiolated gum kondagogu, Mucoadhesive study, Diclofenac sodium, Ellman's method.

INTRODUCTION

Tree gums are natural polymers and are, in recent times receiving consideration as biopolymers since they are non-toxic, inexpensive, simply obtainable, readily improved, environmentally friendly and biocompatible[1]. In the food and pharmaceutical industry, these natural polymers have a number of applications[2]. Gum kondagogu (GK) is an important forest produce of Andhra Pradesh, India, which is collected by tribals by tapping from the tree of *Cochlospermum gossypium* DC (Family: Bixaceae). GK is belonging to substituted rhamnogalacturonans class, which is an anionic polysaccharide. It includes rhamnose, galacturonic acid, glucuronic acid, β-d-galactopyranose, α-d-glucose, β-d-glucose, galactose, arabinose, mannose and fructose with sugar linkage of (1→2) β-d-Gal p, (1→6) β-d-Gal p, (1→4) β-d-Glc p, 4-O-Me-α-d-Glc p, (1→2) α-l-Rha[3]. It absorbs a large quantity of water by developing thixotropic gels and in the course of previous studies, for it has been discovered as sustained release matrix tablets[4], as emulsifying agent[5], as a completely green synthesis of noble metal nanoparticles[6], for the green synthesis of silver nanoparticles with antibacterial application[7], for the mucoadhesive microcapsule preparation in combination with sodium alginate[8], Modification of release behavior of gum kondagogu has been executed by carboxylation on gum kondagogu polymeric backbone[9]. GK has been used with other polymers in combination, such as gum olibanum and guar gum as a mucoadhesive polymer since it alone cannot promise residence of a drug delivery system (DDs) at the desired site[10]. Till date, several drug delivery systems have been designed using mucoadhesive polymers.

The adhesive property of these natural polymers is the cause of their capability to form noncovalent bonds such as van der Waal's interaction, hydrogen bond and ionic interaction. But, because of such weak interaction, DDs cannot remain at a target site for an extensive period of time[2,11]. This demands the exploration of novel mucoadhesive polymers. Thiolated polymers have been show to form a class of novel mucoadhesive polymers. Various natural polymers such as karaya gum[2], chitosan[12-14], pectin[15], xyloglucan[16], tamarind seed polysaccharide[1], hyaluronic acid[17] and xanthan gum[18] have been improved by thiol immobilization on polymer to increase their mucoadhesive properties.

In the current study, the chemical modification of gum kondagogu has been carried out by thiolation. The characterization of thiolated gum kondagogu was carried

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Fabrication of efavirenz loaded nano-formulation using quality by design (QbD) based approach: Exploring characterizations and *in vivo* safety

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ABSTRACT

Quality by design (QbD) approach was practically applied in fabrication of nanostructured lipid carrier (NLC) encapsulating efavirenz (EF) to ensure the quality in product. Initially, risk factors were categorized based on risk priority number (RPN) using risk identification and assessment tools. A central composite rotatable design (CCRD) was employed to assess the influence of critical process parameter (CPP) (pressure of high pressure homogenizer) and critical material attributes (CMAs) (combination of solid lipid and oil; combination of stabilizers) on responses such as particle size, dispersity and entrapment efficiency. ANOVA was applied to evaluate the data for confirmation of statistical significance ($p < 0.05$). The optimum formulation was decided by setting criteria of responses to achieve desired quality product. This formulation was subsequently lyophilized to evaluate solid state characterization. TEM shows spherical particle shape of NLC. The transformation in amorphous state of NLC from crystalline EF was observed by DSC and PXRD. Lack of molecular interactions and intermolecular hydrogen bonding with lipidic atmosphere revealed by FTIR and ^{1}HNMR respectively. *In vitro* drug release 91.21% was obtained at the end of 24 h with Higuchi-matrix mechanism. *In vivo* pharmacokinetic studies improved relative bioavailability 2.95 fold with lower liver toxicity of EF encapsulated in NLC. In conclusion, QbD based approach clearly proved its usefulness to build quality in product resulting high drug encapsulated potential nanocarrier to enhance bioavailability and confirms safety of EF-NLC with promising acceptable criteria.

1. Introduction

Efavirenz (EF) is a leading drug molecule in the regimen of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV). Orally active EF was official by FDA in 1998, belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) mostly prescribed to treat HIV-1 infection [1,2]. However, its pharmacokinetic is unpredictable when taken orally. This could be due to poor aqueous solubility, low gastro-intestinal (GI) absorption and rapid first-pass metabolism disappointing *in vivo* pharmacokinetic results [3]. Moreover, it is highly lipophilic (Log P = 5.4, intrinsic water solubility = 3–9 μg/mL) drug and categorized in biopharmaceutical classification system (BCS) class II (i.e. poor solubility and high permeability) results in low oral bioavailability of 40–45% [4,5]. The development of hepatotoxicity due to prolong administration is another increasingly important issue limiting the clinical applications [6–8].

Therefore, there is necessitate to develop a strategy which modulates to improve solubility and bioavailability issues of EF. The few works on such issues have been reported. For example, EF loaded nanoemulsion improved bioavailability with dosage adjustable formulation for HIV therapy [9]. Nanosuspension containing EF prepared and characterized β-cyclodextrin (β-CD) based polymeric nanosuspension (PNS) to enhance aqueous solubility and dissolution rate as compared to pure drug [10,11]. The optimized Eudragit E100-Efavirenz loaded polymeric nanoparticles developed to increase in dissolution, drug distribution, and bioavailability, which ultimately implies better control over the therapeutic dosing; and physicochemical evaluation confirmed the formulation stability of nanoparticles [12,13].

SLNs prepared for lymph targeting delivery system to understand chylomicron blocking mechanism approach [14], and NLCs engineered for brain targeted delivery through intranasal route [4]. However, no reports have been addressed on issues of hepatotoxicity which develops on prolong oral administration of EF. Therefore, our prime objective was to develop the EF loaded NLCs to augment biopharmaceutical properties.

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Aloin protects against arsenic trioxide–induced myocardial membrane damage and release of inflammatory cytokines

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Abstract

Aloin exerts concentration-dependent pro-oxidant and antioxidant effects when tested in vitro. Such duality of effects has not been investigated through in vivo studies on aloin. We evaluated the effects of aloin at doses ranging between 1 and 125 mg/kg against the arsenic trioxide (As_2O_3)–induced cardiotoxicity in mice. As_2O_3 (5 mg/kg/day) was intraperitoneally administrated for 10 days. Aloin was administered through oral gavage at 1, 5, 25, and 125 mg/kg/day. As_2O_3 induced rise in ST height and QT interval in ECG, increased oxidative stress, and depleted the antioxidative defense. As_2O_3 increased inflammatory cytokine concentrations in the heart. Aloin dose dependently inhibited the As_2O_3-induced cardiotoxicity. There was no evidence of increased oxidative stress in the low-dose aloin-treated mice receiving As_2O_3. Our results indicate that aloin possesses cardioprotective potentials and its pro-oxidant effect is not evident in vivo at tested doses.

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Heterogeneous surface architectured metal-organic frameworks for cancer therapy, imaging, and biosensing: A state-of-the-art review

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ABSTRACT

With recent progress in inorganic material based nanoplatforms for cancer therapy and imaging, multiple nano vehicles have been developed and evaluated. These recent advancements in material science led to the development of metal organic frameworks (MOFs) and nano MOFs (nMOFs) as the potential and versatile delivery platforms for cancer theranostic. With a vast amount of ongoing research on MOFs, various surface architectured MOFs for with variable properties have been developed and tested. The concept of subcellular targeted therapy of cancer has also been employed using MOFs which demonstrated significantly enhanced anticancer therapy. These MOFs have been developed in a way to provide them stimuli-responsive drug release property which can be utilized for externally guided therapy of cancer. Apart from cellular and subcellular targeted platforms and stimuli-responsive platforms, MOFs have also been explored in the field of bioimaging and biosensing. Multiple types of biosensing platforms based on MOFs and nMOFs have been proposed for biosensing of biomolecules related to cancer for sensing and early detection. The bioimaging probes based on MOFs have been employed for multiple diagnostic platforms. The review gives the recent updates for the abovementioned topics along with the toxicity aspects of MOFs for human use. The review overall gives a detailed overview of research done to date in the field of MOFs based nanoplatforms for cancer theranostics.

Contents

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Research Article

Agro-Industrial Waste-Mediated Green Synthesis of Silver Nanoparticles and Evaluation of Its Antibacterial Activity

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Abstract

The development of immaculate etiquette for the green and rapid synthesis of Ag NPs with a natural reducing agent is the spearhead of the expanding field of nanotechnology. Different scientific fraternity with novel natural reducing agents has been contributing numerous strategies daily. Though there is a submerging of many natural reducing agents, still there are plenty of natural precursors remained to be explored. In this research, we fruitfully attempted the synthesis of silver nanoparticles using agro-food industrial waste *Tamarindus* indica shell-husk extract (TSE) as a natural reducing agent. The prepared silver nanoparticles and their stability in different pH were investigated using ultraviolet-visible spectroscopic analysis. Morphological characters were examined using scanning electron microscope (SEM) and transmission electron microscopy (TEM) analysis. The structural and elemental compositions were depicted by Fourier-transform infrared spectroscopy (FTIR) and energy-dispersive X-ray (EDX) analysis, respectively. Moreover, we emphasized on the molecular mechanism involving in the TSE mediated synthesis of Ag NPs. The inherent antimicrobial activity was investigated using agar plate method against both gram-positive and gram-negative species with gentamycin as a control standard for comparison.

Keywords: Green synthesis of Ag NPs; Tamarinds shell-husk extract; Effect of pH; One-pot synthesis; Antimicrobial activity

Introduction

In the recent era, nanobiotechnology has benediction the advantages of the synthesis of nanostructures using living organisms such as plant and microbes. Plant-mediated synthesis of nanoparticles could be advantageous over additional environmentally benevolent biological processes as it eliminates the process involving toxic chemicals and reactants. Biosynthetic processes for nanoparticles would be more expedient if nanoparticles are produced extracellularly using plants or their extracts and in a controlled manner according to their size, dispersity, and shape [1]. Plant-mediated biological synthesis of nanoparticles is gaining significance due to its ease and eco-friendliness. Biosynthetic processes would be more useful if the silver nanoparticles (Ag NPs) were produced using plants or their extracts in a controlled approach according to their dispersity, shape, and size [2]. Although it is a well-known fact

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ORIGINAL ARTICLE

Development of amine-functionalized superparamagnetic iron oxide nanoparticles anchored graphene nanosheets as a possible theranostic agent in cancer metastasis

Mahesh P. More[1,2] · Prashant K. Deshmukh[1]

Abstract
The major objective of the present investigation was to assess the targeting potential of a designed system for breast cancer at metastatic phases with imaging ability. In a nutshell, we have developed surface-engineered graphene oxide (GO) nanosheets by covalent linking with amine-functionalized iron oxide nanoparticles (IONPs) (GOIOIs). Gefitinib (Gf) was selected as a model drug and entrapped in between exfoliated GO sheets (GOIGF) via π-π* stacking before functionalization with IONPs. Preliminary characterization of GO, IONPs, GOIOI, and GOIGF was performed using UV-visible and Fourier transform infrared spectroscopy. Scanning and transmission electron microscopy studies confirmed successful surface engineering of GO with IONPs. The in vitro drug release study demonstrated sustained release of Gf. The magnetic behavior of IONPs and GOIOI demonstrated a sigmoidal-shaped hysteresis loop with superparamagnetic properties. The in vitro cell cytotoxicity assay was carried out on MDA-MB-231 breast cancer adenocarcinoma cell lines. The cell cytotoxicity assay showed 61.18% inhibition of cell growth with 30 ppm concentration containing 64% of the drug, whereas 100% of the pure drug revealed only 56% of inhibition. In the near future, GOIOI could be tailored further for theranostic research, especially for metastatic cancers.

Keywords Carbodiimide chemistry · Gefitinib · π-π* stacking · MDA-MB-231 breast cancer adenocarcinoma cell lines · Magnetic graphene · Drug delivery

Introduction

Cancer is the most devastating disease in human; one out of six deaths is because of cancer, and the estimated death count may increase up to 13.1 million by 2030. It is the major cause of morbidity and mortality at present. In females, breast cancer is the leading site of cancer followed by cancer of the cervix and uteri [1].

Chemotherapy [2], gene therapy [3], radiotherapy [4], surgery [5], photodynamic [6], photothermal therapy [7], hyperthermia [8], or a combination thereof have been used for the treatment of cancer. Unfortunately, no effective therapy could successfully eradicate cancer to date. Theranostic nanomedicine is the latest approach under investigation, which could systemically provide simultaneous diagnosis and treatment at a specific site of infection. This could avoid interaction with normal cells, and only cancer tumor cells get destroyed using suitable carrier molecules [9]. The survival rate in cancer patients was dismal from 5 to 15% from developing to developed countries, respectively. Mutation of cancer cell specifically in the epidermal growth factor can be characterized to identify 50% of adenocarcinomas [10].

With the emergence of 2D materials, graphene has gained attention for its use in various biomedical applications including cancer. Graphene is an allotrope of carbon in the form of a single layer of atoms in a two-dimensional hexagonal lattice in which one atom forms each vertex [11, 12]. There are numerous methods available for the synthesis of graphene oxide (GO), an oxidized counterpart of graphene such as mechanical

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Original Article

Robust Analytical Method for Iron Estimation by Experimental Design Approach

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ABSTRACT

Aim: To perform Iron estimation by UV-Visible spectroscopy using an Experimental design approach. **Objectives:** The robust analytical method was developed for the estimation of iron (III) using 1, 10-phenanthroline reagent. **Methods:** The analytical method is an exploration of the chemical reaction of iron with 1, 10- phenanthroline reagent to form a colored complex which was measured in the UV-Visible region at 509 nm. To monitor the effect of diverse factors like the concentration of reagent (A), volume of reagent (B), pH (C) and time (D) on the formation of iron 1, 10 – phenanthroline complex the full factorial design (two-level) was used. From the Pareto chart, Normal plot and half normal plot, it was studied that a combination of all factors was initiate to be significant. Then significant variables are optimized by response surface methodology (RSM) via Box-Behnken design. The evaluation of design was performed to study the effect on the selected response by quadratic effects and main interaction effects. The contour plot and surface plot used for the determined response of the selected factors for their optimum value. **Results:** The prime reaction state, Beer's law were obeyed in 2.0-10.0 μg/ml concentration range with a correlation coefficient of 0.998. **Conclusion:** The method was successfully applied for the estimation of iron in iron sucrose injection. The optimized method was used for the quantitative analysis of iron sucrose injection.

Key words: Iron sucrose, 1, 10- Pheanthroline, Full factorial design, Box-Behnken design.

INTRODUCTION

Iron is necessary for oxidative metabolism, wound healing, reproduction, cellular growth, execution of several metabolic processes.[1] Iron is employed in the production of oxygen-carrying hemoglobin, myoglobin and proteins which are required for the basic metabolic process in the cell.[2] Iron deficiency anemia are the most frequent forms of nutritional deficiency generally, anemia is distinct as decrease of hemoglobin value.[3] It possesses severe health complications as it causes general weakness, laziness, tiredness, sub-optimal work performance and in certain circumstances psychological obstruction, reduced aptitude and atypical immune response.[4] Optimization states to improving the routine of a method, a practice, or produce to get the highest output from it. The term optimization has been generally used in analytical chemistry as a means of determining situations at which to apply a process that creates the best probable response.[5]

The experimental design is a statistical technique utilized for planning, analyzing and statistical data obtained from primary investigational trials. The experimental design gives exhaustive information from the lowest numeral of trials. Identification of interacting variables characterized the effect of critical factors, evaluation of the effect of preparation and system factors on critical quality attributes.[6]

The conventional optimization approach, varying one variable/factor at a time (OVAT, also called OFAT).[7] One factor at a time (OFAT) does not include interactive outcomes between the variables deliberate as a consequence. OFAT does not include the comprehensive effects of a factor on

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Medicinal Chemistry & Drug Discovery

Exploring Quinazolinones as Anticonvulsants by Molecular Fragmentation Approach: Structural Optimization, Synthesis and Pharmacological Evaluation Studies

Vinod G. Ugale,*[a] Sanjay B. Bari,[b] Saurabh C. Khadse,[a] Pedavenkatagari Narayana Reddy,[c] Chandrakant G. Bonde,[d] and Prashant J. Chaudhari[a]

In recent years, design and synthesis of anticonvulsants effective against multiple seizures has attracted much attention of medicinal chemists. In an attempt to find novel anticonvulsants, herein we have reported structurally optimized sixteen different substituted quinazolinones explored through molecular fragmentation approach. The anticonvulsant activity of synthesized compounds was assessed by using predictable seizure models in mice. Two most promising analogues **8d** (ED_{50} = 35.1 mg/kg, MES, mice, *i.p.*; ED_{50} = 41.5 mg/kg, *sc*PTZ test, mice, *i.p.*) and **8l** (ED_{50} = 21.2 mg/kg, MES, mice, *i.p.*; ED_{50} = 32.4 mg/kg, *sc*PTZ test, mice, *i.p.*) exhibited broad spectrum anticonvulsant action in preclinical models of seizures. Compound **8l** was also shown profound activity against pharmacoresistant limbic seizures produced in 6 Hz test. Most of the synthesized molecules exhibited moderate to high anticonvulsant activity in all seizure models with no symptoms of neurotoxicity and hepatotoxicity. We have also used *in-silico* protocol for prediction of physiochemical and pharmacokinetic properties of synthesized quinazolinones. The promising anticonvulsant activity of synthesized analogues, *ex-vivo* toxicity, *in-silico* molecular docking, physiochemical and pharmacokinetic predictions make us to anticipate emergence of synthesized quinazolinones as valid leads for the treatment of convulsive disorder.

Introduction

Epilepsy is a grievous and chronic neurological disorder affecting over 65 million individuals worldwide.[1] An epileptic seizure is abnormal, excessive or synchronous neuronal activity in the brain.[2] Around 1% of world population at any time is afflicted by epilepsy. This number increases every year by about 2.4 millions.[3] Antiepileptic drugs (AEDs) therapy is mainstay of treatment for many patients with epilepsy. Development of new AEDs resulted into increased treatment options for patients with epilepsy but making drug selection a more complex task.[4] Despite decades of research, it is still not clearly understood how AEDs act to control seizures. Unfortunately, at a present time, there are no AEDs that are significantly effective at different forms and degrees of convulsive disorders.[5]

Ligand based and random screening protocols have been used by many medicinal chemists to design and synthesize potential anticonvulsants.[6–7] Due to insufficient knowledge and complex pathogenesis of human epilepsy; it is difficult to develop novel AEDs using routine methodologies. Ligand based protocol for design of anticonvulsants is focused on utilization of pharmacophores present in clinically effective and reported AEDs.[8–9] Methaqualone and its synthetic analogues proved as good anticonvulsants. The chloro analogue of methaqualone has shown 1.5 times more potency than phenytoin in MES test and 10 times more efficacy than troxidone in *sc*PTZ model.[6,10–12] Some of the potent anticonvulsants with quinazolinone nucleus are depicted in Figure 1. The substitution of quinazolinone by electron withdrawing halogens at 6th, 7th or 8th positions resulted derivatives with optimum anticonvulsant activity and lower toxicity than phenytoin.[12–13] Ralitoline is a recently reported AED, found effective in both MES and kindling models of seizures with rodents.[14] Ralitoline has *N*-(2,6-dimethylphenyl)acetamide as pharmacophoric fragment and shown paramount importance in anticonvulsant potency. Retigabine is an anticonvulsant (ezogabine) approved by the United States Food and Drug Administration (USFDA) and/or by the European Medicines Agency (EMA) in 2011. Retigabine consists of *N*-(2-aminophenyl)acetamide fragment as critical part of its structure and have vital role in its anticonvulsant activity.[15] Careful incorporation of these pharmacophoric fragments from reported potent anticonvulsants into designed molecules may boost

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Topical Review

Recent advancements in bioprecursor derived graphene quantum dots: synthesis, characterization and toxicological perspectives

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Abstract

Graphene quantum dots (GQDs), impressive materials with enormous future potential, are reviewed from their inception, including different precursors. Considering the increasing burden of industrial and ecological bio-waste, there is an urgency to develop techniques which will convert biowaste into active moieties of interest. Amongst the various materials explored, we selectively highlight the use of potential carbon containing bioprecursors (e.g. plant-based, amino acids, carbohydrates), and industrial waste and its conversion into GQDs with negligible use of chemicals. This review focuses on the effects of different processing parameters that affect the properties of GQDs, including the surface functionalization, paradigmatic characterization, toxicity and biocompatibility issues of bioprecursor derived GQDs. This review also examines current challenges and the ongoing exploration of potential bioprecursors for ecofriendly GQD synthesis for future applications. This review sheds further light on the electronic and optical properties of GQDs along with the effects of doping on the same. This review may aid in future design approaches and applications of GQDs in the biomedical and materials design fields.

Keywords: bioprecursor, quenching, GQDs, graphene, functionalization of GQDs, hetero-atom doping, fluorescent material

(Some figures may appear in colour only in the online journal)

1. Introduction

With recent advancements in materials sciences and advanced materials, research on the cost of the effective synthesis of materials has gained a lot of attention. Graphene is one of the most celebrated and fascinating 'wonder materials' and is investigated by many branches of science. The graphene family includes graphene, graphene oxide (GO), reduced graphene oxide (rGO) and graphene quantum dots (GQDs). Graphene-based nanomaterials generally exist as

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ORIGINAL ARTICLE

Perspectives of characterization and bioconjugation of gold nanoparticles and their application in lateral flow immunosensing

Vivek B. Borse[1] · Aditya N. Konwar[1] · Rahul D. Jayant[2] · Pravin O. Patil[3]

Abstract

Gold nanoparticles (AuNPs) are an important component in the field of biomedical diagnostics. Because of its unique physico-chemical properties, AuNPs have been widely used in biomedical applications such as photothermal cancer therapy, drug delivery, optical imaging, labeling, and biosensing. In this review, we have described synthesis and characterization techniques for AuNPs with recent advancements. Characterization of AuNPs has played an important role in directing its application in various fields and elaborated understanding of its functioning. The characterization techniques used for the analysis of AuNPs utilize its intrinsic properties, such as surface plasmon resonance (SPR) and size-dependent shift in absorption. These properties of AuNPs are furthermore used for the characterization of bioconjugated AuNPs. Surface conjugation of the AuNPs with biomolecules is explored widely for its use in numerous biosensing applications. Biosensor-based diagnostic devices use AuNPs conjugated with a sensing probe for the detection of a specific analyte. AuNPs are also commonly used as a colorimetric sensor in various point-of-care diagnostic techniques. Lateral flow immunosensing (LFIS) technique utilizes AuNPs for the rapid and sensitive detection of various analytes. LFIS is a paper-based detection technique, where the sample containing the analyte flows through the membrane, interacts with immobilized counterparts, and produces results using a detection probe. AuNPs are used as color markers in LFIS, and the presence of an analyte is indicated by the appearance of colored lines on the membrane. The color is a result of the accumulation of AuNP complexes containing the analyte and probe. Effect of characterization parameters of AuNPs on the sensitivity of LFIS, advantages, and disadvantages of using AuNPs for LFIS are discussed concerning the recent reports. Recent applications of AuNPs in LFIS development for the detection of various biomarkers are summarized comprehensively in the table. The review may offer significant insight into the utility of AuNPs for application in the LFIS technique for future development.

Keywords Gold nanoparticles (AuNPs) · Characterization · Bioconjugation · Lateral flow immunosensing (LFIS) · Diagnostics

Introduction

Nanotechnology is a comparatively new field in research which has been emergent since its introduction as a separate but interdisciplinary subject. Nanomaterial has characteristic properties, which are attributed to its small size and quantum effects. Special physical and chemical properties include high surface to volume ratio, different optical properties from their bulk counterparts, surface plasmon resonance, photothermal effects, fluorescence emission, etc. These unique physical and chemical properties of nanomaterial have enabled their use in a variety of applications such as optical imaging, cancer therapeutics, medical diagnostics, and drug delivery as shown in Fig. 1 [1–9]. The nanomaterial is fabricated using a variety of components, among which metal nanoparticles have gained much importance. Gold nanoparticles (AuNPs) have been proved to be useful for imaging, cancer therapy, and drug delivery [10, 11]. AuNPs have been used for the development of electrochemical immunosensors for detection of Zika virus proteins [12]. Iron nanoparticles, i.e., iron oxide nanoparticles, have been used as nanocarriers to encapsulate anti-HIV drugs

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Central composite design-based optimization of lopinavir vitamin E-TPGS micelle: *In vitro* characterization and *in vivo* pharmacokinetic study

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ABSTRACT

This study was aimed at formulating Lopinavir loaded Vitamin E-TPGS micelles to enhance its oral bioavailability. Lopinavir is an HIV-1 protease inhibitor with low aqueous solubility leading to poor oral bioavailability and thus frequent dosing. Drug loaded micelles were fabricated using thin film hydration technique and optimized by two-factor five-level central composite design. For this purpose independent variables selected were TPGS to drug ratio and rotational speed of rotary evaporator, whereas dependent variables chosen were particle size and % entrapment efficiency. The effect of an independent variable on the dependent variable was studied by generating a quadratic polynomial model. Results of *in vitro* characterization showed that prepared lopinavir micelles exhibited particle size 91.71 nm, polydispersity index 0.129, zeta potential −24.8 mV, entrapment efficiency 99.36 ± 1.06% and drug loading 20.83 ± 1.23%. Results of DSC and P-XRD evaluation revealed that drugs were successfully encapsulated inside the Vitamin E-TPGS micelles. *In vitro* release studies displayed enhancement in drug dissolution as a result of its loading into micelles. TEM images showed that micelles were spherical. On oral administration of lopinavir micelles; the relative bioavailability was boosted by 3.17 folds compared to lopinavir suspensions. Thus, we can conclude that TPGS based micelles possess the prodigious potential to overcome the challenges of current HAART therapy.

1. Introduction

Based on statistics given by the Joint United Nations Programme on HIV and AIDS of the year 2018, nearly 3.79 crores individuals globally are surviving with HIV/AIDS. Out of these 18 lakhs were children of less than 15 years of age. With a rate of 5000 new infections per day about 17 lakhs people universally newly developed HIV infection [1]. Human immunodeficiency virus also abbreviated and commonly known as HIV is a lentivirus. It causes HIV infection which ultimately causes AIDS (Acquired Immunodeficiency Syndrome). AIDS is a condition where the human immune system progressively fails allowing life-threatening opportunistic infections and cancers to conquer the body. It is estimated that normal lifetime post-HIV infection is 9–11 years, based on the HIV subtype [2]. Therefore, an HIV patient needs constant antiretroviral therapy throughout life. This regimen of anti-HIV medication is commonly known as HAART (Highly Active Anti-Retroviral Therapy), which includes a combination of three or more different antiretroviral drugs. Although a complete cure for HIV does not exist, this treatment slows the progression of the virus in the body by reducing the viral titer in body fluids [3]. Thereby conserving the immune system strength and averting opportunistic infections that may cause death [4].

Lopinavir (LPV) is chemically designated as (2S)-N-[(1S,3S,4S)-1-benzyl-4-([(2,6-dimethyl phenoxy)acetyl]amino)-3-hydroxy-5-phenylpentyl]-3-methyl-2-(2-oxotetrahydropyrimidin1 (2H)-yl) butanamide. It is an integral part of the HAART program. But LPV suffers a major drawback *i.e.*, poor bioavailability due to its poor water solubility and cytochrome P450 as well as P-glycoprotein efflux mediated hepatic first-pass metabolism [5].Thus it is used in combination with ritonavir with the trade names Kaletra® and Aluvia®. Therefore there is a need to develop antiretroviral drug formulation with enhanced bioavailability to improve HAART therapy. Lopinavir and ritonavir both are antiretroviral drugs that are used in combination. Ritonavir is just used as a booster dose for other protease inhibitors and does not have significant antiretroviral activity against HIV and hence it is not prescribed for treatment now a day. It just helps to enhance the bioavailability of Lopinavir. Since after loading into nanocarrier bioavailability of Lopinavir will get enhanced significantly therefore there is no need to use

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Review Article

A comprehensive review on carbon dots and graphene quantum dots based fluorescent sensor for biothiols

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ABSTRACT

Fluorescent carbon-based nanomaterials such as carbon dots (CDs) and graphene quantum dots (GQDs) owing to their high aqueous solubility, stable photoluminescence and good biocompatibility are showing greater interest in sensing of biothiols. Biothiols mainly glutathione (GSH), cysteine (Cys), homocysteine (Hcys), considered to be an important tool in the clinical diagnosis of many disorders and diseases. Therefore, the development of new probes has fascinated considerable attention since they are simple, sensitive, rapid and cost effective. Although conventional sensors have been designed and widely applied in biothiols determination, but unfortunately they present many limitations and challenges. In this review, we provide a focused outline on the most recent developments concerning fluorescent based CDs and GQDs nanosensor for detection of biothiols. The most important reaction mechanisms and strategies for detection of biothiols were outlined and compared in terms of their sensitivity and selectivity against different biothiol species and other interfering substances viz. metal ions, amino acids, etc. Future research and challenges in designing of functionalized CDs and GQDs are discussed and elucidated.

1. Introduction

Nanomaterials are the candidates responsible for making breakthroughs in nanotechnology. Over the last two decades, a variety of nanomaterials have been found and evolved as, CDs and GQDs. Quantum effects provide unique features to these nanomaterials when the size of a material reduces to the nanometer range, which failed to predict at macroscopic or microscopic level. As a result, these nanomaterials enhanced the capabilities of researcher to focus on sensing of a variety of materials which could not have been possible with other conventional materials [1]. Nanoparticles are always attributed with the novel properties irrespective of origin [2]. Evolution of the unique physical, chemical and electronic properties at the nanoscale forms the essence of the various applications of nanotechnology [3].

The interplay between the nanomaterials and biological systems for human health concern is of special significance, especially for the CDs and GQDs which have diverse imaging and sensing applications. Biomedical research has become extremely important from past two decades due to human health concern. Biosensing includes qualitative/quantitative recognition of a specific type of analytes by characterizing spectroscopic, electrochemical and photoluminescence behavior of the systems. Most prominently, various biomolecules viz. proteins, nucleic acids, enzymes and chemical analytes e.g., organic metals, inorganic metals and sugars that help in monitoring the biochemical processes can be detected.

1.1. Fluorescent nanomaterials

Fluorescent nanomaterials *viz.* CDs, metallic nanoclusters, silicon, metallic nanocomposites, and GQDs immensely revolutionized the field of biosensing and bioimaging [4], however promising CDs [5] and GQDs [6] are attracting increasing attention owing to their high aqueous solubility, low cytotoxicity, stable photoluminescence and better biocompatibility.

1.2. Graphene quantum dots (GQDs)

In recent years, GQDs have gained considerable interest in biosensing and cell imaging applications with other potential applications in diverse areas of the medical and pharmaceutical field [7] owing to their distinctive and remarkable quantum confined electronic state and unique edge structure effect, physicochemical properties [8], fascinating optical properties, high photostability, non-toxicity, biocompatibility and nanometer lateral size [9]. GQDs exhibit excellent photoluminescence properties that can be influenced by structural defect and surface functionality such as heteroatom doping [10].

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