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Ultrasonic frequency based development of chrysin nanoparticles: assessment of bioavailability, anti-cancer activity and stability

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ABSTRACT

In present investigation, we are the first to report ultrasonic frequency based development of chrysin nanoparticles (CNPs) with special emphasis on bioavailability, anti-cancer activity and stability assessment. The CNPs were developed by modifying processing parameters to get an optimum nanonization effect. Chrysin (CHR), being a member of flavonoid class, has a strong proven therapeutic value but poor solubility and bioavailability restrict its use as a therapeutic agent. Developed CNPs were evaluated for various physicochemical and performance characteristics like DSC, XRPD, FE-SEM, TEM, particle size, polydispersity index (PDI), zeta potential, production yield, solubility, *in vitro* dissolution, *in vivo* bioavailability and stability study. Oral bioavailability study revealed 2·3-fold increase in relative bioavailability of CNPs compared to pure CHR. *In vitro* cytotoxicity study demonstrated promising cytotoxic effect towards MCF-7 human breast cancer cell line. Developed CNPs demonstrated acceptable particle size and zeta potential indicating significant stability, which was further confirmed by stability assessment. The present study suggests that natural flavonoids like CHR could demonstrate potential cytotoxicity when subjected to nanonization and may prove beneficial as a natural economic alternative to expensive chemotherapy in near future.

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KEYWORDS
Chrysin; probe sonication; bioavailability; cytotoxicity; MCF-7

Introduction

Various health issues have been solved using natural products since prehistoric times [1]. Out of these, polyphenolic compounds comprise a major as well as an important class of secondary metabolites [2,3]. Among these compounds, flavonoids have been acknowledged as one of the most important and ubiquitous groups of all plant phenolics owing to their biological and pharmacological role and their health benefits [4]. Flavonoids comprise a large group of naturally occurring organic compounds found in a wide variety of plants together with vegetables, fruits, cereals, grains, nuts, wine, seeds, tea, propolis and honey [4,5].

Several studies on flavonoids pointed out that they have anti-tumor [6], anti-oxidant, anti-inflammatory, cardiovascular properties [7] along with potent actions on mammalian perception and may oppose age-related declines in memory and learning [8]. Flavonoids also demonstrated other biological effects such as anti-hepatotoxic, anti-ulcer [9], antiviral [10], antimicrobial [11], effective in capillary fragility [12], inhibitory effect on human platelet aggregation [13] and antiallergenic activity [14].

Various studies on prevention and management of cancer have been carried out using natural products [15–18] including curcumin, capsaicin, β-carotene, gingerol, epigallocatechin gallate, genistein and resveratrol. Structural diversity and capability to induce apoptosis, block the cell cycle [19], interrupt mitotic spindle formation [20] or inhibit angiogenesis [21] makes flavonoids as potential candidates against cancer.

Chrysin (5,7-dihydroxyflavone) is a natural flavonoid obtained from herbs, honey, and propolis [22–24]. Numerous research reports available on CHR showed its extensive range of biological and pharmacological properties, like anti-inflammatory, anti-oxidant, anti-allergic and protective effects [25–28]. In recent times, it has also been established that CHR has the ability to inhibit proliferation and induce apoptosis in cancer cells, rendering it a promising anticancer drug [23]. Existing literature prominently revealed that CHR is a promising candidate for cancer therapy in various cancer cell lines; it specifically inhibits cell proliferation and induction of apoptosis [29–31].

Albeit CHR has a strong proven therapeutic value, poor solubility and bioavailability restricts its use severely [32]. During last decade various scientists struggled to develop nanoparticle-based drug delivery systems of natural and synthesized entities for the treatment of cancer.

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RESEARCH ARTICLE

Preparation, Characterization and *In Vivo* Assessment of Repaglinide Nanosuspension for Oral Bioavailability Improvement

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Abstract: ***Aims and Background*:** The objective of the study was to improve the bioavailability of poorly soluble repaglinide (RPG) by preparing nanosuspension with poloxamer 188 using high pressure homogenization (HPH). The recent patents on nanocrystals (US20150337006A1) facilitated selection of drug and polymer.

***Methods*:** Suspensions containing dissimilar sized particles were prepared by ultrasonication and HPH. The prepared aqueous suspensions were lyophilized and then characterized. Further, the dried aqueous suspensions were evaluated for drug content, solubility, *in vitro* dissolution, oral bioavailability study and stability study.

***Results*:** RPG nanoparticles size, polydispersity index (PDI) and zeta potential were found to be 280.8 ± 15 nm, 0.279 ± 0.04 and - 25.81 ± 1.6mV, respectively. DSC and XRD results showed that RPG particles in aqueous suspensions were present in a crystalline state; however, RPG nanoparticles exhibited decreased lattice energy due to smaller particle size. Nanoparticles prepared by HPH exhibited significant improvements in solubility and dissolution rate. Oral bioavailability was found to be enhanced by 1.93 fold in comparison with that of plain RPG. The nanosuspension was found to be stable when stored at 5°C ± 3°C.

***Conclusion*:** The outcomes of the study revealed significant enhancement in dissolution rate and oral bioavailability of RPG due to size reduction to nano range by HPH.

Keywords: Repaglinide, nanosuspension, high pressure homogenization, solubility enhancement, dissolution rate enhancement, oral bioavailability enhancement.

1. INTRODUCTION

Bioavailability and dissolution rate governs the therapeutic success of a poorly soluble drug. Dissolution is the most important constraints for pharmacological action by attaining anticipated absorption of the drug in systemic circulation [1]. Numerous restrictions like growing the dose, increase in the frequency of administration and the considerable incidences of the side effects are associated with the poorly soluble drugs. Absorption of poorly water soluble drugs in the gastro intestinal fluids is governed by the dissolution rate of such drugs. Improvement in the solubility and dissolution rate of poorly soluble drugs thus improves the oral bioavailability.

Repaglinide (RPG) is a meglitinide derivative aimed at managing type 2 diabetes mellitus [2, 3]. RPG was developed in an effort to succeed in dealing with the adverse effects such as hypoglycemia, cardiovascular side effects, and secondary failure of the existing antidiabetic compounds [4]. The blood glucose lowering mechanism by RPG involves binding to a receptor site different from that of sulfonylurea and stimulating the release of insulin. Poor solubility with relatively low and variable bioavailability of RPG is a constraint for good therapeutic prospective [2]. High inter-individual inconsistency in plasma concentrations in clinical trials has been shown by RPG [5-7]. Dissolution rate and bioavailability enhancement of RPG is thus, a valued tactic for improving its therapeutic efficacy.

During last 2 decades, a novel tool for decreasing drug particle size has been established. Pure solid drug particles with a mean particle size below 1 µm are called as drug nanocrystals. Nanosuspensions are the liquid dispersions of the drug nanocrystals stabilized with surfactants or polymeric stabilizers [8]. Enhanced bioavailability is attained by nanosuspensions by improving the saturation solubility and dissolution rate of poorly soluble drugs [9]. Drug nanosuspensions can be prepared by top down process, bottom up process and the combination of these two processes. Amongst these technologies top down process involving HPH is commonly used because of the lack of organic sol-

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Physicochemical characterisation and anti-inflammatory activity of ayurvedic herbo-metallic *Tamra bhasma* in acute and chronic models of inflammation

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ABSTRACT

Current study was aimed to validate traditional claim of *Tamra bhasma* (*TB*) as an antinflammatory agent by investigating the preclinical anti-inflammatory activity of *TB*. Initially, *TB* was characterised by some traditional and modern parameters including scanning electron microscopy (SEM), energy dispersive x-ray analysis (EDAX) and X-ray diffraction (XRD). Subsequently, its anti-inflammatory activity was evaluated in carrageenan, cotton pellet and complete Freund's adjuvant (CFA) model. The % inhibition of paw oedema and granuloma tissue, blood and tissue related pharmacological evaluations were performed for assessment of anti-inflammatory activity. The SEM, EDAX and XRD confirmed presence of nanoparticulate copper as its sulfide or oxide form in *bhasma*. The changes produced by carrageenan and CFA in animals were reversed significantly in *TB* treated animals throughout the study. The results suggest that *TB* has a potential anti-inflammatory activity.

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KEYWORDS
Tamra bhasma; anti-inflammatory activity; physicochemical characterization; *Ayurvedic bhasmas*; preclinical activity

Introduction

The growing recognition of Ayurveda worldwide in recent years has drawn the attention of budding researchers as well as patients from modern medicine to alternative therapies. *Bhasmas* (incinerated ash) are unique metal/mineral/herbal based ayurvedic medicines that have been used to treat numerous chronic ailments since ancient times without any toxicity. Adopting unique set of procedures namely *Shodhan* (purification); removal of toxicity and *Maran* (incineration); produces ash [1] which is a key to safety and maximum therapeutic effect of *bhasmas*. Although *bhasmas* have been used in clinical practice since ancient times, their use is limited in the present era because of safety concerns [2]. In this regard, several recent studies proved they are nontoxic upto certain doses [3,4]. Furthermore, preclinically *bhasmas* possess haematinic [5], antidiabetic [6], anticataleptic, antianxiety, antidepressant [7] activities.

Tamra bhasma (TB) is an ash of metallic copper. According to the ancient literature, *TB* is used to cure *Pandu* (anaemia), *Udara* (ascites), *Svasa* (asthma), *Amlapitta* (hyperacidity), liver disorders, old-age disorders, leucoderma, arthritis [8], *Sotha* (inflammation) and *Sula* (pain) [9]. Several biological studies also reported that it have antihyperlipidemic [10], free radical-scavenging [11] and hepatoprotective activity [12].

To date, only two *bhasmas*, namely Muktashoukti [13] and Raupya [14] reported to possess anti-inflammatory activity. Copper is well known for its anti-inflammatory property stated in many books belongs to ancient cultures of India, Egypt and China [15]. Several published reports suggested that copper has anti inflammatory properties [15–17] and copper complexes of non-steroidal anti-inflammatory drugs (NSAIDs) preclinically exhibit enhanced anti-inflammatory activity and improve gastric protection [18,19]. As available literature supports anti-inflammatory claim of copper, its biological evaluation needs to be performed. The current study focused on pharmacological evaluation of *TB* to check its anti-inflammatory activity.

Materials and methods

Drugs and chemicals

TB was procured from Baidyanath, Nagpur, India. CFA and λ-Carrageenan were purchased from Sigma Aldrich. Rat TNF-α and IL-1β ELISA kits were procured from Krishgen Biosystems, Mumbai, India. All the other chemicals utilized in the study were of analytical grade.

Preparation, dose, and route of TB

The study doses of *TB* were calculated from its specified clinical dose (60–120 mg/day) as per Paget and Barnes, 1964 [20]. The therapeutic equivalent dose (TED) for animal is 5.5 mg/kg. Other study doses were 2.25-(TED/

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Controlled synthesis of blue luminescent graphene quantum dots from carbonized citric acid: Assessment of methodology, stability, and fluorescence in an aqueous environment

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HIGHLIGHTS

- Carbonized Citric acid forms self assembly structure at controlled condition.
- Graphene Quantum dots (GQDs) demonstrated efficient and stable fluorescence.
- GQDs has high luminescence at variable pH and Temperature.
- Reproducible fluorescence for prolonged period of time at ambient temperature.

ARTICLE INFO

Keywords:
Graphene quantum dots
Scientific microwave
Blue luminescence
Aqueous synthesis
Carbonization

ABSTRACT

The present investigation deals with a comparative assessment of various techniques for the synthesis of blue luminescence Graphene Quantum Dots (GQDs) using various equipments like furnace, domestic microwave synthesiser and scientific microwave synthesiser using citric acid as a precursor. A bottom–up method was adapted to develop photoluminescent (PL) GQDs and assessed for luminescence intensity of GQDs at different environmental conditions. The methodology requires very less concentration of NaOH to disperse GQDs. The present approach is advantageous over other conventional organic solvent mediated synthesis, as it requires less time, easy to reproduce and disperse in water, furthermore it produces stable fluorescence for a longer period of time at ambient temperature conditions. The synthesized GQDs are primarily characterized by UV for detection of the fluorescence intensity and simultaneously Ultraviolet–Visible (UV–Vis) spectroscopy and Fourier Transform Infra Red (FTIR) Spectroscopy to assess the up conversion from the precursor molecule. Apart from these techniques, Particle Size and Zeta Potential, Scanning Electron Microscopy (SEM), Elemental Analysis (EDX), Raman Spectroscopy and Fluorescence spectrophotometry were used to characterise synthesized GQDs.

1. Introduction

From last few decades when the nanotechnology starts exploring at the edge; becoming a new area that represents small sized materials, structures, devices, and systems. Nanometer scale size ranging between 1 and 100 nm is considered the most promising application in nano-medicine and other technical approaches [1]. Novel technical aspects can be possible with help of Nanomaterials to produce an efficient system with wide range of applications such as drug delivery systems; performance based medical devices, diagnostic materials, etc. [2,3].

The demand of nanomaterials has increased in recent years, due to their unique properties and structural features. The application area is going to increase day by day with varying its phases or in different types of areas such as catalysis, biomedical, drug delivery and many more areas are still exploiting. Few of these materials includes the carbon-based luminescent nanomaterials (CLNMs), carbon quantum dots (CQDs) [4], nanodiamonds [5], Carbon nanotubes (CNTs) fragment and surface functionalized CNTs [6,7], Graphene quantum dots (GQDs) to name a few, are exploring more due to low toxicity, high luminescence, robust material, chemically inertness and ease for

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Mixed micelles for bioavailability enhancement of nelfinavir mesylate: *In vitro* characterisation and *In vivo* pharmacokinetic study

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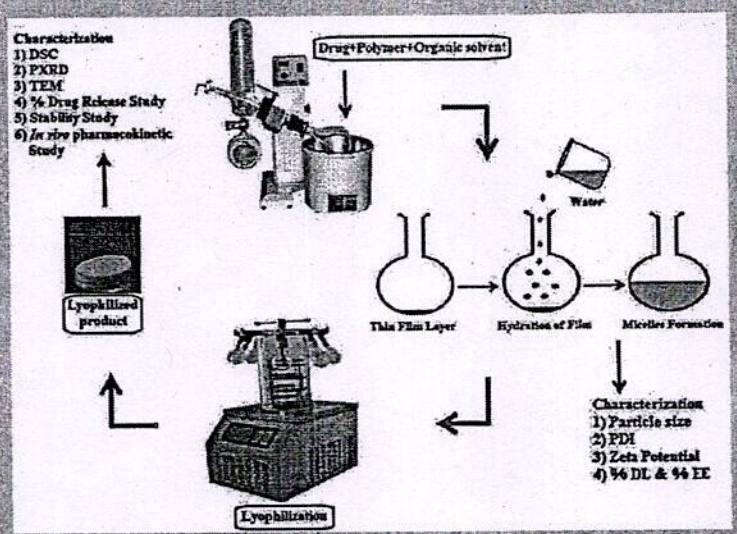
ABSTRACT

The present investigation deals with the fabrication of Nelfinavir mesylate loaded mixed micelles (NFM-MM) to enhance its oral bioavailability. NFM is a Human Immunodeficiency Virus-1 protease inhibitor having poor oral bioavailability and pH-dependant aqueous solubility leading to frequent dosing. Mixed micelles of Pluronic F127 and D-α-tocopherol polyethylene glycol 1000 succinate were prepared by thin film hydration technique. Results of *in vitro* characterisation showed that NFM-MM exhibited particle size 104.1 nm, polydispersity index (PDI) 0.127, zeta potential −10.6 mV, % entrapment efficiency 99.76 ± 1.20 and % drug loading 19.51 ± 1.02. DSC and P-XRD studies confirmed that NFM was encapsulated inside the mixed micelles. The *in vitro* release studies revealed that NFM-MM showed sustained release for upto four days. These mixed micelles were spherical or elliptical in shape as revealed by TEM study. On oral administration of NFM-MM; the relative bioavailability was enhanced about 1.94 fold as compared to NFM suspension. Thus, it can be concluded that PF127/TPGS mixed micelles can be used as a promising delivery system for NFM with increased bioavailability and sustained drug release.



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KEYWORDS
Nelfinavir mesylate; Pluronic F127; TPGS; mixed micelles; bioavailability enhancement

Introduction

World Health Organisation reported that approximately 35 million humans have died of HIV until 2016 and millions are still dwelling with this dreadful virus. The number of newly registered cases every year is stagnant despite the available treatment like highly active antiretroviral therapy (HAART) and efforts taken by the government organisations [1]. However, the biggest challenge for HAART is that the virus remains dormant to ARVs as it generates intracellular and anatomical reservoirs. Also, poor bioavailability of ARVs is a reason for the failure of HIV treatment [2].

NFM, a mesylate salt form of nelfinavir, is a synthetic antiviral agent [3]. NFM inhibits the HIV viral proteinase enzyme which inhibits gag-pol polyprotein bifurcation, ensuing in a non-infectious, undeveloped viral particle [4]. As per the Biopharmaceutical Classification System (BCS), NFM belongs to class IV (drugs with both low permeability and solubility). It is highly lipophilic, almost insoluble at pH 3.5 and 7.4 and non-ionisable in water [5]. The usual dosing regimen of NFM by conventional

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ORIGINAL RESEARCH

Performance overview of an artificial intelligence in biomedics: a systematic approach

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Abstract Artificial intelligence and technological advancements are exceptionally influenced the entire society and mankind. Unprecendented and extensive use of social media, mobile phones and the internet has resulted in accumulation of huge amount of data. Most of this big data are available in unstructured form and it is beyond the capability of traditional systems to manage, maintain, supervise, keeping and analyse the data within a limited time span. Effective analysis and interpretation of health care data provides new insights in the condition of patients and suggest the most appropriate treatment opportunities. Discovery and invention of vital information in medical data helps the health care professionals to arrive at appropriate clinical decisions and improvement of quality of life in a variety of patients. In this article, we have discussed various issues and addressed them with the updated information on big data sources, big data management, big data processing and big data analysis through various tools and techniques. We have also analysed and interpreted the recent applications and advancements in artificial intelligence and big data in the health care technology and m-Health domain.

Keywords Artificial intelligence · Big data · Big data analytics · Health care · m-health · Machine learning

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1 Introduction

Artificial intelligence (AI) is a branch of Computer Science and Engineering that deals with the computational understanding of intelligent behaviour and the creation of artefacts exhibiting such behaviour [61]. The main idea of AI suggests the capability of learning and reasoning through a computerized system [23]. AI has the capability to analyse the complex medical data. It involves an understanding of mechanisms of intelligent behaviour and thought along with their personification in machines [23, 61]. As, AI finds the solutions of complex problems through the use of judgmental knowledge, it can contribute to medical practice. The use of various AI tools and techniques implies the organization of knowledge in such a way that resembles the reasoning techniques of an intelligent human [66]. It is evident that there is a possibility of efficient analysis of medical data and making diagnostic predictions through AI [44, 61, 68]. AI is used in clinical setting either as clinical decision making expert systems or as a knowledge based systems implanted within laboratory instrumentation. Efforts have been made to develop the software architectures that imitate human intelligence [56].

Artificial neural networks, fuzzy logic systems and Bayesian belief networks are AI techniques that involve mathematical models based on human thinking and neuronal architectures. Rather than just making an assumption based on statistical distributions, AI tools generates the

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Fabrication and In-vitro Drug Release Characteristics of Magnetic Nanonanocellulose Fiber composites for efficient delivery of Nystatin

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Abstract

In the present study, one pot fabrication process was used for the synthesis of magnetic nanocellulose fiber composite (MCFNCs), wherein *In-situ* co-precipitation methodology contains reaction of iron with ammonia in controlled temperature environment and cellulose fibers acts as a capping and stabilizing agent. The crosslinked cellulose fibers helps to dissociate Fe ions and avoid aggregation during the nucleation stages. The Nystatin (Nyst) was used as a model drug for studying the release characteristics of MCFNCs. The preliminary confirmation was done by comparing the FTIR spectra of synthesized MCFNCs with its precursor. The fabricated MCFNCs was characterized by X-ray Diffraction, Vibrating Sample Magnetometry, Particle Size, etc. The surface morphology and internal structure were identified by Scanning and Transmission Electron Microscopic observation of respective samples. It shows porous aggregated structure of synthesized nanocellulose, BET surface area and BJH pore size was determined simultaneously and found to be 13.42 m^2/g and 104.48 Å respectively. Due to the porous nature of nanocellulose fiber, it has high loading capacity i.e. around 17.8% amongst porous material category. *In-vitro* drug release characteristics of Nyst loaded MCFNCs compared to pure drug showed sustained deliver for up to 8h time period. The Antifungal activity was evaluated on *Candida Albicans* and showed prominent inhibitory activity. The biocompatible nature of synthesized nanocomposites obtained from the natural nanocellulose fiber has a huge prospective in magnetically guided drug delivery in various parasitic diseases and have a potential of biomedical applications.

Keywords: Nanocellulose Nanofiber, Nanocomposites, Antifungal Activity, Controlled Release, Drug Delivery System

1. Introduction

Nanocellulose based fibers containing Iron oxide composites have gained significant interest in recent years due to interim potential pharmaceutical and bio-medical applications by virtue of their biocompatibility and biodegradability [1, 2]. Nanocellulose based magnetic composites find more promising application as antifungal and antimicrobial activity when studied in combination with silver nanoparticles [3, 4], agents for a hyperthermia based killing of parasites [5], drug delivery [6], vectors for magnetically-assisted active targeting in diseases such as cancer [7, 8], etc. The impressive characteristics of nanocellulose fibers have increased its relevance in different fields due to high specific surface areas and aspect ratio

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Development of graphene-drug nanoparticle based supramolecular self assembled pH sensitive hydrogel as potential carrier for targeting MDR tuberculosis

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ABSTRACT

The *Mycobacterium tuberculosis* (MTB) resides in mononuclear phagocytes (macrophages) hence selective targeting at the molecular level using Graphene Oxide (GO) Air Dried Hydrogel (ADH) is investigated in present investigation. The GO has capability to form supramolecular self assembly, due to $\pi - \pi$ stacking and hydrogen bonding interactions between surface groups of GO and oppositely charged drug molecule in presence of water. The hydrogel was fabricated using GO and Para-aminosalicylic acid (PAS) in solution phase. The fabricated hydrogel was lyophilized to obtain air dried hydrogel (ADH). The ADH showed potent antimicrobial activity and *in-vitro* cytotoxicity against *S. Aureus* and *E. Coli*, and MCF –7 cells respectively. The Alamar blue assay demonstrated the invasive characteristics of ADH in MTB (H37Rv). From the results obtained so far we lead to conclude that ADH is more invasive compared to the equivalent amount of pure PAS.

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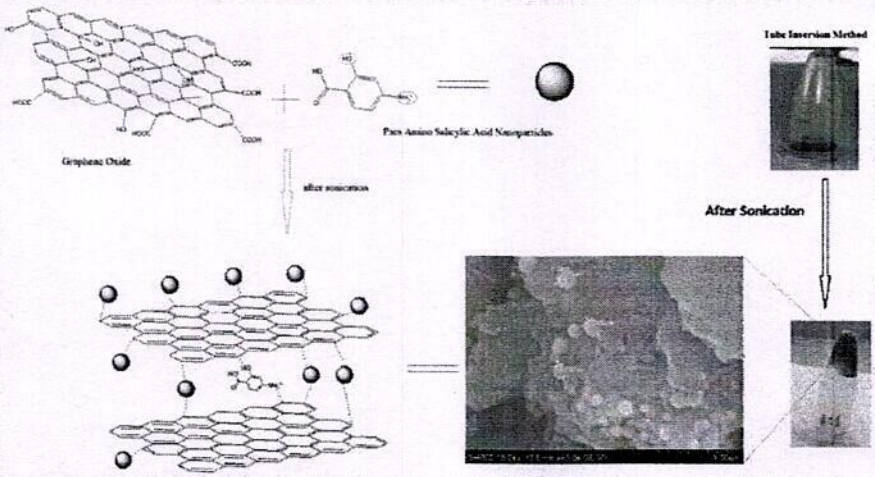
KEYWORDS
Tuberculosis; macrophages; supramolecular hydrogel; antitubercular activity; para amino salicylic acid; cytotoxicity



Introduction

Tuberculosis (TB) is contributing major cause of death amongst global health population Smith [1]. It was considered diseases of the past but eventually about 30% of the global population are affected with TB. The world wide diseases burden comprises major causes of morbidity and mortality is related to TB [2]. It is a chronic, contagious [3], airborne [4], prototypic [5] and fatal respiratory bacterial infection. TB is caused by the rod-shaped, obligate [6], non–spore-forming aerobic bacterium [7]. In 1993, World Health Organization (WHO) declared that TB is a global threat for health community [8].

'Super Carbon' denotes the potential applications of Graphene, it is one-atom thick honeycomb lattice structure, two-dimensional (2D) sheet of carbon atoms and is considered as the potential revolutionary material with electronic potential of zero band gap semimetal [9]. Graphene Oxide (GO), also known as graphitic acid, was discovered long time back [10]. The GO has large number of

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Supplemental data for this can be accessed here.