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RESEARCH PAPER

Influence of Polymer-to-Graphene Oxide Ratio on Drug Loading and Entrapment Efficiency of Methylprednisolone in PEGylated Graphene Oxide Nanostructures

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ABSTRACT

Nano-carrier based drug delivery systems have attracted considerable attention for improving the pharmaceutical performance of therapeutic agents among these systems PEGylated-graphene oxide (Graphene oxide GO functionalized with polyethylene glycol PEG) nanocarrier. PEGylated graphene oxide (GO) has emerged as a promising nanocarrier for drug delivery owing to its high surface area, favorable physicochemical properties and enhanced stability. The loading performance of such system is strongly influenced by carrier composition; therefore, this study focuses on the development of a functionalized GO-based nanocarrier for methylprednisolone (MP) delivery and investigates how functionalization influences drug loading capacity (DLC%) and entrapment efficiency (EE%). GO was functionalized with polyethylene glycol (PEG) and (MP) was then loaded by adsorption. Different PEG: GO (3:1, 1:1, 1:3) mass ratios and different MP % were used. The results showed a clear dependence of drug encapsulation on the PEG content within the nanocarrier system, where the nanoformulation with (PEG: GO, 3:1) exhibited the highest entrapment efficiency indicating improved incorporation of MP into the carrier, in contrast formulation that contains lower PEG ratios demonstrated reduced entrapment efficiency. This improved performance of PEG rich formulation may be associated with the beneficial effect of PEGylation on the dispersion, stability and the presence of additional functional group capable of interacting with MP. Same result was obtained with increasing MP% in the nanostructure, where higher drug availability enhanced the probability of interaction between MP molecules and the PEGylated GO surface. Additionally, PEG: GO ratio of 3: 1 achieved the highest drug loading capacity DLC%, this increased loading capacity of PEG rich formulation might be attributed to improve solubilization and stabilization of MP within PEG layer, while GO provide high surface area for drug adsorption. These synergistic effects of GO and PEG promote greater drug accumulation within the nanocomposite. Overall, these findings demonstrate that carrier composition significantly affected the loading performance of the PEGylated-GO nanocarrier and increasing PEG content enhance both entrapment efficiency and drug loading capacity highlighting the important role of PEG functionalization in optimizing MP-loaded GO nanocarrier for drug delivery applications.

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INTRODUCTION

Drug delivery systems have recently been created with enhanced characteristics including reduced vertical size, enhanced permeability and solubility, efficacy, specific site targeting, stability, and sustained delivery compared to traditional dosage form that can greatly enhance the performance of medicinal agents [1]. The expansion of nanoscience and the use of nanoparticles (NPs) in a variety of fields have been fuelled by their small size on the nanometre scale which ranges from 1 - 100 nm, which affords them more significant surface areas than the corresponding large forms, better reactivity and a tuneable nature of various features [2]. The discovery of the graphene family (graphene, graphene oxide and reduced graphene oxide) led to a significant technological advancement in nanotechnology. These materials exceptional equalities make it feasible to create innovative polymeric nanocomposites for a range of uses in several industries including pharmaceuticals [3] Graphene oxide (GO) is a graphene derivative is two-dimensional structure composed of a monolayer of carbon atom with oxygen containing functional groups, these functional groups like hydroxyl and carboxyl give graphene oxide hydrophilicity and pH- responsiveness ,furthermore GO is a perfect option for drug delivery applications due to its huge surface area and special mechanical and electrical characteristics. Its biocompatibility, high drug loading capacity and adjustable surface chemistry provide numerous potentials for effective therapeutic agents encapsulation and controlled release [4] Additionally, GO distinct surface chemistry allows for easy chemical modification or functionalization with biomolecules, targeted ligands and polymeric coatings significantly increasing graphene oxides potential in drug delivery applications. Drug loading capacity, release kinetics and site-specific biological targeting can all be precisely controlled using this kind of functionalization [5, 6]. Polyethylene glycol functionalization (PEGylation) is one of these strategies that is especially crucial because it improves GO aqueous stability and biocompatibility, decreases nanoparticle aggregation, extends systemic circulation time and lessen the reticuloendothelial systems quick recognition and clearance. As a result, PEGylated GO is a viable nanocarrier for enhancing the therapeutic efficacy of traditional medication. Methylprednisolone (MP) is a corticosteroid with modest potency that is used to suppress the immune system and reduce the inflammation [7]. It is widely used in the treatment of various inflammatory and autoimmune disease including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and inflammatory bowel disease as well as severe allergic and dermatological condition [8]. However, it is associated with a variety of side effects on the digestive, cardiovascular, ophthalmic, musculoskeletal and nervous systems [9]. Furthermore, MP must be administered

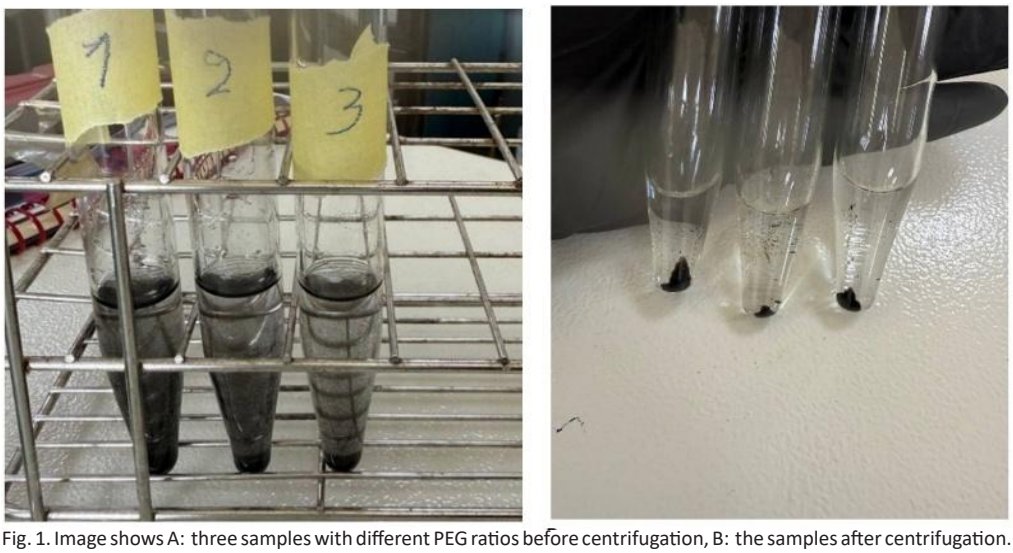

Fig. 1. Image shows A: three samples with different PEG ratios before centrifugation, B: the samples after centrifugation.

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often due to its quick systemic clearance which may rise the risk of related adverse effects [10]. Incorporating methylprednisolone into a PEGylated GO nanocarrier may help overcome these limitations by enabling sustained drug release and improved pharmacokinetic behaviour. Therefore, the present study focuses on the development a functionalized GO-based nanocarrier for MP delivery and investigates how functionalization influences drug loading efficiency and entrapment efficiency of the prepared nanocomposite.

MATERIALS AND METHODS

Carrier system preparation

The nano carrier system was developed through a solution blending method GO powder was first dispersed in deionized water followed by sonication in an ultrasonic cleaner for 15 minutes to 25°C to obtain a well distributed GO suspension in the aqueous medium before introducing PEG solution [11,12]. Subsequently PEG solution prepared by dissolving PEG crystals and deionized water, was incorporated into the GO dispersion. This modification was carried out to enhance the stability of GO in biological environments and reduce its potential toxicity. The mixture was then continuously stirred for 24h to allow PEG molecules to absorb onto the GO surfaces through physical interactions (Fig. 1A) [11,13]. Then the suspension was subjected to ultracentrifugation at 12,000 rpm to eliminate unbound PEG present in the supernatant the precipitated Pilates formed after the portion of the centrifuge tubes representing PEGylated-GO were collected and used in the subsequent drug loading steps (Fig. 1B) [14, 15].

To evaluate the influence of PEG functionalization on drug loading efficiency and the overall physicochemical properties of the drug delivery system, three PEG: GO mass ratios (1:1, 1:3, and 3:1) were prepared.

Methylprednisolone (MP) Loading onto nanocarrier

MP stock solution was prepared by dissolving Methylprednisolone in a mixed solvent system consisting of water and ethanol at a ratio of 2:1. The inclusion of ethanol was necessary to promote complete dissolution of MP's due to its limited solubility in aqueous media [10]. The mixture was then heated at 50°C for 10 minutes to promote interaction between the drug molecules and the nanocarrier followed by continuous stirring at room temperature overnight to facilitate effective adsorption and stabilization of MP on the carrier surface. Then the suspension was centrifuged at 12,000 rpm for 10 minutes to separate the drug- loaded carrier from the unbound drug. The

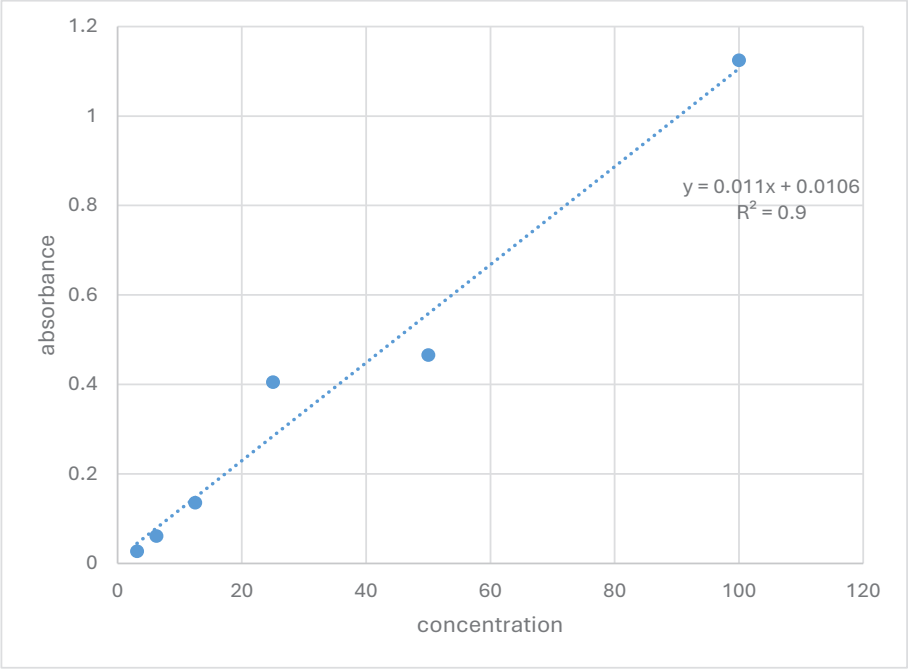

Fig. 2. Calibration curve for MP.

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supernatant containing the unloaded MP was carefully decanted [16]. The collected pellets were washed with buffer solution to remove any residual free drug and this washing process was repeated 3 times to ensure purification of the loaded nanocarrier system. Drug loading and successful Carrier formation where subsequently evaluated and characterized using Fourier transform infrared spectroscopy FTIR, Scanning electron microscopy SEM, Energy dispersive X-ray spectroscopy EDS and X-ray diffraction XRD.

In order to investigate the effect of MP concentration on drug loading, three different MP %, was utilized (14%,20%,33.5%).

Entrapment efficiency (EE)

Entrapment efficiency is one of the leading variables for the characterization of nanocarriers. EE is measured by determining the concentration of the unentrapped drug in the supernatant layer after centrifugation and Depending on the chemical structure of the drug [17]. Numerous studies demonstrate that EE% is significantly affected by the physicochemical properties of the drug, Certain modifications such as PEGylation, tend to lower EE% but improve targeted release [18], the loading efficiency can be quantitatively determined by UV spectrophotometry [17]. And according to the following equation:

%EE = Initial amount of the drug - Free unentrapped drug/Initial amount of the drug* 100

Drug loading capacity (DLC)

Drug loading capacity it is a term describes how much drug is being loaded onto the nanocarrier system (PEGylated graphene oxide) relative to the weight of drug loaded system (PEG-GO-MP).

DLC% = wt. of drug loaded /total wt. of drug-loaded nanoparticles*100

Calibration Curve of MP

Calibration Curve of MP was constructed using UV-vis spectrophotometer, UV-vis measures the amount of UV light absorbs by a substance. It can be used to determine analyte concentrations or the chemical conversion of a component. The range of reflection and absorption is measured so that the substance visible and ultraviolet optical activity is defined [19,20]

Calibration curve was constructed using Stock solution of MP 0.1 mg/ml in Water: ethanol (2:1) solvent and serial of dilutions with concentrations of (3.125, 6.25, 12.5, 25, and 50µg/Ml), (1 mL)

Table 1. Shows EE% of three PEG: GO mass ratio, The 1:1 PEG: GO formulation showed an entrapment efficiency of 66.25%, while the 1:3 ratio exhibited a lower value of 57%. Interestingly, increasing PEG content to a 3:1 PEG:GO ratio resulted in a comparable and slightly higher %EE (66.5%).

PEG: GO mass ratio	EE%
1:1	66.25%
1:3	57%
3:1	66.5%

Table 2. shows EE% of three different MP%, where higher MP% contributed to a higher EE%.

MP%	EE%
14%	56%
20%	60%
33.33%	66.5%

Table 3. Drug loading capacity DLC% of PEG:GO ratios, where the 3:1 PEG:GO ratio exhibited the highest DLC% as compared to the other two ratios.

PEG: GO mass ratio	DLC%
1:1	6.625%
1:3	8.4%
3:1	15%

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of each concentration was analysed by UV spectrophotometer at the wavelength of 242 nm and repeated 4 times, The absorbance readings were plotted against the concentrations to construct the calibration curve [10] as shown in (Fig. 2).

RESULTS AND DISCUSSION

Drug loading and Entrapment efficiency (EE)

Entrapment efficiency (%EE) and drug loading content (DLC%) are critical parameters for evaluating the performance of nanocarrier-based drug delivery systems, as they reflect the capacity of the carrier to incorporate and retain the therapeutic agent. Characterization by FTIR, SEM, EDS and XRD confirmed successful incorporation of drug onto PEG-GO nanocomposite without structural compromise (data not shown). The %EE values obtained for different PEG: GO mass ratios demonstrated a clear dependence on carrier composition. (Table 1).

The reduced entrapment efficiency observed at the 1:3 ratio (Table 1) may be attributed to insufficient PEG coverage, which can lead to partial aggregation of graphene oxide sheets and a reduction in the effective surface area available for drug adsorption. In contrast, PEGylation improves dispersion stability and provides additional functional groups capable of interacting with methylprednisolone molecules through hydrogen bonding and hydrophobic interactions. However, excessive PEG may also shield some GO adsorption sites; therefore, the comparable efficiencies observed for 1:1 and 3:1 ratio suggest that PEG contributes not only to stabilization but also to enhanced drug retention within the nanocomposite structure [21].

The influence of (MP) concentration on drug loading was further investigated using drug percentages of 14%, 20%, and 33.33% (Table 2). A gradual increase in %EE was observed with increasing drug concentration, rising from 56% at 14% MP to 60% at 20% MP and reaching 66.5% at 33.33%. This trend indicates that higher drug availability enhances the probability of interaction between MP molecules and the PEGylated GO surface, promoting adsorption until the carrier approaches saturation of available binding sites.

Drug loading capacity (DLC)

As observed in (Table 3) the DLC% increased markedly with higher PEG proportion, reaching 15% for the 3:1 PEG: GO formulation compared with 6.625% and 8.4% for the 1:1 and 1:3 ratios, respectively. The higher DLC in the PEG-rich formulation suggests improved drug incorporation within the nanoparticle matrix, possibly due to enhanced solubilization of MP and improved stabilization of drug molecules within the PEG layer. While GO provides adsorption sites, PEG appears to facilitate higher drug accommodation within the overall nanostructure, increasing the drug fraction relative to total nanoparticle mass.

Overall, the combined EE% and DLC% results indicate that both carrier composition and drug concentration strongly influence loading performance. An optimized PEG:GO ratio enhances nanocomposite stability while maintaining efficient drug–carrier interactions, leading to improved encapsulation and higher drug payload [11, 13]. These characteristics are essential for achieving sustained release behaviour and reducing dosing frequency in PEGylated graphene oxide–based drug delivery systems.

CONCLUSION

The developed PEGylated GO nanocarrier has shown efficient loading of MP where carrier composition was identified as a key determinant of the loading performance of PEGylated-GO nanocarrier and that increasing PEG content and drug concentration significantly enhanced both entrapment efficiency EE% and the loading capacity DLC%, with the PEG ratio of 3:1 providing the most favorable loading characteristic, therefore PEG-rich GO formulations represents promising nanocarrier system for improving the incorporation of MP in drug delivery applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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