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Preparation of Polycaprolactone-Graphene Oxide Hydrogel as Potential Drug Delivery Carrier

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Polycaprolactone-graphene oxide (PCL-GO) hydrogel composite was prepared using a facile method and characterized by Fourier transform Infrared (FTIR) and scanning electron microscopy (SEM). The swelling capacity of the hydrogel at varying temperature and equilibration time was also determined. IR analysis revealed a shifting of bands, which indicates H-bonding interactions between polycaprolactone and graphene oxide. Characteristic peaks of graphene oxide at 3500 cm^{-1} for -OH stretching and peaks of polycaprolactone at 1456, 1370, 1304 cm^{-1} for CH_2 bending vibrations were observed. SEM images validated IR results with the occurrence of larger hollow regions, pores and insets indicating reaction of OH groups with the polymeric chains. The swelling ratio of the PCL-GO hydrogel was higher than polycaprolactone and graphene oxide at 4 h and 8 h equilibration time. The swelling ratio of PCL-GO at 40 ºC and 12 h equilibration time was 4.3, which was the highest among the swelling ratios. These data could imply that the PCL-GO prepared has the potential to be a potential drug carrier.

Keywords: Drug delivery, Swelling, Hydrogel, Polycaprolactone, Graphene oxide.

INTRODUCTION

Drug availability is augmented if drug delivery to targeted tissues is effective. This is the very essence of drug delivery systems (DDS), which is for the controlled release of drugs in humans. To achieve the enhanced restorative effects of drugs, DDS is employed to transport drugs at predetermined rates. However, the efficacy of DDS highly depends on the availability of an appropriate medium. For many years, the unique properties of hydrogels have been explored in their use in drug delivery applications to prolong a drug's stay in the body for complete absorption. Hydrogels which are crosslinked hydrophilic polymers have been discovered to be a promising system for an effective drug delivery. They are able to absorb huge quantity of water. This property of hydrogels, called swelling capacity, is a very important characteristic for drug delivery system. Hydrophilic functional groups in the polymer chains are responsible for the swelling behaviour of hydrogels [1].

One of the polymer which is becoming popular for drug delivery application is polycaprolactone (PCL). It is a thermoplastic polymer and one of the typical hydrophobic, non-toxic synthetic semi-crystalline aliphatic polyesters and having excellent compatibility with other polymers. It has also important characteristics such as high permeability and low toxicity. Its melting temperature ranges between 59 ºC and 64 ºC. Due to its biocompatibilty and biodegradable with slower degradation rate, polycaprolactone (PCL) is considered as a promising material for many biomedical applications. Liu *et al*. [2] used PCL and polyglycolide (PGA) as the carrier of ciprofloxacin drug. Sahoo *et al*. [3] utilized chitosan with PCL in 80:20 proportion for the controlled delivery of doxycycline. Reni *et al*. [4] worked on polycaprolactone/polyvinyl alcohol (PCL/PVA) core-shell nanofibers with pH-responsive properties as carriers for anticancer drug paclitaxel.

Polycaprolactone (PCL) has five hydrophobic -CH_2 moieties in its repeating units, which makes it relatively hydrophobic. This feature poses limits to its capacity to deliver hydrophilic drugs. To address this limitation, the possibility of PCL to combine with an environmentally acceptable filler to improve its hydrophilicity can be explored. Based on PCL's chemical structure, it is capable of interactions like H-bonding, van der Waals and hydrophobic interactions when a filler like graphene oxide (GO) is added. This interaction opens up the possibility of enhancing the hydrophilicity of PCL thus possibly improving its property as a drug carrier [5,6].

Graphene oxide (GO) reactivity is highly dependent in various oxygen-containing functionalities present in its structure such as epoxide, carbonyl, carboxyl and hydroxyl groups. It is a derivative of graphene which is produced from graphite using various chemical oxidation method. The modification of GO can be easily achieved due to the presence of oxygen functionalities. Interactions of H-bonding with organic polymers such as PCL can improve its solubility, processability and interactions [7].

Graphene oxide (GO) with biocompatible polymers is a promising composite for drug delivery and controllable release of drugs. The surface of GO which is composed of oxygen groups allows π-π stacking and hydrophilic interactions with drugs. Moreover, to enhance its biodegradability, drug loading and target delivery, studies on the modification of GO with various polymers such as natural and synthetic polymers are explored [8]. Bai *et al*. [9] graphene oxide- poly(vinyl alcohol) (GO-PVA) composite hydrogel was synthesized for selective drug release at physiological pH. Rasoulzadeh & Namazi [10] graphene oxide was combined with biodegradable carboxymethyl cellulose (CMC) *via* physically crosslinking with $FeCl_3 \cdot 6H_2O$ for drug delivery system. Maio *et al*. [11] employed a one-pot synthesis for decorating polycaprolactone with graphene oxide for poten-tial application of such devices in water treatment. In another study, PCL/GO/Fe_3O_4 nanocomposite fibers as biocompatible scaffolds were produced for biomedical applications [5].

Unagolla & Jayasuriya [12] conducted to prepare scaffolds by an extrusion based 3D printer using a blend of PCL and GO as a possible platform for bone tissue engineering. Rostami *et al*. [13] prepared nanocomposite PCL-based scaffolds with GO for the delivery of osteogenic drugs, *e.g*. dexamethasone and simvastatin. Results showed that the integration of GO improved the hydrophilicity, cell viability, and osteogenic differentiation in comparison with PCL scaffolds. However, there is a challenge on how to improve the efficiency of drug delivery system of PCL-GO to encapsulate hydrophilic drugs because of PCL's hydrophobicity. Saeed *et al*. [14] reported that GO has an excellent nucleating effect on the crystallization of PCL, however the composite produced is not in hydrogel format.

Due to the valuable properties of hydrogels for drug delivery system, this work investigated the potential of PCL-GO in hydrogel format as a drug carrier for hydrophilic drugs. Specifically, this work was focused on the investigation of the properties of PCL-GO hydrogel by FTIR spectroscopy and SEM analysis. Furthermore, the swelling capacity of PCL, GO and PCL-GO hydrogel as a function of temperature and equili-bration time were also addressed in this study.

EXPERIMENTAL

Preparation of polycaprolactone and polycaprolactone-graphene oxide (PCL-GO): Polycaprolactone was prepared from the monomer, ε-caprolactone. The method employed was reported by Ibale and Chakraborty [15]. ε-Caprolactone (2 mL) and tin-2-ethylhexanoate (0.20 g) was placed in a test tube containing 5-6 beads of dried molecular sieve. Toluene (2 mL) was added and the mixture was purged with N_2 for 1 min. It was polymerized at 130 ºC with constant stirring and heating at a circulating water bath. After 12 h, the sample was filtered by vacuum filtration. The filtrate was added with a large amount of methanol for precipitation. It was centrifuged, decanted and then the solid residue (ε-polycaprolactone) was air dried.

Polycaprolactone-graphene oxide (PCL-GO) hydrogel was prepared based on a method used by Hua *et al*. [16]. Graphene oxide (GO) was prepared as according to the previous work [17]. About 0.025 g of GO and about 5 g of ε-caprolactone were sonicated for 30 min. The resulting suspension was added with 0.25 g of tin-2-ethylhexanoate and ascorbic acid, transferred to a three-necked flask and heated in an oil bath at 130 ºC for 12 h with vigorous stirring. The product was subjected to centrifugation and the precipitate was rinsed with ethanol.

Characterization of PCL-GO hydrogel: Fourier transform infrared (FTIR) spectroscopy using Perkin-Elmer spectrum 100 was used to detect the functional groups. The morphology was examined by scanning electron microscopy (SEM) using on JEOL, JSM- 67001 instrument. Swelling test was performed as part of the composite's characterization. Pre-weighed PCL-GO, GO and PCL samples on different test tubes were added with 5 mL buffer solution (pH 7) and placed in water bath. The temperature in the water bath and equilibration time were varied. The excess buffer was pipetted out and the dispersion was air dried and weighed. The swelling ratio (Q) was calculated based on the eqn. 1:

$$Q = \frac{(M_s - M_d)}{M_d}$$

where M_s = weight swollen, M_d = weight dry.

RESULTS AND DISCUSSION

FTIR studies: Table-1 showed the characteristic bands of PCL, GO and PCL-GO composite and the shift of the wavenumber of the peaks. Fig. 1 shows the overlay IR spectra of PCL, GO and PCL-GO. Results for GO sample confirmed the presence of oxygenated groups, the absorption peaks of COOH and C-OH groups at 1771 and 1183 cm^{-1}, respectively. At 3500-3000 cm^{-1}, a broad and weak peak is attributed to the OH groups. An absorption peak of C-C group at 1592 cm^{-1} corresponds to the remaining sp^2 character of graphite [13].

Fig. 1 also revealed characteristic peaks of the prepared PCL such as C=O stretching vibrations at 1750 cm^{-1}, CH_2 bending, wagging and stretching deformations in skeletal structure of the polymer chain modes at 1456, 1370, 1304 cm^{-1} and CH_2 symmetric stretching at 2825 cm^{-1}. The C-O-C stretching vibrations yield peaks at 1216, 1136 and 1095 cm^{-1}. The band at 1181 cm^{-1} was assigned to C-O stretching. These results were well-matched with the earlier reports [18,19].

After PCL was decorated with GO, PCL retained all of its key infrared bands as shown in the overlay IR spectra in Fig. 1. The index peaks of PCL were visible at 1752 (carbonyl group C-O), 1218, 1094, 1161 (C-O-C groups) and at 1181 cm^{-1} (C-O stretching). The FTIR spectrum confirmed that in composite hydrogel (PCL-GO), GO phases have been successfully added into the PCL matrix. A typical mode centered at

TABLE-1
CHARACTERISTICS PEAKS OF PCL, GO AND PCL-GO

Characteristic peaks /vibrational modes exhibited				
	Type of bond (description of vibrations)	Band/Wavenumbers (cm^{-1})		
		PCL	GO	PCL-GO
c	C-O stretching	1181	1183	1181
a, b, d	C-O-C stretching	1216, 1095, 1136	–	1218, 1094,1161
e, f, g	CH_2 bending	1456, 1370, 1304	–	1457, 1371, 1304
h	C=O stretching (shifted)	1750	1771	1752
i	CH_2 stretching (shifted)	–	2900	2977
j	OH stretching (shifted)	–	3000-3500	3519
k	C=C stretching (shifted)	–	1592	1600

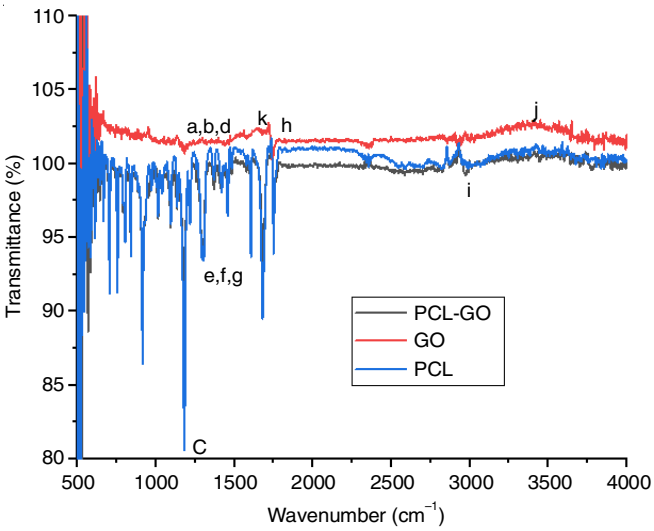

Fig. 1. Overlay IR spectra of PCL, GO and PCL-GO

1600 cm^{-1}, ascribed to C-C bond of graphenic lattice, (ii) a weak broad band at 3519 cm^{-1} attributable to O-H stretching and (iii) the CH_2 stretching of the graphite sp^2 hybridization at 2977 cm^{-1}. A shift in wavenumber signified changes in bond length, which may occur due to the change in electronegativity of the neighbouring atom. This means that interaction like inter/intramolecular hydrogen bonding has occurred PCL-GO [20].

SEM studies: Scanning electron micrographs of ε-caprolactone (PCL) in Fig. 2 revealed a randomly oriented and 3D interconnected porous structure which was similar to the work of Evlashin *et al.* [21]. SEM of graphene oxide (GO) in Fig. 2c revealed a similar morphological characteristics as reported earlier [17]. Graphene oxide (GO) was observed to be flat and smooth and surfaces indicated stacking of the GO sheets which may have been due to van der Waals forces and π-π staking interaction.

In Fig. 3, composite PCL/GO showed hollow regions and pores, which are indicative of the reaction of OH groups with the polymeric chains [3,22]. The reaction can be attributed to the formation of hydrogen bonds between OH and COOH groups in GO structure with carbonyl (C=O) groups in PCL, the π-π interactions between CH_2 groups in GO and PCL as well as the van der Waals forces. Moreover, the fluffy-like morphology of the hydrogel can be attributed to the hydrophilic behavior of GO which allows water molecules to enter in the matrix [13].

Swelling studies: The swelling ratio is usually used to measure the equilibrium water content of the polymeric hydrogel. In Fig. 4, the swelling ratio of PCL, GO and PCL-GO hydrogel at varying equilibration time at a fixed temperature was compared. It can be found that the composite hydrogel exhibits a higher swelling capability than that of PCL and GO at 4 h and 12 h equilibration time. Presence of GO in the PCL matrix generates a more porous and fluffy structure that enables water to pene-trate the matrix much more easily than in the PCL without GO [22]. The oxygen functionalities in GO can easily yield to the intermolecular forces governing polar H_2O molecules. This supported with the FTIR results that hydrogen bonding does occur when PCL is decorated with GO. Due to these interactions, there was an increase in the swelling capability of PCL-GO composite hydrogel that makes it a potential candidate for drug delivery.

Swelling behaviours of PCL-GO hydrogel at different temperatures were investigated at different equilibration time. At 4 h and 12 h equilibration time, the swelling ratio of the

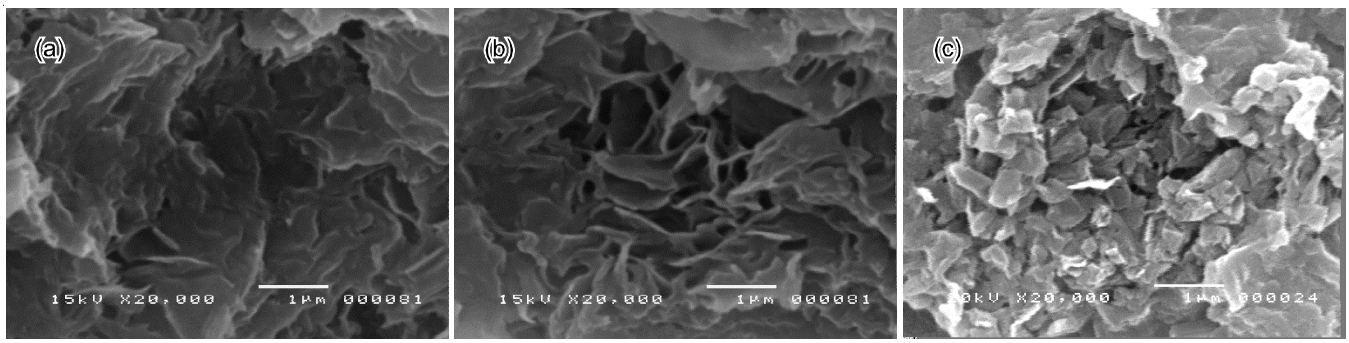

Fig. 2. SEM images of ε-polycaprolactone (PCL) at different magnifications (a-b) and graphene oxide (GO) (c)

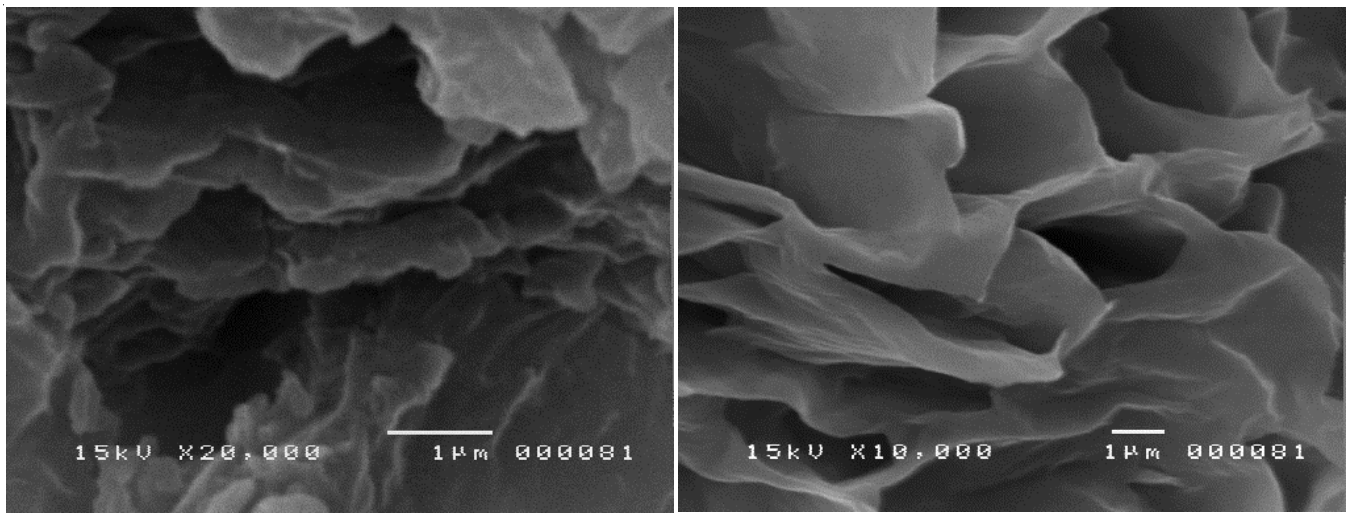

Fig. 3. SEM images of PCL-GO

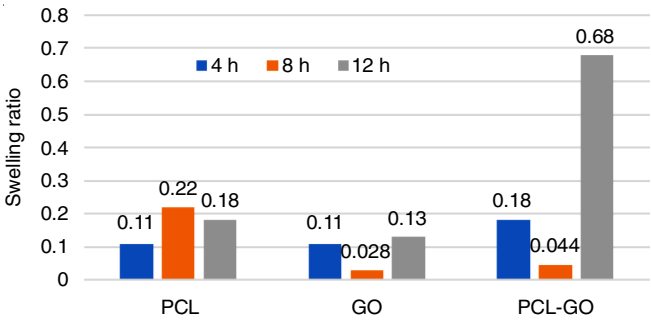

Fig. 4. Swelling ratio of PCL, GO and PCL-GO hydrogel at varying equilibration time at a fixed temperature, RT

PCL-GO hydrogel at 40 ºC was 4.3 (Fig. 5). This observation was similar with the work of Gupta & Shivakumar [23] in which, an increase in temperature made the polymer swelled faster. At higher temperature, the breaking of hydrogen bonding between polymer molecules and destruction of the polymeric chains were promoted. This could be due to the increased mobility of the polymeric chain at higher temperature. Such temperature responsiveness was due to the porosity of PCL-GO. More pores would mean increased uptake of water during swelling in comparison with less porous hydrogels [23].

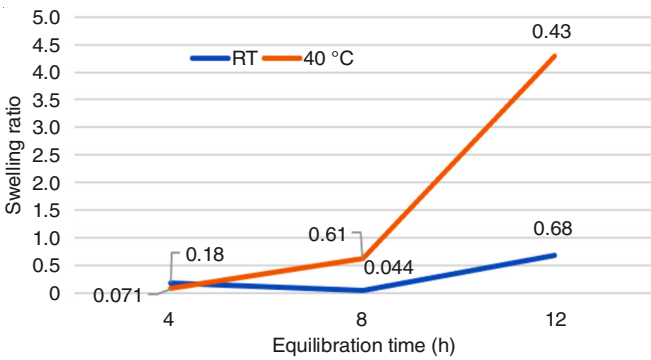

Fig. 5. Swelling ratio of PCL-GO hydrogel at varying temperature and equilibration time

Fig. 5 also demonstrated that swelling ratio of PCL-GO increased with equilibration time. The similar observation was also observed by Wang & Wang [24]. With prolong contact time of PCL-GO, formation of hydrogen bonds between OH and COOH groups in GO structure with carbonyl (1700 cm^{-1}) groups in PCL and the π-π interactions between CH_2 groups (2900 cm^{-1}) in GO and PCL were more pronounced as revealed in the IR spectra of PCL-GO in Fig. 6. These interactions increased the hydrophilic behaviour of PCL-GO, thus producing a more porous structure which tends the water molecules to enter in the matrix.

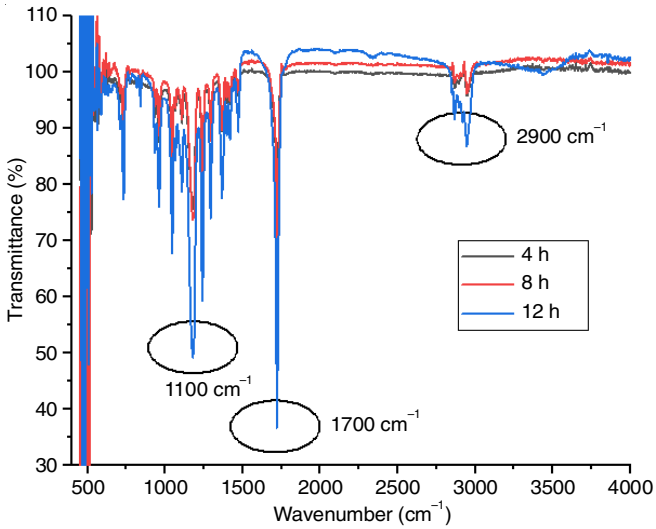

Fig. 6. Overlay IR spectra of PCL-GO at varying equilibration time

Conclusion

In this work, ε-polycaprolactone (PCL) was successfully decorated with graphene oxide (GO) to form the composite hydrogel (PCL-GO). Presence of GO in the PCL matrix was confirmed by FTIR and SEM analyses, which exhibited the H-bonding interactions between PCL and GO. Furthermore, the potential of PCL-GO hydrogel for drug delivery application was investigated by swelling studies and results revealed that swelling ratio of PCL-GO at 4.3 was highest at 40 ºC and at 12 h of equilibration time.

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CONFLICT OF INTEREST

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

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