International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 17s, 2025
https://theaspd.com/index.php

Development And Characterization Nano-Conjugates Of Folic Acid Modified Gamma-Oryzanol Targeted Therapy For Rheumatoid Arthritis

Jinendra Sardiya[1], Neeraj Sharma[2], Praveen Sharma[3], Sandesh Asati[4], Rituraj Singh Chundawat[5], Vaishali Pandey[6]
[1]Faculty of Pharmacy, Bhagwant University, Ajmer, Rajasthan
[2]IPS Academy College of Pharmacy, Indore, M.P.
[3]Indore Institute of Pharmacy, Indore, M.P.
[4]Radha Raman College of Pharmacy, Bhopal, M.P.
[5]School of Pharmacy, Sangam University, Bhilwara, Rajasthan
[6]Mansaovar Global University, Bhopal, M.P.

Abstract
To improve the effectiveness of drug delivery in the treatment of RA, a variety of adaptable nanocarriers with modifiable physicochemical characteristics, adjustable drug release profiles, or active targeting capabilities were created. The carbon nanotube is one of the most well-known nanomaterials with a high surface area, which is utilized to illustrate a consistent drug release. Nevertheless, researchers have obtained encouraging outcomes in targeted delivery for arthritis illness utilizing either single-walled carbon nanotubes (SWCNT) or multi-walled carbon nanotubes (MWCNT). This viewpoint employs functionalized carbon nanotubes to improve medication accuracy, control drug release, and reduce adverse side effects in order to create a targeted therapy for rheumatoid arthritis. In this study, gamma oryzanol (GOZ) was modified with folic acid (FA) to prepare FA-f-MWCNTs-GOZ nano-conjugate of multi-walled carbon nanotubes. The stability, sustained release, anti-inflammatory effect, and therapeutic impact were evaluated using in vitro tests. FA-f-MWCNTs-GOZ nano-conjugate demonstrated high stability, prolonged release, and anti-inflammatory properties. A variety of adaptable nanocarriers with tailorable drug release patterns, regulated physicochemical characteristics, or active targeting capabilities were created to improve medication delivery efficiency in the treatment of RA. Carbon nanotubes are among the most well-known nanomaterials with a large surface area that are used to show a consistent release of medications. However, researchers have obtained encouraging results using either single-walled carbon nanotubes (SWCNT) or multi-walled carbon nanotubes (MWCNT) in targeted delivery for arthritis. This method uses functionalized carbon nanotubes to deliver medicines with greater precision, control drug release, and reduce undesirable side effects.to create a targeted therapy for rheumatoid arthritis. Approaches. In this work, folic acid was created by modifying gamma oryzanol (GOZ) with folic acid (FA). In vitro experiments were used to assess the therapeutic, anti-inflammatory, sustained release, and stability of FA-GOZ. The findings revealed that FA-GOZ had a high level of stability, sustained release, and anti-inflammatory activity.
Key words: - *Gamma Oryzanol, Functionalization, Folic acid, Rheumatoid Arthritis, Carbon nanotubes*

INTRODUCTION

A crucial step in evaluating the biological production of nitric oxide (NO) is determining whether there is an excessive production of free radicals and/or oxidants, which can lead to oxidative stress and oxidative damage to the biological inflammatory process (Perkins, 1999). NO is able to stimulate cyclooxygenase, the rate-limiting enzyme in the inflammatory process, as well as elevate the synthesis of tumor necrosis factor (TNF) and interleukin-1 (IL-1) (Jang, 1998). Rice bran is a valuable by-product of rice milling, especially high in dietary fiber, and it also has a large amount of protein, starch, vitamins, and dietary minerals. The oil that is produced from the germ and inner husk of rice is called rice bran oil (RBO). It is a good source of sitosterol, necessary vitamin E complex, gamma-oryzanol, and tocotrienols (Chotimakorn, 2008). The phytosteryl ferulate esters in RBO are a mixture of gamma-oryzanol (GOZ) (Scavariello, 1998). Gamma-oryzanol was first believed to be a single chemical. But it was just discovered to be a combination of 10 phytosteryl ferulate esters. The major constituents of gamma-oryzanol are cycloartenyl ferulate, 24-methylenecycloartanyl ferulate, and campesteryl ferulate (Cicero, 2001). Gamma-oryzanol is said to have health benefits such as lowering total plasma cholesterol, enhancing the plasma

lipid profile, raising HDL cholesterol levels, and preventing platelet aggregation (Kim,1995). Additionally, it has been shown that gamma-oryzanol has antioxidant capabilities (Ryu, 1998). Depending on the colors that accumulate in the pericarp and bran layer of the rice kernels, rice can come in a variety of hues in Thailand, including black, purple, and red. The ethnic minorities also utilize the rice in traditional medicine and religious rituals, in addition to using it as a food source. Thai purple rice has also been well-liked in Thailand for its health-promoting and disease-preventing properties. Thai purple rice continues to garner attention as a high value-added crop and has emerged as a key factor in the economic growth of rural Thailand. According to several studies, purple and black rice have two to three times as much anthocyanin, gamma-oryzanol, and phenolic compounds as white rice (Fujita, 2010). Additionally, it has been demonstrated that colored rice bran has more phenolic compounds and has higher antioxidant activity than white rice bran (Ricciotti, 2011).

Prostanoids, such as prostaglandins and thromboxane A2, are key lipid mediators of inflammatory response activation (Surh, 2001). The enzyme prostaglandin-endoperoxide synthase, often referred to as cyclooxygenase enzymes (COX), produces prostanoids from arachidonic acid. The COX enzymes exist in two isoforms: COX-1 and COX-2. COX-1 is continuously expressed, while COX-2 is inducedly expressed in response to stimulation by growth factors and inflammatory cytokines (Flower, 2003). According to several lines of evidence, COX-2 is mostly in charge of producing pro-inflammatory mediators, and selective COX-2 inhibition shows strong pharmacological anti-inflammatory and anticancer activity (Mestre, 2001).

For the creation of therapeutic anti-inflammatory drugs, COX-2 is thus a useful target (Guha, 2001). In both human and murine macrophages, bacterial lipopolysaccharide (LPS) strongly triggers inflammation and mediates a large number of pro-inflammatory genes (Xu, 1999). LPS specifically binds to the Toll-like receptor 4 receptor complex and activates NF-kB via a MyD88-dependent or TRIF-dependent pathway (Islam, 2008). NF-kB regulates general inflammatory responses by inducing a wide range of inflammatory mediators, including COX-2, inducible nitric oxide synthase, and proinflammatory cytokines such as interleukin (IL)-1b, tumor necrosis factor (TNF)a, and IL-6 (Akihisa, 2000). The nuclear factor (NF)-kB, CRE, C/EBP, and activator protein (AP)-1 are just a few of the cis-acting elements that are present in the 50-flanking region of the human and murine Cox-2 [14,15,16]. Depending on the cell types and stimuli, several transcription factors, such as activator protein (AP)-1 and C/EBP, can also regulate COX-2 expression independently of NF-kB, even if NF-kB is one of the most important transcription factors involved in inflammatory responses and many studies have linked NF-kB to trans-activating the Cox-2 gene (Limtrakul, 2015). Rice is a key food in Asia. A bioactive ingredient called g-oryzanol is extracted from rice bran oil and is made up of a combination of phytosterol ferulic acid esters (Yasukawa, 1998).

It has a variety of pharmacological effects, such as anti-inflammatory (Li J Zhang, 2006, Kesharwani, 2012, Goyanes, 2006) and anti-tumor properties. In RAW264.7 macrophages, g-oryzanol has been shown to lessen LPS-mediated COX-2 expression by regulating NF-kB and AP-1. But the mechanisms by which goryzanol suppresses COX-2 expression apart from NF-kB are not well understood. The goal of this research was to find further ways by which g-oryzanol inhibits Cox-2 transcription mediated by LPS. According to our findings, the transcription factor Egr-1 is essential for the highest level of COX-2 induction after LPS stimulation, and g-oryzanol lowers Egr-1 expression to block LPS-mediated COX-2 expression in RAW264.7 macrophages (Butt, 2015). We created folic acid conjugated multiwalled carbon nanotubes loaded with gamma-oryzanol (G-OZ/FA-MWCNTs) as a way to increase the availability of gamma-oryzanol. The produced γ-OZ/FA-MWCNTs were further characterized using Fourier transform infrared (FT-IR) spectroscopy. The proposed mixture was ultimately subjected to tests for cytotoxicity, in vitro release profile, and entrapment effectiveness.

MATERIAL AND METHOD

We purchased multi-walled carbon nanotubes (MWCNTs) produced by chemical vapor deposition (CVD) from Platonic Nanotech Private Limited in Jharkhand, India. With a diameter × length of 110-170 nm × 5-9 μm and a melting temperature ranging from 3652 to 3697°C, the MWCNTs are 99.3% pure. In Punjab, India, we also bought gamma-oryzanol from A. P. Organic Pvt Ltd. The following reagents were acquired from commercial suppliers: folic acid (FA), N-hydroxysuccinimide (NHS),

dimethylsulfoxide (DMSO), tetrahydrofyran (THF), N,N-dimethyl formamide, and ethylene diamine.

Purification of carbon nanotubes

Purification of MWCNTs is based on the ideas of selective oxidation, where carbonaceous impurities oxidize more quickly than CNTs, and metallic impurity dissolution by acids (Peng-Xiang et al., 2008). The unpurified MWCNTs were treated with HCl to remove amorphous and catalytic impurities. After obtaining a specific quantity of unpurified MWCNTs, they were magnetically agitated for five hours in strong hydrochloric acid. A 0.45 µm polytetrafluoroethylene (PTFE) filter (Sigma Aldrich, USA) was then used to filter the mixture. Acid-purified MWCNTs were put in an oven set at 530°C for 30 minutes in order to remove the amorphous carbon (Sardiya, 2024).

Cutting → Carboxylation → Acylation → Amidation of purified MWCNTs:

The chemical group that should be linked to the nanotubes depends on the kind of polymer that has to be strengthened. Since carboxylic acid groups can initiate a variety of chemical processes, many writers (Hartmann, 2009) have proposed that their existence on the surface of carbon nanotubes (CNTs) is a frequent means of achieving this objective. The purified MWCNTs were oxidized for 15 minutes in a sonication tube using a 3:1 ratio of concentrated H2SO4 and HNO3. The made suspension was placed into a round-bottom flask (RBF) after sonication and magnetically agitated at 60 ± 2°C for 4 and 12 hours. Following that, it was filtered and washed using deionized water. Finally, the black solid residue was vacuum-dried at room temperature (RT) for the duration of the night. The carboxylated MWCNTs were constantly stirred at 70 ± 2°C for 24 hours while 30 mL of thionyl chloride (SOCl2) and dimethyl formamide (DMF) were added in a 20:1 ratio. The resulting suspension was filtered, and the remaining material was treated five times with anhydrous tetrahydrofuran (THF) to eliminate any remaining thionyl chloride. The residual solid was dried in a vacuum oven. For two days, 20 mg of acyl-chlorinated MWCNTs were reacted with 10 ml of ethylene diamine solution (EDA) at 100 ± 2°C. To remove extra diamine, the MWCNTs were cooled to room temperature and then five times in ethanol. In the end, the dark solid residue was vacuum-dried at room temperature for a full night.

Conjugation of folic acid to amine modified MWCNTs

500 milligrams of folic acid were introduced to a beaker that contained 25 milliliters of methanol and a known quantity of amine-modified MWCNTs. Acetone was added to the reaction to create a yellow precipitate after it had been processed for five days at room temperature with constant stirring. FT-IR, H-NMR, and XRD were used to examine the dried and filtered folate conjugated MWCNTs (f-MWNCTs).

Loading of drug (Gamma-oryzanol) in MWCNTs

The characterisation method of FA conjugated MWCNTs included an assessment of their drug-holding and drug-release properties in release media. Twenty milligrams of gamma-oryzanol and ten milligrams of f-MWCNTs (2:1 ratio) dispersed in phosphate buffer saline (pH=7.2) were mixed together and stirred overnight to aid in drug encapsulation. Following encapsulation, the drug-loaded f-MWCNTs were extracted from the fluid by ultracentrifugation. The amount of GOZ trapped in systems based on f-MWCNTs was independently ascertained by measuring the amount of GOZ in supernatant using a UV spectrophotometer (Shimadzu 1601, Japan). With pristine MWCNTs, a comparable procedure was employed (Sardiya, 2024).

In vitro Drug release studies

Under physiological conditions (PBS; pH 702), the in vitro release of medication from two different formulations (pristine MWCNTs and f-MWCNTs) was determined. For release investigations, the dialysis membrane (MWCO; 2000 Da) was chosen. After inserting five milligrams of the formulation into the dialysis sac and sealing it from the outside, it was suspended in 100 milliliters of aqueous receptor release medium right away. The in vitro drug release experiment was performed in the receptor compartment at 37±0.5°C with continual stirring under tight sink conditions. At each of the prearranged intervals, one milliliter of the sample was taken out and replaced with an equivalent volume of new medium. Drug was measured using a spectrophotometer (UV/Vis Shimadzu 1601, Japan) at 314 nm after the proper dilutions.

RESULT AND DISCUSSION

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The MWCNTs were purchased from Platonic Nanotech Private Limited in Jharkhand, India. The FT-IR spectra of the purified virgin MWCNTs show only one peak, which suggests that no contaminants are present. MWCNTs with amine ends were linked with folic acid. The FT-IR spectra of FA conjugated MWCNTs (f-MWCNTs) show the aromatic carbon-hydrogen bending peak as well as the aromatic carbon=carbon bending and stretching peak.

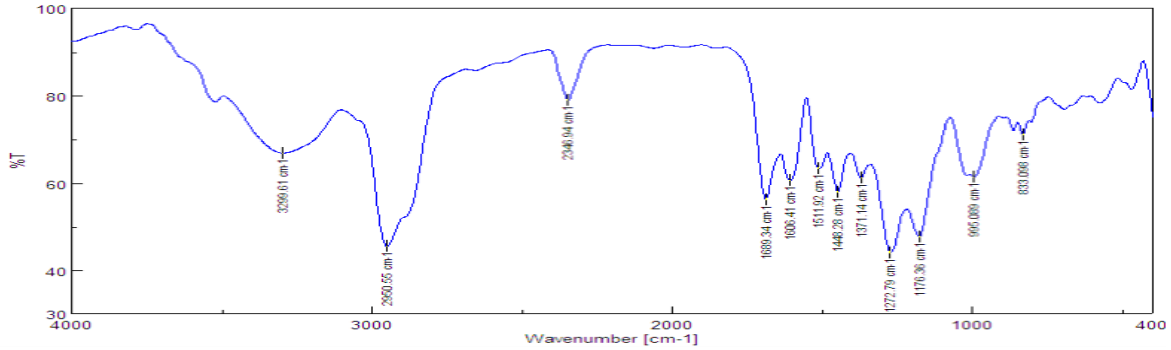

Figure 1. - FT-IR spectrum GOZ

Gamma-oryzanol was loaded into pristine and conjugated folic acid-containing MWCNTs using the equilibrium dialysis technique. The drug loading experiment was conducted at room temperature in a phosphate buffer saline pH 7.2 dispersion medium. The drug loading for folic acid conjugated MWCNTs (FA-MWCNTs) were higher, at 85.5 ± 1.4%. Conversely, pure MWCNTs displayed a reduced drug loading of 63.4 ±1.8%. In order to assess the release of GOZ from folic acid connected MWCNTs and pristine MWCNTs, the equilibrium dialysis method employed phosphate buffer saline pH 7.2 as the receptor media. The drug release from pristine MWCNTs was found to be 69.26±1.5% over a 24-hour period, while that from folic acid conjugated MWCNTs was 58.96 ± 68%.

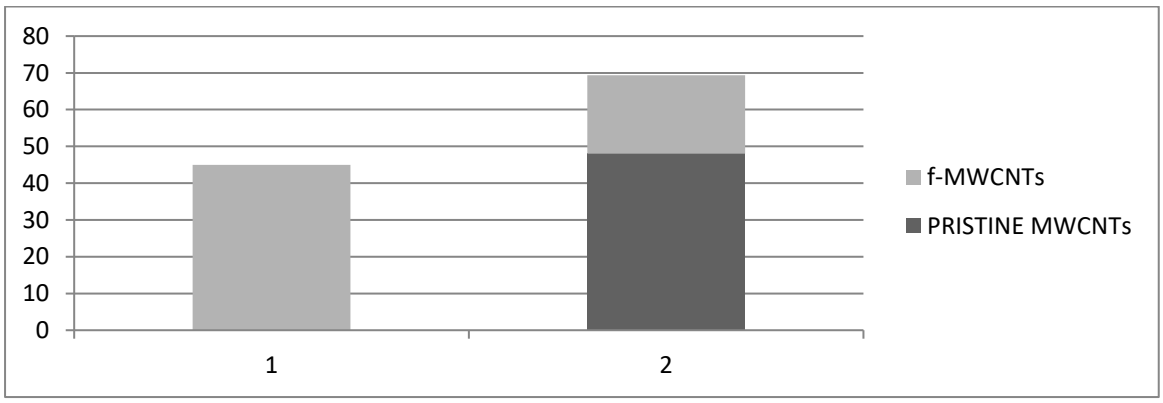

Figure 2. Drug loading efficiency (n=3)

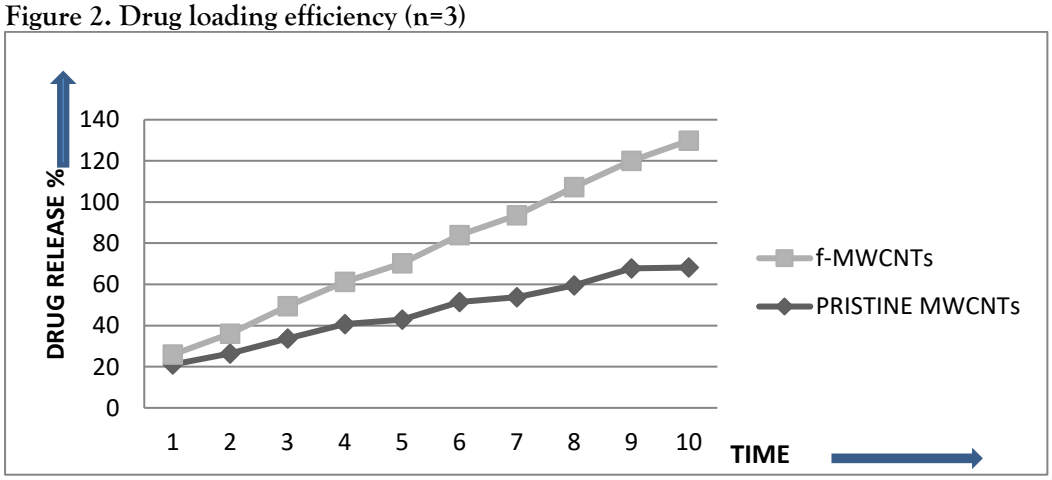

Figure 3. % Drug Release of GOZ in Pristine & Folic acid attached MWCNTs (n=3)

In vivo studies

Since a variety of variables, such as the pH of various biological fluids, the enzyme system, and the varying affinity of the carrier system for the different biological fluids, including the tissue, are anticipated to affect the performance of any drug delivery system, it is crucial to assess it in vivo. The drug release profile and biological distribution in vivo from a new carrier system are influenced by these variables. Additionally, in vivo investigations are necessary to determine the bioavailability of drugs from planned formulations. Following the guidelines set forth by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), the Institutional Animal Ethics Committee carried out the experiments on male Albino rats with an average weight of 200 ± 20 g. The animals were kept in cages with a thermoneutral atmosphere and provided with water and regular rat chow ad libitum.

Induction of arthritis

For assessing acute inflammation, the carrageenan-induced arthritis technique was chosen (Hartmann, 2009). The foundation of this experiment is the single intra-articular injection of 2% carrageenan and 4% kaolin. As the phlogistic agent in this experiment, we used a 0.1 mL combination of 4% kaolin and 2% carrageenan. By injecting a mixture of carrageenan and kaolin into the knee joint and measuring the resulting change in the volume of the inflamed knee joint after 24 hours, joint inflammation was ascertained. The plethysmometer (UGO, Basile, Italy) was used to determine the volume of the inflamed knee joints.

$$\% \text{ Inhibition of arthritis} = \frac{V_{control} - V_{treated}}{V_{control}} \times 100$$

Where,

Vcontrol = volume of rats in control group

$V_{treated}$ = volume of rat in test group.

Knee joint swelling

Pilot studies were conducted to compare the time-dependent effects of the various treatments on the swelling of the knee joint. The increase in the diameter of the joints 48 hours after the C/K injection was a sign of joint inflammation. The cross-sectional area was computed using the formula a×b×π, where 2 a and 2 b are the anteroposterior and mediolateral diameters, respectively, which were measured using a caliper square. An objective and straightforward way to assess joint inflammation is by looking at the changes in the knee cross-section (Fig. 4). The cross-sectional area of the C/K-injected knees was about 35% larger than that of the contralateral knees 48 hours after the challenge, but GOZ and PC treatments reduced it by around 20%, with GOZ completely restoring it to the level of the saline-injected knees.

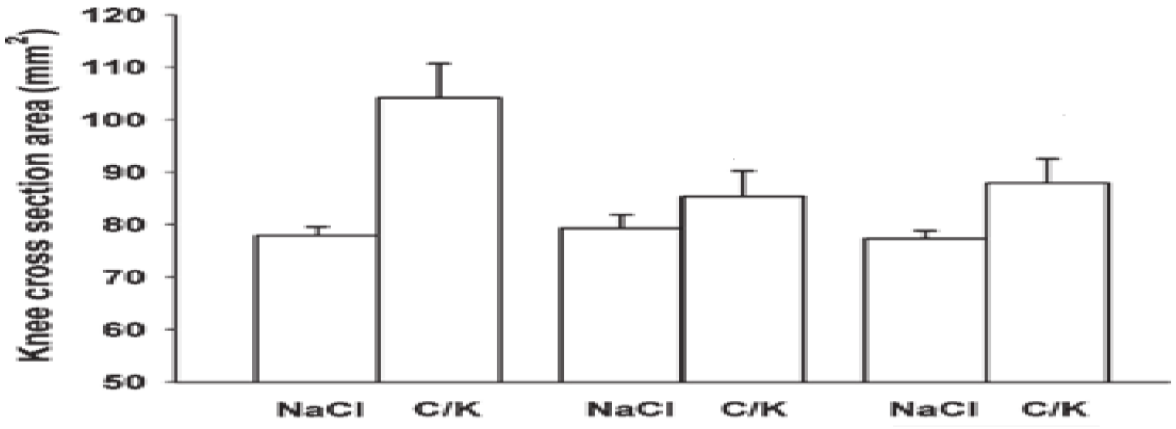

Figure 4. The effects of GOZ or the saline vehicle on the carrageenan/kaolin (C/K)-induced changes in knee joint swelling (expressed as knee cross-section).

The contralateral knees were injected with saline. Data are presented as means ± S.E.M. P < 0.05 vs control limb; P < 0.05 vs C/K + saline (two-way ANOVA, Bonferroni test).

CONCLUSION

CNTs are a new kind of carrier that can be utilized to deliver drugs to specific sites and targets. CNTs are an efficient biological carrier for anticancer drugs due to their distinct mechanical, chemical, and

physical properties. Carbon nanotubes (CNTs) provide a variety of locations for covalent and noncovalent functionalization with therapeutically active compounds because of their unique chemistry and hexagonal carbon atom arrangement. This implies that CNTs could be employed as nanocarriers to deliver therapeutic medicines to particular sites within cancer cells. These functionalized CNTs exhibit a considerable propensity to pass through cell membranes via endocytosis-dependent or independent pathways. It may be concluded that the formulation of GOZ-loaded folic acid-MWCNTs displayed efficient GOZ release to the targeted site with an improved therapeutic margin of safety.

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