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PLGA NANOPARTICLE AS A CARRIER IN COLON TARGETING DRUG DELIVERY SYSTEM

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ABSTRACT

Nanoparticles is a drug delivery system appropriate for almost all type of administration routes of the drug delivery. Over the years, different type of natural and synthetic polymers has been inspected for the formation of nanoparticles, of which Poly (glycolic acid) (PGA), Poly (lactic acid) (PLA) and their copolymers (PLGA) have been widely investigated as it is biocompatibility and biodegradability. Poly (lactic-co-glycolic acid) (PLGA) is one of the effective biodegradable polymeric nanoparticles (NPs). It is approved by the US FDA to be used in drug delivery systems due to its controlled and sustained- release feature, less toxicity, and biocompatibility with cells and tissue. Targeted nano-drug delivery to the colon is advantageous for colon-specific diseases as nanoparticles gets accumulate in diseased parts that improve the efficacies of therapeutics, and localizes treatments, that reduces systemic toxicity. This article deals with the different approaches of PLGA based nanoparticles, that has been used toward the different types of colon drug delivery system.

KEYWORDS

PLGA, Nanoparticles, Colon Cancer, Irritable bowel syndrome (IBS) and Ulcerative colitis.

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INTRODUCTION

Colon is very frequently infected with number of diseases such as inflammatory bowel disease (IBD), colon cancer, irritable bowel syndrome, diverticulitis, colonic dysmotility and parasitic diseases[1]. Colon cancer is ranked third for the cause of cancer related death[2] and ranked second as leading cancer worldwide[3].

The satisfactory therapeutic outcome is usually not observed with conventional drug therapies. Delivery of drug to colon often encounters various challenges such as in parental drug delivery system there is a

distribution of drug though out the body which can cause unwanted adverse effect[4]; unwanted systemic distribution can be overcome in rectal but in rectal administration in ascending colon cannot be reached and may not be suited for colon treating disease[5]. In general, oral route in most preferred route of administration as it has patient compliance, but there are hurdles also like acidic and enzymatic drug degradation and systemic drug absorption from the small intestine could lead to adverse effects and decreased drug availability at the disease site[6].

Physiology of colon also varies with number of aspects like transit time of colon is 6-48 hours[7] which is affected by steroidal hormone[8], high calory intake, fibres-based diet[9]; vareable colonic pH of ascending, transverse and descending (6.4, 6.6, and 7.0, respectively)[10]; fluid volume also reduces from ascending colon towards descending colon and lesser the water content effects dosage solubilization and thus absorption[11].

Use of colon specific polymer has emerged as a solution to overcome the above-mentioned challenges. The polymers that are widely used for colon targeted drug delivery are given as polysaccharide-based polymers namely chitosan, dextran, pectin, ethyl cellulose; biodegradable polymer like PLGA (poly lactic co-glycolic acid), PLA (Polylactic acid); acrylic acid-based polymers like eudragit and carbomer; other allied polymer like polyethylene glycol (PEG), gelatin[12]. PLGA has shown promising result in colon targeting as it is a synthetic polymer, put together by co-polymerization of the glycolic acid (GA) and lactic acid (LA) cyclic dimers. It is nontoxic, biocompatible, and biodegradable as hydrolytic products are simply metabolized by Krebs cycle within the body[13]. With the help of nanoparticle, we can modify the target drug delivery with reduced dosing regimen as shown in [Figure No.1].

"Nano" refers to the measure in nanometres (nm). Nanotechnology includes the design and engineering of nano objects <500 (nm) in size. Different types of nanoscale drug delivery systems include liposomes, micelles, dendrimers, quantum dots, nano capsules, nanotubes, and nanoparticles (NPs) and many more[14,15]. Nanotechnology-based drug delivery systems to the cancer tissue offer better therapeutic efficacy as they specifically target cancer cells. More tumour victims have enhanced permeability and retention (EPR) mechanism. Furthermore, it can also help to overcome the dose dependant and low efficacy targeted to normal cells and cytotoxic effects of conventional chemotherapeutic agents[16].

This article comprises of different articles based on PLGA nanoparticle on different types of colons targeting drug delivery with its outcome.

PLGA BASED NANOPARTICLES USED IN DIFFERENT COLON DISEASE

PLGA NANOPARTICLE IN IRRITABLE BOWEL SYNDROME

Eluxadoline loaded eudragit coated PLGA NPs for treatment of irritable bowel syndrome (IBS). The result showed 6.8-fold enhanced Bioavailability of plain drug loaded NP and 18.5-fold enhanced bioavailability of enteric coated (eudragit) NPs when compared to drug suspension. The enhanced bioavailability could be due to colon specific release of eudragit coated PLGA NPs which are pH responsive. Further a sustain release of drug over a period of 24 hours was observed[17.]

Oral delivery of folate-targeted resveratrol-loaded nanoparticles for inflammatory bowel disease therapy in rats. The result showed resveratrol encapsulated in FA-conjugated PLGA (RSV-FA-PLGA) was transported across Caco-2 cell monolayer more than both resveratrol encapsulated PLGA (RSV-PLGA) and free resveratrol. High release of resveratrol was also observed in both formulation over 24 hours and was a targeted nanoparticle with folic acid[18].

Glycyrrhizin acid-loaded pH-sensitive poly- (lactic-co-glycolic acid) nanoparticles for the amelioration of inflammatory bowel disease [Figure No.2]. The result shows that the nanoparticle particle size range for a drug loaded uncoated PLGA and ES100/PLGA NPs are 197.6 ± 2.28nm and 203.57 ± 11.5nm respectively. There is a negative charge on surface of ES100/PLGA NPs due to presence of

Eudragit S100 which prevent aggregation. It has a sustained release of 72 hours and double protective layer from acidic pH[19].

Design and *in vitro* characterization of multistage silicon-PLGA budesonide particles for inflammatory bowel disease as shown in [Figure No.3]. The result shows that particle density index (PDI) was found to be 0.21 observed under microscope (SEM) and because of smooth spherical surface aggregation don't occur. Entrapment efficiency is also high (about 93.14%) but due to silicon entrapment its degradation gets effected by change in pH like at pH 1.8, only 20% of silicon content degrades and 80% and 50% degradation of silicon at pH 6.8 and 5.5 respectively. The highest release can be observed 1 hours after incubation at pH 7.4, with 80% of silicon degrades after 4 hour and reaches around 100% degradation after 24 hours in multistage vector of budesonide Nanoparticles (MSV-BNP). MSV-BNP were accumulating in higher levels in the inflamed epithelial IBD model, which reduces release of pro-inflammatory cytokines IL-8 and IL-1β[20].

PLGA NANOPARTICLE IN COLON CANCER

Enhanced antitumor efficacy in colon cancer using EGF functionalized PLGA nanoparticles loaded with 5-Fluorouracil and perfluorocarbon as mentioned in [Figure No.4]. The results show particle size of 5-Fluorouracil loaded PLGA nanoparticles observed under microscope (TEM) was found to be 200nm. Zeta potential analysis showed that epidermal growth factor of PLGA in 5-Fluorouracil and perfluorocarbon nanoparticles has a negative surface charge of -23.7 ± 1.4mV with encapsulation efficiency and drug loading efficiency is 81.6±5.7% and 7.29±0.14% respectively[21].

The nanoparticle exhibits a biphasic drug release pattern that is initially accelerated release followed by sustain release which last over 7 days and has an increased cellular uptake as it binds to epithelial growth factor (EGF) receptor[21].

PHBV/PLGA nanoparticles for enhanced delivery of 5-Fluorouracil as promising treatment of colon cancer. The results show that coefficient of determination (R2) was found to be 0.82 and in about 4 hours 100% of 5-Flurouracil was released. Nanoparticle improves low cellular uptake of hydrophilic drug[22].

PHBV nanoparticles are taken up by endocytosis pathway in the HeLa cells[23] as shown in [Figure No.5]. It has also been reported that endocytosis is a major pathway in uptake of PLGA nanoparticles[24]. The value for IC50 for 5-Flurouracil and 5-Flurouracil loaded in nanoparticles was found to be 107.15 and 46.77μM, respectively.

Results also showed that PHBV/PLGA nanoparticles does induce less than 5% of haemolysis. The entrapment efficiency % and particle size was found to be 43.86% and 135 nm, respectively[25].

Chemopreventive Effect of 5-Flurouracil Polymeric Hybrid PLGA-Lecithin Nanoparticles against Colon Dysplasia Model in Mice and Impact on p53 Apoptosis. The result shows that particle size ranges from 138nm- 210nm with percentage entrapment efficiency of polymer PLGA lipid hybrid nanoparticles were found to be 58.7%- 75.6%. An *in vitro* study showed that there was a burst release of 17.22% of 5-Flurouracil at 7 h and furthermore, there was a controlled release up to 78.23% for 24 h. The nanoparticles exhibited a biphasic drug release pattern with initial accelerated release than followed by sustained release over 7 days[21,26].

Enhanced drug retention, sustained release and anti-cancer potential of curcumin and indole-curcumin analogy-loaded polysorbate 80-stabilizied PLGA nanoparticles in colon cancer cell line SW480. The result shows that drug loaded nanoparticle exhibits lesser cytotoxicity as only 50% of the drug gets released within 48 hours and it also induce nuclear fragmentation in SW 480 cells. Indole analog of curcumin- loaded PLGA nanoparticles and Cur-loaded PLGA nanoparticles treats SW480 cell line expresses lower level of COX-2[27].

Reparation and characterization of PLGA-PEGPLGA polymeric nanoparticles for co-delivery of 5- Fluorouracil and Chrysin. The result showed that zeta potential of PLGA-PEG-PLGA empty

nanoparticles is -0.9mV while with chrysin and 5-Fluorouracil zeta potential changes to – 12.8Mv. It acts on HT29 cell line[28].

PLGA NANOPARTICLE IN COLORECTAL CANCER

Gambogic acid-loaded biomimetic nanoparticles in colorectal cancer treatment. The result shows that red blood cells membrane- Gambogic acid/PLGA shows the best reduced tumour volume as compared to gambogic acid/PLGA, gambogic acid, red blood cell membrane-PLGA and nanospheres. As it properly inhibits the proliferation of SW480[29].

α-Mangostin-encapsulated PLGA nanoparticles inhibit colorectal cancer growth by inhibiting Notch pathway. The result shows uptake of α-Mangostin nanoparticles was observed in 10 minutes and maximum uptake was observed at 30 minutes. It inhibits self-renewable capability of cancer stem cells by suppressing Notch signalling pathway by reducing Notch receptors (Notch 1 and Notch 2) their ligands (Jagged 1 and DLL4), gama- secretase complex protein (Nicastrin) and downstream target Hes-1. It also prevents causes of heterogenous lineages of cancer cell as it inhibits expression of stem cell markers (CD133, CD44, Musashi and LGR5) and pluripotency maintaining factors (Oct-4, Sox-2, KLF-4, c-Myc and Nanog) in cancer stem cells[30].

Co-Administration of iRGD Enhances Tumor-Targeted Delivery and Anti-Tumor Effects Of Paclitaxel-Loaded PLGA Nanoparticles for Colorectal Cancer Treatment. The results show PLGA paclitaxel co-administered with iRGD significantly increases accumulation of nanoparticles preferably enhance therapeutic activity *in vivo*. PLGA Paclitaxel inhibits cell cycle arrest in G2/M phase and resulted in caspase activation and cell apoptosis and at low concentration, PLGA Paclitaxel inhibits tumour cell migration. PLGA paclitaxel iRGD targets integrin and neuropilin-1 receptor on LS174T tumor cells to trigger tissue permeation and drug delivery[31].

Effect of Oxaliplatin-Loaded Poly (d,l-Lactide-co-Glycolic Acid) (PLGA) Nanoparticles Combined with Retinoic Acid and Cholesterol on Apoptosis, Drug Resistance, and Metastasis Factors of Colorectal Cancer. The results show Oxaliplatin-containing nanoparticulated DDS exhibits a prolonged activity as compared to the free drug, which suggests an increased bioavailability inside the cancer cells[32].

PLGA NANOPARTICLE IN ULCERATIVE COLITIS

Colon-targeted delivery of cyclosporine A using dual-functional Eudragit FS30D/PLGA nanoparticles ameliorates murine experimental colitis. The results demonstrates that the PDI (Polydispersity index) was less than 0.3, which shows a monodisperse size distribution[33]. It also overcome cyclosporine A side effects such as nephrotoxicity, neurotoxicity, and opportunistic infections[34]; as it is targeted drug delivery system and avoids high systemic concentration

Orally targeted galactosylated chitosan poly (lactic-co-glycolic acid) nanoparticles loaded with TNF-α siRNA provide a novel strategy for the experimental treatment of ulcerative colitis. The results demonstrates that entrapment efficiency found was to be low (85.18±0.01%) in galactosylated chitosan coated PLGA nanoparticle formed at low PLGA concentration (1.0mg/mL), with high PLGA (2.0mg/mL) entrapment efficiency was high (90.10±0.01%) and with PLGA (3.0mg/mL) entrapment efficiency decreases (77.77±0.01%); so the optimum amount is needed as high concentration will increase the viscosity. At the end, after optimising the particle size was found to be 245.60±0.33nm, zeta potential was 13.03±0.65mV, polydispersity index (PDI) was 0.30±0.01 and entrapment efficiency was 90.11±0.01%[35].

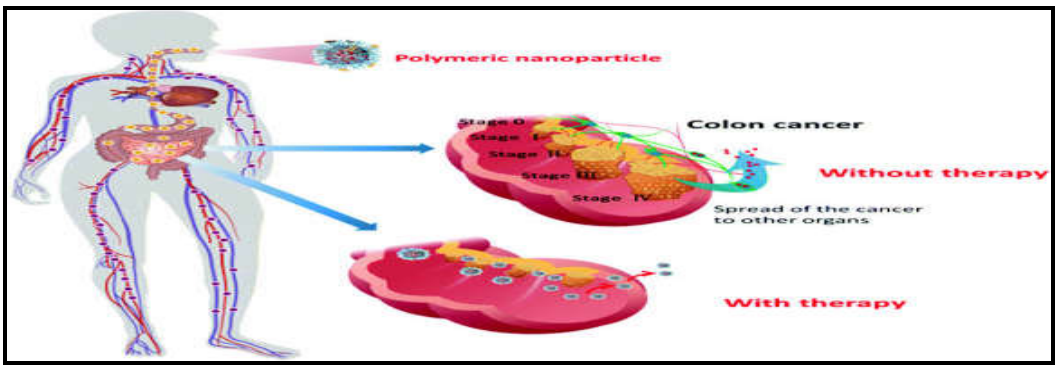

Figure No.1: Demonstration of therapy with the help of nanoparticles

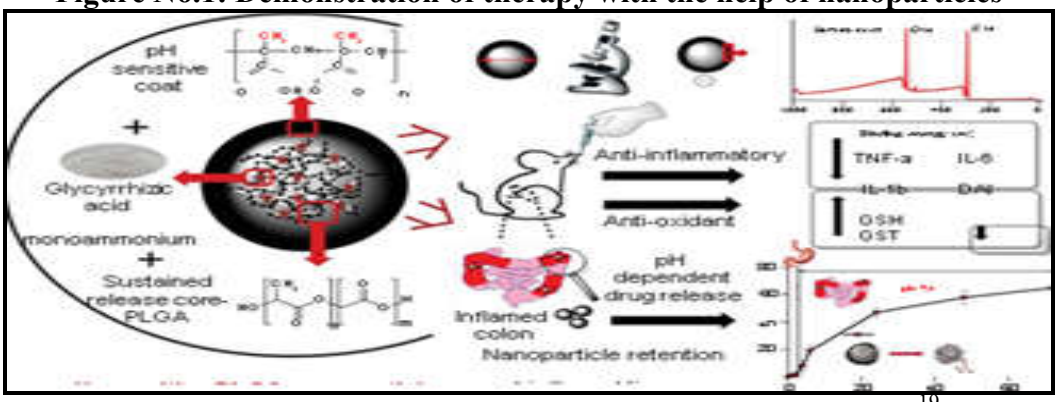

Figure No.2: Glycyrrhizin acid-loaded PLGA nanoparticle[19]

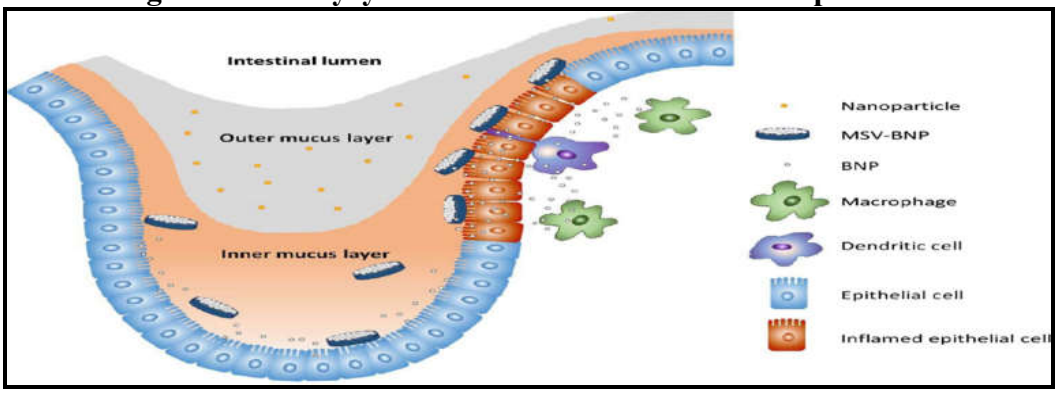

Figure No.3: Silicon PLGA budesonide particle for inflammatory bowel syndrome[20]

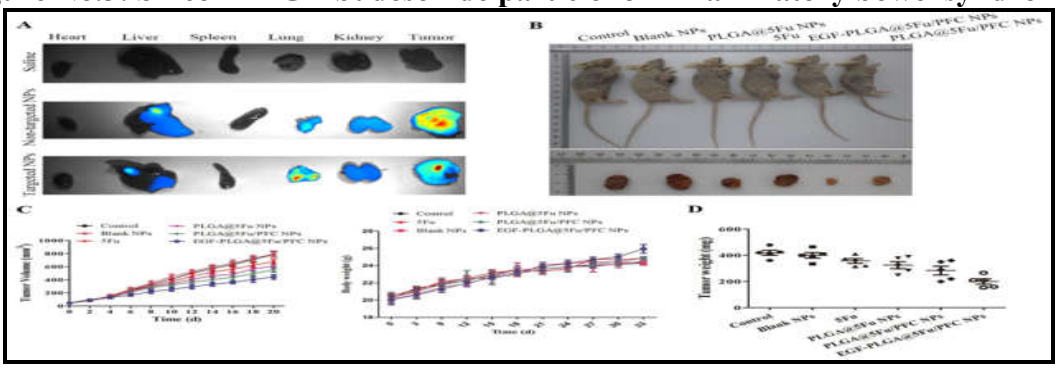

Figure No.4: PLGA nanoparticles loaded with 5-Fluorouracil and perfluorocarbon

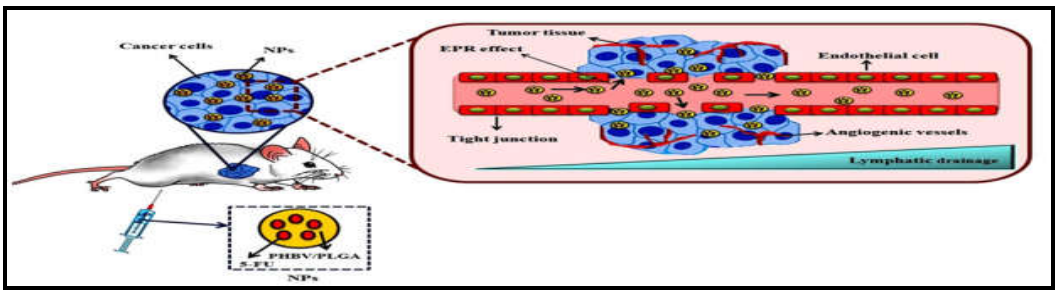

Figure No.5: PHBV/PLGA nanoparticles for enhanced delivery of 5-Fluorouracil[25]

CONCLUSION

We have successfully seen that constructionof a biocompatible nanodrug delivery system that could selectively accumulate in at the targeted site and overcome different type of diseases resulting in the improved therapeutic effects. It provides systems stability with lesser aggregation of particles. Reduced side effects can be seen with increased entrapment efficiency and better zeta potential range that gets more compatible as PLGA is a biodegradable polymer that is more compatible for human body. With a combination of nanoparticle and PLGA polymer the effectiveness of drug increases. Nanoparticles not only relates the optimization for size, drug loading and drug release, but also contributes to biocompatibility, pharmaceutical up scaling and batch-to-batch reproducibility.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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