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ORIGINAL ARTICLE

Formulation and characterization of 5-Fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer

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Abstract 5-Fluorouracil is used in the treatment of colorectal cancer along with oxaliplatin as first line treatment, but it is having lack of site specificity and poor therapeutic effect. Also toxic effects to healthy cells and unavailability of major proportion of drug at the colon region remain as limitations. Toxic effects prevention and drug localization at colon area was achieved by preparing enteric-coated chitosan polymeric nanoparticles as it can be delivered directly to large bowel. Enteric coating helps in preventing the drug degradation at gastric pH. So the main objective was to prepare chitosan polymeric nanoparticles by solvent evaporation emulsification method by using different ratios of polymer (1:1, 1:2, 1:3, 1:4). Optimized polymer ratio was characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), entrapment efficiency and particle size and further subjected to enteric coating. *In vitro* drug release studies were done using dialysis bag technique using simulated fluids at various pH (1.2, 4.5, 7.5, 7.0) to mimic the GIT tract. 5-FU nanoparticles with drug: polymer ratio of 1:2 and 1:3 has shown better particle size (149 ± 1.28 nm and 138 ± 1.01 nm respectively), entrapment efficiency (48.12 ± 0.08% and 69.18 ± 1.89 respectively). 5-FU E1 has shown better drug release after 4 h and has shown 82% drug release till 24 h in a sustained manner comparable to the non-enteric coated tablets, which released more than 50% of the drug before entering the colon region. So we can conclude that nanoparticles prepared by this

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method using the same polymer with the optimized ratio can represent as potential drug delivery approach for effective delivery of the active pharmaceutical ingredient to the colorectal tumors.

1. Introduction

Among the various types of cancers, colorectal cancer is a significant source of morbidity and mortality in the United States and other Western countries. The cancer is one of the most dreaded and threatening diseases in the world, causing more than 6 million deaths a year (Ramanathan et al., 2003). Colorectal cancer is the second leading cause of death followed by lung cancer (Dhawale et al., 2010).

Various cytotoxic drugs are used for the treatment of colorectal cancer like 5-Fluorouracil, Oxaliplatin, and Cisplatin. The first line treatment generally includes the combination of 5-fluorouracil and oxaliplatin by intravenous administration. The rationale behind using cytotoxic drug over others is their toxicity to the cells that are rapidly dividing which can be attributed to the fact that cancer cells undergo rapid growth proliferation. Most of these drugs are administered by intravenous route to attain maximum bioavailability, still treatment failure is observed for most of the cytotoxic drugs. The main problem for the treatment failure is the drug inability to act particularly at the target site, which leads to lack of site specificity leading to the side effects to both healthy cells and tumor cells by the drug. Some of the other limitations associated with the anti cancer drugs are their hydrophobic nature, improper biodistribution and their susceptibility to develop drug resistance (Wong et al., 2007; Duran et al., 2008).

Therapeutic strategies currently used in the treatment of colorectal cancer are chemotherapy, surgery, radiation and biological therapies (immuno therapy and hormonal therapy). The benefits of traditional chemotherapy are limited by the toxicity associated with anticancer drugs in healthy tissues. The common features of cancer and healthy cells make it difficult to achieve pharmacoselectivity of drugs at the target site (Cirstoiu-Hapcaa et al., 2009).

Lack of site specificity is one of the major reasons for the drug in reaching the target site in therapeutic concentrations in colorectal cancer (Michor et al., 2005; Krishnaiah and Satyanarayan, 2001). Generally in order to compensate the lack of site specificity, increase in the dose size is preferred which leads to various toxicities. Researchers have proved targeting the drug to the tumor tissues. Also localization of the drug at the colon area helps in getting drug released at colon region leading to the major amount of the drug entering the colon. Coating the drugs with various polymeric substances like cellulose derivatives (Levine et al., 1987) and acrylic polymers (Rasmussen et al., 1982) can deliver them directly to large bowel. The main rationale behind using these types of polymers is their ability to prevent drug degradation in the gastric environment in the stomach and their ability to release the drug after entering the distal ileum (Levine et al., 1987; Rasmussen et al., 1982).

5-Fluorouracil (5-FU or 5-fluoro-2,4-pyrimidinedione) has broad spectrum of activity with a broad spectrum of activity against solid tumors (of the gastrointestinal tract, pancreas, ovary, liver, brain, breast, etc.), alone or in combination with chemotherapy regimes. The mechanism behind the cytotoxicity and cell death activity of 5-FU is its interference with nucleoside metabolism in RNA and DNA (Arias, 2008).

To maintain therapeutic serum concentration, constantly dose administration of 5-Fluorouracil has to be given leading to severe toxic effects after certain limit (Zhang et al., 2008b; Arias et al., 2008). The overall response rate for advanced colorectal cancer of 5-FU alone is still only ≈ 10%, and the combination of 5-FU with other antitumor drugs has merely improved the response rates to just ≈ 45%. 5-FU injection is generally used with the specification of 0.25 g/10 ml (Grem, 2000; Malet-Martino and Martino, 2002).

So the main objective is to develop 5-fluorouracil chitosan nanoparticles with different polymer ratios using solvent emulsification evaporation method. Eudragit L-100 polymer was used which can provide enteric coating thereby protecting the drug at acidic environment in the stomach and releasing the drug at basic p^H starting from the intestine to colon. The other novelty associated with this study is the administration of the nanoparticles orally to improve the patient compliance and also making available the dosage form directly to large bowel via the GIT tract so as to localize the maximum amount of drug in the colon area and also attaining the sustained release.

2. Materials and methods

2.1. Materials

5-Fluoro uracil, used as active pharmaceutical ingredient was obtained from Sigma Aldrich, Mumbai. Chitosan (purified), used as polymer was obtained from M/s Panacea Biotech, Chandigarh, India. Eudragit S100, used for enteric coating was obtained from Degussa, Germany. Dialysis bag and triethyl citrate were purchased from Himedia. Polyvinyl alcohol was obtained from BDH Laboratories. All other chemicals were of analytical grade. Doubly distilled water was used throughout the study.

2.2. Preparation of chitosan polymeric nanoparticles

The method used for the preparation of chitosan nanoparticles containing 5-FU is solvent emulsification evaporation technique. Different ratios of drug: polymer (1:1, 1:2,1:3, 1:4) was selected in order to optimize the best one and also to observe the effect of polymer on the formulation.

Acetic acid was used as organic solvent and PVA as surfactant in a fixed concentration of (0.5% w/v). Drug was dissolved in 40 ml water with varying polymer ratios (1:1, 1:2, 1:3, 1:4). Then it was followed by addition of aqueous surfactant polyvinyl alcohol using high speed emulsifier and was stirred continuously for 3 h. Then the emulsion was subjected to