CONTROLLED RELEASE OF CHEMOTHERAPEUTIC DRUGS THROUGH CHROMONIC NANOPARTICLES

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by

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CERTIFICATE

This is to certify that the thesis entitled **"Controlled release of Chemotherapeutic drugs through Chromonic Nanoparticles",** being submitted by **Mr. Rahul Misra** to the Indian Institute of Technology Delhi, New Delhi, for the award of the degree of **Doctor of Philosophy** in Chemical Engineering, is a record of bonafide research work carried out by him. Mr. Rahul Misra has worked under my guidance and supervision and has fulfilled the requirements for the submission of the thesis.

The results contained in this thesis have not been submitted in part or in full to any other university or institute for the award of any degree or diploma.

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ABSTRACT

In conventional chemotherapy cycles, the concentration of drugs administered in the bloodstream varies with time between a maximum concentration (which may represent a toxic level) and a minimum value (below which the drug is ineffective). In each cycle, the drug concentration inside the body reaches a toxic level (referred as “peak”) and then decreases after a particular period of time. These toxic levels not only kill cancer cells but also affect healthy tissues of the body. Ideally, a constant therapeutic level of drug is desirable, to avoid the toxic effects on healthy cells. Controlled drug delivery strategies aim to provide such constant drug concentrations in the body over long periods of time. This also reduces the frequency of high peaks in toxicity and the deleterious impact of healthy tissue. Past studies have shown the potential of drug loaded nano-carriers to target cancer cells and release the drugs at site in controlled manner. Most of these nano-carriers can effectively carry the loaded drugs to target site but they release the drugs in a burst rather than in a controlled manner. Moreover, the drug loss reported with these nano-carriers is in the range of 15-40%. Nano-carrier of ordered material show high encapsulation. Chromonics represents such class of materials. Chromonic materials show high order self-assembly which are driven primarily by enthalpic forces. Even at low concentrations, these molecules self-assemble into ordered stacks or columns. These stacks can act as hosts for different guest molecules (dyes, drugs, proteins), and be used as vehicles for their delivery. Nanoparticles from self-assembled chromonics solutions would include guest molecules which could be delivered and released in controlled way. These guests generally interact with aromatic ring complexes to participate in ordered self-assemblies. Since they can be engineered to form ordered nanoparticles, they offer several advantages like low drug loss, high encapsulation and control release.

In the present study, folates as chromonic material has been explored for controlled drug delivery. Folic acid is a natural vitamin, easy to digest, biocompatible in nature. They form ordered aggregates (even at low concentration of 0.1 wt. %) to form liquid-crystalline solutions. The major objectives of this study were to develop folate nano-carriers in size range 50-500 nm from liquid crystalline folate solutions and encapsulate the anti-cancer drugs in these nanoparticles. This study also aimed to develop a method for controlled release of encapsulated drugs through folate nano-carriers.

The present study reports a method to engineer nanoparticles made from folate liquid crystalline solutions and the mechanisms for control of their sizes was developed. Liquid-crystalline folate solutions, when mixed with HPMC (Hydroxy Propyl Methyl Cellulose) polymer, form nano-domains in a continuous phase of HPMC. The size of nano-domains formed strongly depends upon the relative concentrations of folate and HPMC. These nano-domains are cross-linked with multivalent salts to form stable nanoparticles. We have reported that by controlling the size of nano-domains and their cross-linking, release of encapsulated drugs can be controlled. These folate nanoparticles were encapsulated with different anticancer drugs (methotrexate, doxorubicin and cytarabine), ensuring high guest loading and low drug losses (4-5%). XRD profile of folate with these drugs shows the participation of drugs in folate assembly. The release behavior of these cancer drugs was extensively studied. Based on these studies, a method has been reported to control the release of drugs from the folate nanoparticle. In addition, this study shows that folate nanoparticles can disintegrate in a controlled fashion resulting in controlled release of the folate ions and drug molecules. This disruption can be controlled by manipulating the size of nanoparticles, amount of cross-linking and cross-linking cation. The drug release

process is optimized through response–surface methodology. Further with the help of mathematical modeling, a mechanistic model has been developed to understand the mechanism of drug release. For a given values of mass-transfer coefficient and surface concentration, the model developed can predict the release behavior of different size of nanoparticles cross-linked with same cation. With the help of MTT assay, the cytotoxic effectivity of drug loaded-folate nano-carriers was studied at different time intervals on HeLa cells. Moreover, the uptake of nanoparticles was studied through fluorescence microscopy and the images suggested active targeting by folate nanoparticles.

Thus, the folates present a potential nano-carrier that is biocompatible, can be controlled in the size scale of interest and presents multiple design variables that can be used to control the release profile. At least with *in- vitro* studies, folate nanoparticles present a strong case as a versatile nano-carrier.

Keywords: Chromonics, folates, self-assembly, chemotherapy, controlled drug delivery