SUMMARY OF UGC MINOR RESEARCH PROJECT REPORT FOR WEB SITE

Grant Details

F. No.: 47-391/07 (WRO), dated 09.05.08

Title: Studies on the photosensitive and phototoxic potential of pharmaceutical substances

Name of PI: Dr. (Mrs.) Anuradha S Majumdar

Duration: 2008-2010 (Two years)

College: Bombay College of Pharmacy

Effective date of starting the project: 2nd September 2008

Total Grant Approved: Rs. 60,000/-

Project Report-Summary

Autoimmune chronic inflammatory diseases are conditions in which body mounts an immune response to itself. Initiation of such diseases is not well understood, but involves both genetic predisposition and environmental factors. Such diseases are usually classified clinically in a variety of ways. For example, autoantibodies or self-reactive lymphocyte can be transferred to an otherwise healthy individual to see if the disease can be reproduced. Other ways to characterize autoimmune inflammatory diseases include establishment of animal models, family history, involvement of immune cells and antibodies and responsiveness of the disease to immunosuppressive pharmaceuticals.

Autoimmune inflammatory diseases such as rheumatoid arthritis are difficult to treat primarily because their causative mechanisms are so difficult to understand. Autoimmune inflammatory diseases are multifactorial - a variety of events must occur before the disease symptoms become apparent. The interplay of these events is highly complex.

Accordingly, treatments for rheumatoid arthritis have been difficult to develop. Conventional therapeutic strategies have focused on monotherapies i.e. administration of single active compound to treat the disease. The drugs used to treat rheumatoid arthritis are generally divided into two categories: non steroidal anti-inflammatory drugs (NSAIDS); corticosteroids (oral, intra-articular and parenteral routes) which provide rapid symptomatic relief but has no effect on the progression of joint damage; and disease modifying anti-rheumatic drugs (DMARDS) which reduce disease activity and slow down the progression of joint damage, thereby preserving function. The most common monotherapies are based on a class of pharmaceuticals known as DMARDS. These pharmaceuticals are generally administered over a period of time, and can, in some cases, provide temporary relief for patients suffering rheumatoid arthritis.

An estimated 2.1 million adults worldwide are affected by rheumatoid arthritis. Methotrexate (MTX) is largely prescribed as second line treatment for long term therapy in rheumatoid arthritis used alone or in combination with other DMARDS, including the newer biological agents.

PROBLEM:

Methotrexate (also known as MTX; N-(4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl)glutamic acid; 4-amino-N-10-methylpteroyl glutamic acid; 4-amino-10-methyl folic acid; methyl-aminopterin; amethopterin) is a folic acid analog and antagonist. Methotrexate has therapeutically employed in numerous chemotherapeutic applications, including the treatment of psoriasis, leukemia, cancers and other disorders resulting from cell proliferation. Methotrexate had also been used as immunosuppressant and for treating dermatomyositis, psoriasis, psoriatic arthritis and autoimmune disease like rheumatoid arthritis (RA).

Methotrexate (MTX) is largely prescribed as second line treatment for long term therapy in rheumatoid arthritis used alone or in combination with other DMARDS, including the newer biological agents. Traditionally the drug is available in oral and injectable formulations but oral or injectable route of MTX administration leads to cessation of the therapy in the first year due to the adverse effect associated with the drug and inadequate drug regimen to contain the same. Also the *in vivo* half-life of MTX is short, and repeated administrations are required for optimal efficacy. MTX is known to undergo photodegradation. Thus patients undergoing high-dose methotrexate show photosensitization. Long term use revealed localized eruption on nose spreading to involve cheeks, eyelids, and palate during the treatment duration. However discontinuation of the drug revealed clear skin. Although the drug efficacy is strong, systemic use of MTX provokes number of side effects such as severe gastrointestinal problems, high first pass effect and hematological disturbances.

The project lead to the development of Novel Methfolate topical semi-solid formulation is a completely unique topical composition comprising of methotrexate loaded niosomes and folic acid thereof and atleast one of the flavonoids such as hesperitin, rutin, quercetin, kaemferol for treatment of chronic inflammatory conditions such as psoriasis, rheumatoid and psoriatic arthritis. This novel Methfolate composition provides advantage of improved photostability, sustained release of MTX as well as folic acid supplementation, which will help to reduce the incidence of liver function abnormalities, will help to overcome hematological disturbances that occur on long term use of the MTX. Thus novel Methfolate topical semi-solid formulation will improve tolerability to the MTX therapy by providing sustained release thereby restricting to once a day application and reducing the systemic toxicity associated with oral and/or parenteral administration of MTX.

ADVANTAGEOUS EFFECT:

Novel Methfolate topical semi-solid formulation is a completely unique topical composition comprising of methotrexate loaded niosomes and folic acid thereof and atleast one of the flavonoids such as hesperitin, rutin, quercetin, kaemferol is a unique preparation with respect to the processing step. It offers an altogether different route of drug delivery of MTX loaded niosomes and folic acid in combination for the treatment of rheumatoid, psoriatic arthritis and

psoriasis. The novel composition of Methfolate provides synergistic and sustained release of MTX from the topical semi-solid formulation. Thus it is efficacious in preventing the progressive stages of chronic inflammatory diseases which have underlying immunological pathogenesis at lower doses of MTX compared to the oral or/ parenteral routes thereby overcoming the systemic side effects of the same. Novel Methfolate topical semi-solid formulation is a complete package of a safe, efficacious, photostable, effective and a sustained release formulation of MTX restricting to once a day application.

SUMMARY OF THE INVENTION:

The present invention revealed a unique composition of a fixed combination containing MTX incorporated in a particulate, colloidal and/or nanocarrier with essential ingredients such as folic acid and at least one of the flavonoid like hesperetin, rutin, quercetin etc. formulated as sustained release, safe, cost effective and patient friendly novel topical semi-solid dosage form.

Also, the present invention provided a process of preparing a novel pharmaceutical composition of MTX providing an advantage of reduced systemic toxicity at low doses of MTX for topical delivery with improved efficacy, photostability and sustained release of MTX therein as well as overcoming the hematological disturbances associated with MTX by co-administering folic acid in the same semi-solid topical dosage form.

Further, the invention provides a novel method of treating a subject having a chronic inflammatory condition like psoriasis, psoriatic and rheumatoid arthritis etc. by administering to the subject with a combination of MTX, Folic acid and at least one flavonoid thereby providing a sustained and effective release rate of MTX.

In addition, this novel Methfolate semi-solid topical formulation will be effective for treating autoimmune diseases preferably rheumatoid arthritis.

Thus the present invention is based on the finding that novel Methfolate semi-solid topical application led to greater anti-inflammatory effect in an inflammatory arthritis animal model.

INDUSTRIAL APPLICABILITY:

MTX loaded niosomes is easy to scale up by lipid film hydration method and further addition of other ingredients such as Folic acid and at least one of the flavonoid like hespertin, rutin, quercetin into a suitable semi-solid dosage form like ointment, creams, gels, lotions etc will be easy to manufacture on a large scale. Thus a scale up and commercial and pharmaceutical production of the same is feasible.

Also the ingredients added to the semi-solid dosage form possessed multipurpose role in providing a synergistic effect to achieve a therapeutic concentration to alleviate the inflammatory condition.