Chapter - 2

Research Envisaged, Aim and Objectives
2. RESEARCH ENVISAGED, AIM AND OBJECTIVES

2.1 RESEARCH ENVISAGED

Treatment of skin diseases such as psoriasis, acne and eczema has ever been a big challenge, while severity of the disease is increasing to a large extent, and a large number of people are being affected. Psoriasis is one of the most frequently occurring skin diseases affecting more than 125 million people worldwide with the total money spent on it as around $11 billion annually. This has led to its becoming a one of the thrust areas for clinical researchers considering the severity of the problem in the current scenario. However, unfortunately, while researchers have been quite enthusiastic in investigating new treatment modalities at the clinical level, meager efforts have been initiated towards the search for newer ways and means on the formulation side of pharmaceutical research. Another variance in this area has been the frequent use of potent corticosteroids and systemic path of delivering drugs to reach out to the skin surface, where diseased targets are really located. In the state of affairs, on the contrary, local delivery through topical route should have been the first choice. This speaks of the failure of presently available topical products which in turn only reveal the failure of their formulation design. In fact, as of now, the latter has not been addressed sufficiently and scientifically. It truly demands the extensive and intensive research in order to exploit the external ways of application rather than exposing and jeopardizing the entire biological system at a stretch by administering the drugs through oral or parenteral route(s).

Accordingly, the present doctoral work entitled, “Development, optimization and characterization of supramolecular carrier system(s) for the delivery of methotrexate and cyclosporin A” has been conceived and planned systematically after thrashing the issues across the entire background. The two molecules selected here, viz. methotrexate (MTX) and cyclosporine A (CysA) are the most frequently prescribed drugs, but through the aforesaid systemic route only. It is intended in the work to explore the possibility of using them topically in order to achieve the desired safety, efficacy and patient compliance.

Methotrexate (MTX) is one of the oldest and the most widely used drug in cancer therapy. It is not only used as chemotherapeutic agent, but also used in the treatment of autoimmune diseases and for the prevention of graft-versus-host disease after hematopoietic transplantation. It is a folic acid analogue and exhibits much more
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affinity to bind dihydrofolate reductase than folic acid that inhibits the cell proliferations. It also inhibits calcineurin dependent DNA synthesis, followed by nuclear factor – κB (NF-κB) inhibition. Moreover, it indirectly inhibits AICAR transformylase that also reduces cell growth and inflammation at the site of application. Despite its unequivocal advantages, there are some limitations too regarding the clinical use of MTX. It has a very short plasma half-life, comprising its limited duration of efficacy in cancer chemotherapy. Moreover, it causes non-specific toxicity on normal proliferating cells when applied frequently or large dose. Resistance development is another point of concern, especially in patients receiving long-term therapy with MTX. Its systemic use may provoke numerous side effects, including nausea, vomiting, fatigue, headache, dyspnea, leukopenia, thrombocytopenia, anemia, and hepatic toxicity. To reduce such undesired effects, it is quite logical and preferable to administer MTX topically. In the past, a number of attempts have been made in this direction. However, none could succeed to a level of success to make it clinically useful because of scanty efforts in research. Development of a novel formulation therefore, is needed for site-specific delivery of MTX to reduce the undesired side effect and enhance the efficiency at the desired site.

Cyclosporine A is a cyclic peptide of 11 amino acids and a potent immunosuppressive agent, highly useful in a range of immune inflammatory skin disorders. It forms a complex with cyclophilin, which inactivates calcineurin phosphorylase, preventing the phosphorylation of nuclear factor of activated T cell and, therefore, the transcription of interleukin-2, interferon-gamma and granulocyte macrophage colony stimulating factor. This results in depletion of lymphocytes and macrophages in the epidermis and dermis. Consequently, this inhibits the activation of T-cell, natural killer cells and antigen presenting cells. Further, CysA also inhibits keratinocyte hyperproliferation, inhibits the release of histamine from mast cells and down-regulates the expression of cellular adhesion molecules on dermal capillary endothelium. Despite its high efficacy, the drug is known to affect the entire immune system as well as the multiple sites of physiological importance owing to its conventional mode of administration, i.e., oral. Therefore, this drug like the earlier one, presents a very strong case for topical delivery which can be achieved by the local immunosuppression at the site of action. The importance of external application of CysA is, however, more pronounced, as it is known to be deactivated by non-specific protein binding (through oral route) and also quickly distributed widely to require dose at higher level than what would it be otherwise.
On investigating the underlying causes for the failures of these two molecules i.e., MTX & CysA, its problems can be sensed at several planes. First, the specific physicochemical characteristics such as solubility, partitioning, molecular weight and structure do not permit these to interact and penetrate in the deeper layers of skin. Secondly, skin in the disease condition like psoriasis and eczema acquiring a 'difficult-to-access' barrier in the prevailing phathophysiological ambience. Finally, it is the empirical understanding of vehicular composition which remains short of the mark for the appropriate delivery of the molecules into the domains of disease. Hence, it calls for the novelty in the approach as per the specific requirement of the drug in order to break the barriers.

Currently, there are many opportunities for improvement in the available methods of drug delivery, based on the different fundamentals. Amongst them, the lipid made self-assembly constituted carriers are one of the most attractive way, full of promises. These, unlike skin-disturbing solvents and vehicles, and physical methods (e.g. ultrasound, electroporation and iontophoresis), tend to exploit the novel bio-compliant materials like phospholipids in association with other excipients for the generation of supra-molecular self aggregates. The latter can be tailored by changing the nature of lipids, composition, methods and experimental conditions, as per the physicochemical make-up of the molecules under study. Due to distinct hydrophilic and lipophilic domains, these aggregates provid biphasic solubility to drugs. Depending upon the design and structure, several isotropic and anisotropic liquid-crystalline phases with distinct microstructures, such as cubic, hexagonal and lamellar phases, can be formed. It can promote changes in structural features and consequently in the mechanical behavior, and may constrain the extent of mobility and direction of movement of molecules dissolved in such systems. All these characteristics may prove to be useful in molding the delivery of drug.

In the present research work, microemulsion (ME) system was chosen for the topical delivery of methotrexate. The hypothesis behind selecting microemulsion as delivery systems lies in its unique composition which would provide biphasic solubility at the molecular level and partitioning into the skin tissue for improved topical delivery. These systems will also have complete and uniform association with the drug molecule(s) for which they have been preferred as against the vesicular systems. The latter were found to have limited entrapment owing to the negative Log P value of the hydrophilic drug molecule.
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Cyclosporine A is another drug selected for the topical delivery, but posing different challenges like unfavorable peptide nature, large molecular weight and unfavorable Log P to find its skin application ineffective. The conventional vehicles, earlier attempted, could not surmount the purpose because of inappropriate interiors of the vehicle. Henceforth, the vesicular system christened as organosomes have been conceptualized for the purpose. These are the unique vesicular systems generated, \textit{in situ}, out of reverse micellar system as a result of the micellar to vesicular transition. This way of preparing vesicles is supposed to yield multiple advantages such as high degree of entrapment and ease of processing and monitoring. Phospholipid is one of the major constituents in this system to impart its skin enriching effect to make the delivery and action of the drug more impact bearing.

Further, to avoid pitfalls of conventionally applied optimization, which would also be time-consuming and quite expensive, the most modern systematic, rational, productive, federally accepted way of optimization using FbD is made applicable here for both drugs. This approach was selected to locate “the best” region of interest with desirable qualities within the entire design space so as choose the optimal formulation for further exploratory investigations.

2.2 AIMS AND OBJECTIVES

The aim of present study is to design and development a novel topical formulation for the potential delivery of MTX and CysA for the treatment of skin ailments. To achieve the said aim, research work has been divided into the following key objectives:

Objective 1: Drug identification and the study of various physicochemical parameters such as solubility, partitioning, etc.

Objective 2: Development and validation of analytical technique(s) for the estimation of drug(s) at various experimental stages.

Objective 3: Development, systematic FbD optimization and characterization of (1) methotrexate microemulsion and (2) cyclosporine organosomes.

Objective 5: \textit{In vitro}, \textit{ex vivo} and \textit{in vivo} studies on both the developed and FbD-optimized formulations.

Objective 6: Stability studies (physical and chemical).