2 RESEARCH ENVISAGED AND PLAN OF WORK

Skin is well-recognized since the time immemorial as a route of drug administration or application. Being the most accessible tissue with a large surface area, skin certainly offers some exciting opportunities for straightway transportation of drug molecules in and through it. Further, it obviates the salient shortcomings of the oral route (e.g. GI disturbances, metabolic degradation of drug and erratic drug absorption) and parenteral route (e.g. painful invasion, inconvenience to user and aseptic costly technology) too. Skin delivery also offers advantage in medication of the pediatric and geriatric patients who are incapable to take medicines per orally. Moreover, it is the most effective, safe and convenient approach to alleviate various dermal and external musculoskeletal inflammatory disorders.

Nevertheless, the pitfalls associated with the current topical approaches did not allow drug to realize its fullest potential. The major hurdles in eliciting the desired therapeutic action are the poor delivery of the active medicaments and its presentation to the receptors in question. These formulations do not take into consideration the physiological and structural aspects of skin (e.g., stratum corneum as the tough barrier to drug transport), as well as the needs of drug molecules related to their physicochemical characteristics. Association of these myriad pitfalls with traditional topical dosage forms, the systemic routes are compulsively employed for the delivery of many drugs. As a matter of fact, the topical route could still have been more appropriate choice for the treatment of ailments of external nature (i.e., muscle pain, inflammation and dermatological diseases) wherein the opportunity of direct accessibility of the drugs is offered.

The failures of traditional drug products may be addressed using some innovative systems and strategies. In this regard, numerous literature reports appears on the diverse aspects and applications of phospholipid-based vesicular (i.e., liposomes) and non-vesicular (i.e., organogels) supramolecular assemblies, with exquisite characters and exceptional bio-mimicking dynamism. These systems can be tailor-designed to suit the purpose of delivering the drugs, either to the desired target site or in its vicinity. Thus, considering the remarkable potential of these carriers, they have been chosen herein to improve the therapeutic performance of the selected drug candidate(s) through topical route.
Accordingly, two promising drug candidates viz. tamoxifen citrate (TAM) and diclofenac diethylamine (DLF) have been selected in the current project keeping in view their delivery problems. In all plausibility, the entrapment of TAM and DLF in the flexible membrane vesicles and lecithin organogels would deliver the drug molecules near or onto the desired target sites, and thus, significantly improve their pharmacokinetic (i.e., dermatokinetic) as well as pharmacodynamic (i.e., therapeutic efficacy) potential. Being encaged within the exquisitely structured multi-phasic interiors of these carriers, drug molecules would acquire a new set of physicochemical properties or milieu. The latter would help in navigating these drug moieties to the desired site of action, while preserving the originality en-route.

In case of TAM, the major goal of present investigation would be to explore the alternative route (i.e., topical) for its improved delivery. The latter is also the most potential route for its application as a topical agent for different skin problems, e.g., psoriasis, keloids, cutaneous melanoma, etc. Also it has immense promise for its direct delivery into the breast tissue for management of chronic conditions, like mastalgia and gynecomastia, and in controlling breast density associated with breast cancer. In case of DLF, however, the task will be focused on to addressing the problems of its existing conventional topical products by formulating its novel carrier-based topical product(s).

TAM is a non-steroidal selective estrogen receptor modulator, available since early 1970s as the treatment of metastatic breast cancer in women. Serendipitously, it was found during a study that chronic plaque psoriasis of breast cancer patient responded quite favorably to TAM administration. There have been a few of more of such reports in support of TAM in the management of psoriasis. Similarly, in another case of papular erythematous patches, the patient showed marked improvement during TAM therapy. Moreover, owing to its multiple mechanisms of action, TAM has been reported to possess high potential in treating some other complicated dermatological disorders like cutaneous melanoma (i.e., skin cancer) and abnormal dermal scarring (i.e., keloid and hypertrophic scars).

However, the oral administration of TAM, which is the only available route of administration so far, is marked with several limitations like low bioavailability (owing to extensive hepatic metabolism), low therapeutic efficacy at site of action.
(owing to its wide distribution in body) and considerable serious health risks like endometrial cancer and hyperplasia, polyps, deep vein thrombosis, pulmonary embolism, changes in liver enzyme levels, and ocular disturbances, including cataract. The wider distribution of TAM in body, after oral administration, also potentially decreases its therapeutic efficacy. Alternatively, non-systemic delivery may reduce the incidence of these aforementioned problems and deliver the drug directly to the site of action. Therefore, it is quite judicious and rational to search an alternative (i.e., topical) route of administration for this drug, when the problems are to be treated on topical site per se. Topically administered TAM might pose fewer or no such risks, eliminating the likelihood of first-pass metabolism too. Moreover, it will find an improved access to the target sites within skin to treat various disorders. Hence, the topical administration of TAM is considered as most promising strategy for its delivery to target sites.

In this pursuit, several attempts have already been made for developing topical TAM formulations, but so far have failed to yield expected results, because of the inability of drug molecules to cross over the horny layer (i.e., stratum corneum) of the skin. The drug is devoid of the requisite solubility and partitioning attributes restricting its penetration into skin. And the conventional topical delivery systems, in this context, are not fully equipped to tackle the lacunae suffered by TAM. Hitherto, there is no topical formulation of TAM available in the global market. Development of an effective and safe topical formulation of TAM, therefore can be highly advantageous and desirable. Hence, banking upon the potential of phospholipid-based vesicular and non-vesicular systems in the optimized form, it was planned to deliver TAM to the desired target site via topical application to attain its maximum desired therapeutic effects.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay in the management of inflammation and pain associated with soft-tissue injuries, rheumatic complaints and osteoarthritis. The main disadvantage of all classical oral NSAIDs is that they carry a risk of upper GI side effects, with up to 30% of long-term NSAID users developing gastric ulcers. Until recently, COX-2 inhibitors were, therefore, seen as a relatively safe arthritis treatment option. However, as illustrated by recent worldwide withdrawals of Vioxx® (rofecoxib) and Bextra® (valdecoxib), the COX-2
inhibitors could also lead to serious adverse side effects, especially on cardiovascular system.

Topical NSAIDs offer the possibility of achieving local therapeutic benefit while reducing or eliminating the risk of systemic side effects. However, topical NSAIDs failed to fulfill their promise. It may be due to the difficulty associated in delivering drug molecules, through the skin in sufficient quantities to exert a therapeutic effect in a manner that makes the treatment favorable. It is generally believed that clinical efficacy, in case of OA, requires absorption of the active ingredient and its penetration in sufficient quantities into the underlying inflamed tissues including the synovium and synovial fluid of joints. Despite nearly four decades of extensive research, the success of transdermal drug delivery remains fairly limited with only a small number of transdermal drug products commercially available. In the light of the foregoing research, there is a considerable need for improvement in the development of a topical formulation of NSAID suitable for acute as well as for chronic use.

DLF, a potent and popular NSAID, was selected for its delivery through topical route. Considering the limitations of currently available topical formulations, as well as the potential of appropriately composed lipid-vesicles and organogels in transcutaneous drug delivery, it was aimed to develop novel drug delivery based topical formulations of DLF.

In order to achieve the set objectives, following studies are planned to be undertaken:

1. **Selection of drug delivery systems:** This would entail the studies on varied phospholipid-based supramolecular vesicular or non-vesicular microstructures viz. FMVs and reverse-micellar LOs to attain the desired topical delivery of selected drug(s).

2. **Selection of appropriate formulation components:** To achieve the above formulation design, the task planned included selection of appropriate formulation components to obtain the desired quality attributes in the developed formulations. It is also envisaged to explore the feasibility of employing cost-effective substitutes for expensive components such as PLs and Pluronics.
3. **Selection of formulation technique(s):** It was planned to screen various preparatory techniques for formulating drug-loaded delivery systems with an aim to obtain maximum process efficiency, ease and reproducibility.

4. **Formulation optimization studies employing systematic DoE methodology:** Systematic optimization studies employing DoE approaches were planned to be conducted to develop the formulation(s) under the given set of conditions to save time, effort and developmental cost, to obtain “the best” formulation(s). An appropriate experimental design like CCD, D-OMD or mixture design would be employed to ascertain the effect of various formulation factors on the response variables like drug entrapment, vesicle count, size and flexibility, drug permeation parameters, rheological profile, stability, etc. Response surface analysis and generation of mathematical model would be carried out using Design-Expert® software. Quadratic and cubic polynomials would be generated using MLRA. Numerical and graphical methods like grid search, desirability function and overlay plot would be employed to search for the optimum formulation(s). The generated mathematical model would be validated by formulating the check-points (i.e., confirmatory runs), and the results would be critically compared with those predicted using RSM. Linear correlations between predicted and observed values would be explored, and their statistical significance discerned.

5. **Standardization of developed formulations:** The prepared formulations would be characterized and standardized for various quality control parameters, followed by stability testing at different storage conditions.

6. **Performance evaluation of the developed formulation(s):** Finally, the validated formulations would be evaluated for their *in vitro* drug permeation and cytotoxicity studies. The pharmacodynamic performance would be evaluated employing varied animal models. The clinical performance would also be assessed on suitable patients or human subjects.