AIM OF PRESENT INVESTIGATION
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Acne is the most common cutaneous disorder of multifactorial origin with a prevalence of 70-80% in adolescents. The pathogenesis of acne is complex. An interaction between hormones, keratinization, sebum and bacteria somehow determines the cause and severity of the disease. Acne by its very nature is an unstable, fluctuating disease with unpredictable exacerbation & temporary remission. Hundreds of touted treatments for acne have turned out to be useless or only marginally effective. The goals of acne therapy include controlling acne lesions, preventing scaring & minimizing morbidity.

Topical retinoids constitute the core of nearly all therapeutic programs in the mild to moderate acne with an ability to be used to treat non inflammatory & inflammatory acne. The therapeutic success in acne is highly dependent on a regular application of the topical agents over a prolonged period of time. But there are several factors which would seem to indicate that topical application may be problematic. Among them is the extremely low solubility of the compounds limiting incorporation into an acceptable vehicle, photo-instability which may render topically applied drug ineffective & tolerability problem leading to significant erythema, dryness, peeling, scaling & irritation of skin. This results in discontinuation of treatment or compliance problems in patients who continue treatment.

Isotretinoin (ITN), a derivative of retinoic acid (13-cis-retinoic acid) is the most effective compound with potential to suppress acne over the long term. It appears to derive its effectiveness from increased production of the antimicrobial protein neutrophil-gelatinase associated lipocalin in the skin reducing sebum levels and in turn reducing levels of P.acnes. An ongoing trial in patients with antibiotic resistant P.acnes indicates that ITN is highly effective; treatment of P.acnes may well become a new
indication for this drug. So, ITN, reducing the growth of P.acnes in a secondary manner was selected for further study. However despite these interesting features, its low solubility limits its incorporation in a suitable vehicle while its poor photostability renders the topically applied drug ineffective. The launched topical preparations such as cream also show systemic absorption & significant skin irritation. So it is necessary to improve skin uptake & reduce systemic absorption of ITN using a carrier with an ability of skin targeting.

Tazarotene, 6-[2-(4,4-dimethylthiochroman- 6-yl)ethynyl] nicotinic acid ethyl ester, (TZR) is a member of a new generation of receptor selective, synthetic retinoids for the topical treatment of mild to moderate plaque psoriasis, acne vulgaris and photoaging. It is quickly hydrolyzed to its active metabolite tazarotenic acid. It normalizes the keratinization pattern and decreases the coherence of follicular keratinocytes, resulting in destruction of comedones and prevention of new ones. Also, it may exert a direct inflammatory effect. Dermal safety studies indicated that tazarotene did not show phototoxic or photoallergic potential. However, mild to moderate local cutaneous irritation, with burning, itching, erythema, peeling, and/or dryness, was observed in approximately 25% of treated patients. So, it is necessary to improve the topical delivery and reduce adverse effect of TZR using a carrier with an ability of skin targeting.

Novel drug delivery strategies like liposomes, niosomes, aspasomes, microsponges, microemulsion, hydrogels & solid-lipid nanoparticles can play a pivotal role in optimizing & enhancing the topical delivery of antiacne agents by either modulating their physicochemical & biopharmaceutical properties or minimizing/eliminating the side effects associated with them, thus offering better patient compliance.
Microemulsions offer an interesting & potentially a quite powerful way for drug delivery as colloidal drug carrier due to their versatility & attractive advantages. The favourable cutaneous drug delivery properties due to large concentration gradients provided by large drug solubility potential of vehicle affinity for the drug together with ease of formulation, their physical & thermodynamic stability makes microemulsions very promising vehicles for future topical formulations. Also topically applied microemulsions have demonstrated to significantly increase the cutaneous absorption of both lipophilic and hydrophilic drugs compared to conventional vehicles e.g. aqueous solutions, neat oil phases, micellar solutions, emulsions and liposomes.

In view of this, exploring the potential of microemulsion in improving the delivery of topical retinoids seems worthwhile. Topical forms of retinoids in the form of MEs are not available. A further advantage of topical use of MEs is the possibility of increasing the rate of penetration of the active ingredient through the stratum corneum. Drug release is known to be much faster when microemulsion based gels (MBG) are used rather than conventional formulations. So microemulsion based gels using a suitable polymer that is capable of modifying the rheological behaviour was developed and evaluated. In order to make ME systems pharmaceutically acceptable it is necessary to formulate such systems using non toxic safe substances. In order to find out innovative ways for administering ITN and TZR and alleviating their disadvantages the present work investigates the development of ME containing these drugs.

The main aim of our investigation was to develop & evaluate microemulsion based gel using GRAS listed components for topical delivery of ITN and TZR. It was hypothesized that oily core present around them would result in reduction of irritation when presented in the form of microemulsion. The present study focused on the
formulation considerations, characterization, and skin targeting evaluation with an ability to improve photo-stability & skin tolerability of ITN and TZR loaded microemulsions.

The work was carried out as per the following plan:

- Screening of various excipients to solublize drug for preparation of novel topical microemulsions.
- Development of methodology for the preparation of topical microemulsions and non-alcoholic microemulsion based gel and its optimization.
- To develop an appropriate analytical methodology for the determination of solubility of drug in various excipients, drug content and in vitro diffusion study of prepared formulations.
- Physicochemical characterization of prepared formulations.
- Evaluation of the effect of the formulation on the uptake of a relevant drug in vitro using the Franz diffusion cell across rat skin.
- Histological studies of rat skin to evaluate the possible toxicities of formulations.
- Evaluation of the photostability of the prepared formulations.
- Primary skin irritation study of optimized formulation in laboratory animal.