LITERATURE REVIEW:

Over the past few years there has been considerable interest in developing colloidal drug carriers as an effective targeted drug delivery system (Katare et. al. 2010). Also various products of herbal origin are evaluated for their effectiveness in the treatment of psoriasis.

The principal advantages of combination product over conventional monotherapy formulations available as creams, solutions, ointments, lotions, gels, and foams, is that the second ones have major limitation of inconvenience of administration. In general, treatment of psoriasis involves first application of Vitamin D formulation to the skin, followed by corticosteroid formulation after determined duration which is a major limitation as far as the patient compliance is concerned. Topical pharmaceutical composition comprising a combination of vitamin D analogue and topical corticosteroid would likely result in better patient compliance.

Furthermore, tolerability and safety end points, such as irritation, dryness, erythema, itching, stinging and burning will be key factors in determining its usefulness. A brief account of literature available on the topical treatment of psoriasis is mentioned below.

A topical anhydrous semisolid was developed by Pavliv et al., 1994, for a novel thymidylate synthase inhibitor chemical entity to maximize delivery of drug in the target organ, the skin. Using in vitro skin studies, the semisolid product delivered approx. 3-times more drug into the skin than a previous clinical solution formulation without significantly increasing receptor values. In vivo rat studies indicated that the semisolid product delivered approximately 8-times more drug than the previously tested clinical solution formulation.

Zonneveld et al., 1998, studied the effectiveness of tacrolimus for topical treatment of chronic plaque psoriasis. Author reported for the first time on the efficacy of nonocclusive topical tacrolimus in the treatment of psoriasis. After a washout phase of 2 weeks, patients were randomized to receive 0.005% calcipotriol ointment twice daily, placebo ointment once daily, or 0.3% tacrolimus ointment once daily. One psoriatic plaque was treated with a surface area of 40 to 200 cm². Efficacy was estimated using the local psoriasis severity index. The reduction in the local psoriasis severity index score after 6 weeks was 62.5% in the
calcipotriol group, 33.3% in the tacrolimus group, and 42.9% in the placebo group. This concluded that there was no statistically significant difference between the efficacy of tacrolimus and placebo ointment. Calcipotriol ointment, applied twice daily, had a better effect than tacrolimus ointment and placebo ointment once daily.

*Mrowietz et al., 2003,* studied Pimecrolimus which was highly effective in treating plaque-type psoriasis when applied under Finn-chamber occlusion. A two-centre, randomized, double-blind, vehicle- and positive-controlled within-patient study was conducted in 23 adult psoriasis patients. Pimecrolimus 1% was applied, twice daily, in an experimental ointment formulation, along with the corresponding vehicle, 0.005% calcipotriol ointment and 0.05% clobetasol-17-propionate ointment to test sites without occlusion for 21 days. Erythema, induration and scaling were evaluated. It was concluded that pimecrolimus 1% in the experimental ointment formulation was significantly more effective than its corresponding vehicle, but less effective than calcipotriol and clobetasol ointment.

*Scheinfeld, 2004,* reviewed the utility of Tacrolimus ointment and Pimecrolimus cream. Tacrolimus and Pimecrolimus are both calcineurin inhibitors and functions as immunosuppressants.

*Mansouri et al., 2006,* tested the effect of Pimecrolimus 1 percent cream in the treatment of psoriasis in a child. On the basis of their case observation, pimecrolimus 1 percent cream appears to be a safe and effective treatment for children with plaque type psoriasis involving periorbital and anogenital regions. It was an open clinical trial rather than a controlled study. The excellent clinical response in the patient suggested that controlled studies to evaluate efficacy of topical pimecrolimus for the treatment of psoriasis are indicated.

An accurate and precise HPLC assay has been established by *Chmielewska et al., 2006,* for simultaneous determination of fluocinolone acetonide and additives in gel. Drugs were chromatographed on a C
\textsubscript{18} reversed-phase column with 55:45 (v/v) methanol–water as mobile phase and detection at 238 nm. Solution concentrations were measured on a weight basis to avoid the use of an internal standard. The method was statistically validated for linearity, accuracy, precision, and selectivity.
Brune et al., 2007, evaluated the effectiveness of Tacrolimus ointment for Psoriasis on face and Intertriginous areas in paediatric patients. Eleven patients between 6 and 15 years of age with facial psoriasis were evaluated in a six month open-center, open-label trial. Clinical evaluations and severity was assessed. Within the first 30 days of treatment every patient had cleared with the use of tacrolimus ointment. Statistically a significant improvement was achieved in each sign of disease and the overall severity score. The only adverse event reported in six months of observation of significant pruritis in one patient. Therefore it was concluded that tacrolimus ointment is an effective treatment for Psoriasis on face and Intertriginous areas in children.

Racheva, et al., 2008, studied the treatment of plaque psoriasis with Elidel. The study includes 12 patients with only with small plaques psoriasis lesions. Elidel 1% cream was used – twice a day. On the basis of the performed clinical observations of patients with plaque psoriasis, treated with Elidel-cream, it was concluded, that this is an inspiring alternative for local treatment of the plaque forms of this disease, and especially of psoriatic plaques, localized on the face and the folds.

Johnston et al., 2010, developed a new stability-indicating reversed-phase HPLC (RP-HPLC) method and validated for simultaneous assay of betamethasone dipropionate (BD) and chlorocresol and also for the estimation of BD related compounds in a pharmaceutical cream matrix. In addition, this newly developed RP-HPLC method was also demonstrated as suitable for a pharmaceutical ointment product that does not contain chlorocresol. This RP-HPLC method was successfully validated per ICH guidelines and proved to be suitable for routine quality control use.

Kurian et al., 2011, reviewed the new topical treatments and varying vehicle delivery advances to manage the psoriasis effectively. He concluded that to ensure therapeutic success, proper patient education about the disease, available treatment options, vehicle selection and adverse effects is essential. Focusing on these areas will help to adequately address the primary reasons for poor patient adherence to topical therapy and result in more optimal clinical outcomes.
Singh et al., 2011, developed and validated a stability-indicating high-performance liquid chromatography method for determination of Calcipotriene. A Zorbax 300 SB-C\textsubscript{18} column in isocratic mode, with mobile phase consisting of a mixture of solution methanol: water (70:30) was used. The quantitation performed at flow rate of 1.0 mL/min at 264 nm and run time was 7.5 min. The analytical method was validated as per ICH guideline for linearity, accuracy, precision, specificity, limit of detection, limit of quantification, and stability. The relative standard deviation values for precision was less than 2\%, and % recovery was greater than 98\% for Calcipotriene.

Pasupathi et al., 2012, formulated a topical combination of corticosteroid & Vitamin D derivative provide a balanced approach to psoriasis treatment. When Calcitriol is used in combination with topical steroids, Psoriasis improves more than one agent alone. The main side effect of Calcitriol is skin irritation. Topical steroids Clobetasol used in conjunction with Calcitriol may lessen skin irritation. Combination reduces hazards associated with long term use of topical Corticosteroids (atrophy and rebound) as well as irritation associated with Calcipotriol.

Molin et al., 2013, reviewed about the types of vehicle of topical corticosteroids available in the market and their impact on its efficacy and patients’ adherence to treatment. The review gives a thorough overview on the substance mometason furoate and the available clinical data with a special focus on the newly developed galenic formulations.

Roy et al., 2013, developed a simple precise NP-HPLC method validated the method for simultaneous determination of Betamethasone Dipropionate and Calcipotriene in topical formulation. Chromatographic separation of drug was achieved on Inertsil Silica 100A\textdegree{} column with two mobile phases Stability indicating capability of developed method is established by analysing forced degradation samples in which spectral purity of Betamethasone Dipropionate and Calcipotriene along with separation of degradation products from analytes peak. The method was validated as per ICH guidelines.

The NDDS with their unique advantageous features provide favorable skin interactions as desired in the psoriasis. Considering the benefits, there have been several recent attempts to
use the NDDS approach to improve the existing topical drug formulations in psoriasis. A brief account of the efforts presents here the current scenario.

_Trotta et al., 1996_, developed oil in water (o/w) microemulsions of Methotrixate having six fold higher permeation flux than that from the corresponding solutions in mice skin.

_Agarwal et al., 2002_, developed Dithranol entrapped in liposomal and niosomal vesicles (0.5%) and found both of them superior to conventional formulation, while liposomes showed better results than niosomes employing mice skin. They found both of them superior to conventional formulation, while liposomes showed better results than niosomes.

_Gidwani et al., 2003_, in their patent application revealed the usefulness of mixed vesicular systems of dithranol with and without salicylic acid.

_Mei et al., 2003_, developed SLNs and microemulsions of Triptolide, a diterpenoid triepoxide in order to explore their potential for the topical delivery of Triptolide. The results indicated that these SLN dispersions and microemulsions could serve as efficient promoters for the TP penetrating into skin.

_Verma et al., 2004_, reported increased transport of Cyclosporin A across skin employing alcoholic liposomes.

_Mishra et al., 2004_, prepared Methotrixate loaded SLN by hot microemulsion congealing technique.

_Shah et al., 2007_, studied in vitro permeation through rat skin indicated that SLN-based tretinoin gel has a permeation profile comparable to that of the market tretinoin cream.

The study on liposomal dithranol continued by _Saraswat A et al. 2007_, resulted in the development of a product which showed that dithranol in greatly reduced doses (0.5%) in liposomes could clear the psoriasis plaques to match that of 1.15% commercially available dithranol ointment.
Katere et al., 2009, demonstrated successful topical delivery of Cyclosporin A through multicompartamental liposomes and microemulsified systems.

Kim et al., 2009, studied Cyclosporin A (CsA)-loaded solid lipid nanoparticles (SLN) for improved skin penetration for the treatment of atopic dermatitis.

Lin et al., 2010, developed Nanostructured Lipid Carriers (NLCs) loaded with both Methotrexate and calcipotriol and reported enhanced drug permeation with limited skin irritation in animal models.

Agarwal et al., 2010, formulated and characterized Acitretin loaded Nanostructured Lipid Carriers (ActNLCs), by solvent diffusion technique

Baboota et al., 2011, has studied the effect of addition of corticosteroid such as Betamethasone Dipropionate and a keratolytic agent such as salicylic acid in nanocarrier based microemulsions formulation for enhancement and sustaining of corticosteroid delivery rate leading to better anti-psoriatic activity.

Although there are wide ranges of therapies available for the treatment of psoriasis, the use of topical therapy remains a key component of the management of almost all psoriasis patients. A wide range of efforts has been made which are mostly centered on the development of carrier-based formulations but very few literatures are available on the combination product. Although the topical corticosteroids are the first line of treatment of psoriasis both as a monotherapy and a complement to systemic therapy, Vitamin D analogs in combination with topical corticosteroids is highly effective for short-term control. However, the drugs belonging to corticosteroids and vitamin D3 analogues are stable at different pH values, combination of the same is challenging to manufacture (Wheeler et al., 2008). Although few conventional products are recently approved by FDA, development of combination product for better treatment and patient compliance is the need of the hour.