LITERATURE REVIEW:

1. **Wolf et al. (1939)** was introduced the tape stripping technique in the early 40’s by Wolf, who investigated the topography of the skin by removing layers of corneocytes with transparent adhesive tapes and by examining them microscopically. In the 50’s, Pinkus applied the new technique to investigate the epidermal regeneration process. By taking punch biopsies of stripped skin sites, he observed that tape stripping stimulated the mitotic rate in the stratum basal. The mitotic rate was maximal after 3 days, and a couple of weeks were required for complete skin renewing. Further studies investigating the epidermal growth kinetic after standardized injury of healthy and atopic dermatitis skin by tape stripping were performed.

2. **Choi et al. (2003)** was proved that tape stripping induces the production of cytokines such as interleukins, tumor necrosis factor - interferon, enhances the enzymatic activity, and increases the ceramides synthesis. The artificial removal of the stratum corneum barrier by tape stripping has become a frequently used model for simulating diseased skin and for assessing the efficacy of skin care products in restoring the barrier. Moreover, a percutaneous penetration enhancement of macromolecules like peptides and oligonucleotides, which usually do not penetrate healthy skin, was observed after removal of the stratum corneum, thus opening the possibility of topical vaccinations.

3. **Dupuis et al (1987)** was standardized the methodology by Dupuis et al, making of tape stripping a method widely used in dermatological research to non-invasively investigate the topical bioavailability and percutaneous penetration of topically applied substances in the 80’s. The investigation of the topical activity of antymykotic and antiviral, the investigation of vehicle effects, barrier function and reservoir formation within the stratum corneum, and the investigation of the percutaneous penetration and absorption of topical corticosteroids are some important examples of application areas.

4. **Van der Molen et al. (2002)** topically applied titanium dioxide could still be detected after removal of 40 tapes because of an accumulation in superficial skin furrow was observed by him, thus falsifying the results. In addition, interseasonal differences have been observed. Among the extrinsic factors, the type of tape used (e.g., cellophane, polyester, polypropylene, polyethylene, rayon), the pressure with which the tape is applied onto the skin, the duration of the ressure, and the force of removal (slow/quick)
influence the stratum corneum removal. These are the parameters which can and must be standardized.

5. **Surber et al. (1999)** standard protocol for tape stripping experiments was outlined by him. The protocol implies the use of a template to delineate the stripping area, and the exertion of a definite pressure e.g., with a roller on each tape before removal. The use of a roller has been shown to prevent artifacts due to furrows and wrinkles. Because of inter-individual differences in stratum corneum thickness, the complete stratum corneum of one skin site should be stripped.

6. **Weigmann et al. (2002)**, Weigmann et al. used the tape stripping method to calculate horny layer profiles, in which the amount of drug penetrated is correlated not only to the tape number stripped in newer investigations but also to the depth of the stratum corneum. This correlation enables the localization of the drug within the stratum corneum layers. For this purpose, the removal of the entire stratum corneum and the quantification of both corneocytes and drug on the tapes are required. Recently, Jacobi *et al.* reported a procedure for the estimation of the removed stratum corneum amount on each tape, thus providing a possibility to avoid the complete removal of the stratum corneum.

7. **Arima et al. (1998)** investigated the effect of hydroxypropyl-P-cyclodextrin (HP-P-CD) on the cutaneous penetration and activation of ethyl 4- biphenylacetate (EBA), a prodrug of the nonsteroidal anti-inflammatory drug 4-biphenylylacetic acid (BPAA), from hydrophilic ointment, using hairless mouse skin *in vitro*. When the hydrophilic ointment containing a complex of EBA with HP-P-CD was applied to full-thickness skin, HP-P-CD facilitated the penetration of EBA into the skin. When the ointment containing the EBA:HP-P-CD complex was applied to the skin, the BPAA flux through the tapestripped skin was greater than that through full-thickness skin, while the activation of the prodrug in the skin was slowed by TS. Their results suggest that the enhancing effect of HP-P-CD on the cutaneous penetration of EBA would be largely attributed to an increase in the effective concentration of EBA in the ointment.

8. **Curdy et al. (2001)** piroxicam from a commercially available gel to human volunteers was administered by, both passively and under the application of an iontophoretic current. After treatment, the SC at the site of application was progressively tape-stripped and piroxicam transport into the membrane was assessed by UV analysis of drug
extracted from the tape-strips. Current application enhanced drug uptake into the SC, as indicated by both increased piroxicam concentrations in the horny layer and detectable concentrations at greater depths in the membrane. The total amount of drug recovered in the SC postontophoresis was significantly higher than that found following passive diffusion for each application time.

9. Escobar-Chávez et al. (2005) the penetration of sodium naproxen, formulated in Pluronic F-127 gels containing Azone® and Transcutol as penetration enhancers, through human skin in vivo by using the TS technique was determined. It was found that the combination of Azone® and Transcutol in PF-127 gels enhanced sodium naproxen penetration, with up to two-fold enhancement ratios compared with the formulation containing Transcutol only. These results were confirmed by TEWL and ATR-FTIR spectroscopy, suggesting a synergistic action for Azone® and Transcutol®.

10. Esposito et al. (2005) monoleine (MO) dispersions produced and characterized as drug delivery systems for indomethacin. An in vitro diffusion study was conducted using Franz cells associated to SC epidermal membrane on cubosome dispersions viscosized by carbomer. In vivo studies based on skin reflectance spectrophotometry and TS were performed to better investigate the performance of cubosome as an indomethacin delivery system. Indomethacin incorporated in viscosized MO dispersions exhibited a lower flux with respect to the analogous formulation containing the free drug in the aqueous phase and to the control formulation based on carbomer gel.

11. Ganem-Quintanar et al. (2006) Naproxen-loaded nanoparticles was used to prepare, in a one-step process, unilaminar films of Eudragit E-100. Nanoparticle films and conventional films were characterized in vitro by drug release studies through a cellulose membrane using Franz-type cells, and in vivo by penetration experiments with the TS technique. Concerning in vivo penetration studies, no statistical differences were found for the amount of naproxen penetrated across the SC and the depth of penetration for the two films.

12. Herkenne et al. (2006) pig ear skin as a surrogate for human skin in the assessment of topical drug bioavailability by sequential TS of the SC was investigated. Ex vivo experiments on isolated pig ears were compared with in vivo studies in human volunteers. Four formulations including ibuprofen in different propylene glycol (PG)-water mixtures
were compared. Derived DPK parameters characterizing the diffusion and partitioning of the drug in the SC \textit{ex vivo} were consistent with those \textit{in vivo} following a 30 minute application period. Furthermore, non-steady-state \textit{ex vivo} results could be used to predict the \textit{in vivo} concentration profile of the drug across the SC when a formulation was administered for 3 h (i.e., close to steady-state). Taken together, the results obtained suggest that pig ear skin \textit{ex vivo} is promising as a tool for topical formulation evaluation and optimization.

13. \textbf{Hostýnek et al. (2006)} shed light on the long-standing controversy on whether wearing copper bangles benefits patients suffering from inflammatory conditions such as arthritis. Sequential TS was performed on healthy volunteers to examine the diffusion of copper through human SC \textit{in vivo}, following application of the metal as powder on the volar forearm for periods of up to 72 h. Exposure sites were stripped 20 times, and the strips were analyzed for metal content by inductively coupled plasma mass spectroscopy. The results indicate that, in contact with skin, copper will oxidize and may penetrate the SC after forming an ion pair with skin exudates. The rate of reaction seems to depend on contact time and oxygen availability. A marked inter-individual difference was observed in baseline values and amounts of copper absorbed.

14. \textbf{Lodén et al. (2004)} bioavailability of ketoprofen in a photostabilised gel formulation without photoprotection using a new DPK tape stripping model was compared and an established \textit{ex vivo} penetration method using human skin. Analyses of the SC showed cm$^2$ of ketoprofen were absorbed into the skin from the formulations. The area under the ketoprofen concentration–time curve (AUC0–6) for the photo-stabilised gel/transparent gel ratio was 73\%. The rate of penetration of ketoprofen through isolated skin was 2h for both formulations. The ratio’s AUC0–36 was 84\%. Thus, the two methods did not disagree in terms of the relative efficacy of the two gels. The comparison of the amount of ketoprofen in the skin after 45 minutes with the amount penetrated through the excised skin during 36 h, suggests a change in the thermodynamic activity of ketoprofen during exposure. A supersaturated formulation may have been formed initially due to evaporation of ethanol.

15. \textbf{Wagner Heike et al. (2002)} penetration experiments carried out to investigate several incubation times with three different skin flaps using the Saarbruecken penetration model
and the lipophilic model drug flufenamic acid. Drug distribution within SC was obtained by the TS technique, while the drug present in deep skin layers was determined by cryosectioning. In addition, for the lipophilic drug flufenamic acid, a direct linear correlation was found between SC/water partition coefficients and the drug amounts penetrated into the SC for all the time intervals tested. The authors concluded that SC/water-partition coefficients offer the possibility to predict drug amounts within the SC of different donor skin flaps, without a time consuming determination of the lipid composition of the SC.

16. Pellanda et al. (2006) The aim of Pellanda et al. was to investigate the effect of i) dose and ii) application frequency on the penetration of triamcinolone acetonide (TACA) into human SC in vivo. The experiments were conducted on the forearms of 15 healthy volunteers, with i), single 222) and multiple 2) TACA doses. SC samples were collected by TS after 0.5, 4 and 24 h (i) and after 4, 8 and 24 h (ii). In Experiment 1, TACA amounts within SC after application 222 were only significantly different immediately after application, and were similar at multiple applications of 3 x 100 2 yielded higher TACA amounts compared to a single application of 1 x 300 2 at 4 and 8 h. At 24 h, no difference was observed. In conclusion, by using this simple vehicle, considerable TACA amounts were retained within the SC, independently of dose and application frequency.

17. Lboutoune et al. (2002) the sustained bactericidal activity of chlorhexidine base - aprolactone) nanocapsules against Staphylococcus epidermidis inoculated onto porcine ear skin was investigated. The antimicrobial activity of these colloidal carriers was evaluated (i) in vitro against eight strains of bacteria, and (ii) ex vivo against Staphylococcus epidermidis inoculated for 12 h onto porcine ear skin surface treated for 3 minutes either with 0.6% chlorhexidine base loaded or unloaded nanocapsules suspended in hydrogel, or 1% chlorhexidine digluconate aqueous solution. Chlorhexidine absorption into the SC was evaluated by the TS technique. The results showed that chlorhexidine nanocapsules in aqueous suspension with a 200–300 nm size and a positive charge exhibited similar minimum inhibitory concentrations against several bacteria, compared with chlorhexidine digluconate aqueous solution.

18. Fresno-Contreras et al. (2005) an all-trans retinoic acid (RA) topical release system that modifies drug diffusion parameters in the vehicle and the skin in order to reduce systemic
absorption and side-effects associated with the topical application of the drug to the skin was designed) was studied. RA, either in free form or encapsulated in SC lipid liposomes, was included in hydrogels prepared with Carbopol® UltrezTM 10 and hyaluronic acid. The results show that RA encapsulation not only prolongs drug release, but also promotes drug retention in viable skin. At the same time, interaction between RA and hyaluronic acid has an obstructive effect on diffusion, which contributes to the formation of a reservoir.

19. **Padula *et al.* (2002)** the behavior of a skin bioadhesive film containing lidocaine, *in vitro* and *in vivo*. Film characterization included *in vitro* and *in vivo* drug transport studies with and without iontophoresis. The release rate was compared with a lidocaine commercial gel. The permeation kinetics across the skin was not linear but the patch acted as a matrix controlling drug delivery. Additionally, permeation rate increased with drug loading. The *in vivo* experiments with TS indicated that the presence of water during film application is essential to achieve not only the proper adhesion, but also an effective accumulation. The application of an electric current to the patch can further increase the amount of drug accumulated in the SC.

20. **Bashir *et al.* (2005)** the keratolytic efficacy of topical preparations containing salicylic acid (SA) in humans by the TS technique, quantifying SC removal by protein analysis was studied. In combination with TS, squamometry was used to evaluate the influence of SA on skin surface scaliness and desquamation. Furthermore, skin barrier perturbation and skin irritability were recorded and related to the dermatopharmacological effect of the preparations. In contrast to squamometry, TS combined with protein analysis was sensitive in detecting the keratolytic effect of SA within hours of application. Importantly, whereas the pH of the preparations had only a minimal influence on efficacy, local dermatotoxicity was significantly increased at an acidic pH. This indicates that the intent to increase the amount of free, non-dissociated SA is, in fact, counterproductive, as more acidic preparations resulted in skin irritation and barrier disruption.

21. **Abdulmajed *et al.* (2004)** a novel synthetic technique to synthesize the co-drug retinyl ascorbate (RA-AsA) ester from all-trans-retinyl chloride (RA) and l-ascorbic acid (AsA) suspended in ethanol at low temperature was used. The flux and permeation coefficient
were determined using heat separated human skin membrane, and skin penetration was
determined by TS using full thickness human skin. All experiments were performed in
parallel with retinyl palmitate and ascorbyl palmitate. Overall, the data suggest the
potential value of RA-AsA co-drug for treating damage to skin resulting from UVinduced
production of free radicals Aquaporine-3.

22. Morgan et al. (2003) the contribution of SC barrier and microvascular perfusion in
determining dermal tissue levels of two hydrophilic drugs (acyclovir and pencyclovir) in
vivo was measured. Removal of the SC by TS resulted in a 1300-fold increase in
pencyclovir absorption and a 440-fold increase in acyclovir absorption, confirming that
SC is the major barrier to hydrophilic drug absorption.

23. Jarvis et al. (2004) the in vitro dermal delivery of a new class of lipophilic, highly potent
was determined and uniquely selective anti-Varicella Zoster virus nucleoside (VZV)
analogue compared with acyclovir. Three test compounds (Cf1698, Cf1743 and Cf1712)
and acyclovir were formulated in propylene glycol/aqueous cream, and finite doses were
applied to full-thickness pig ear skin for 48 hours in vertical Franz-type diffusion cells.
Depth profiles were constructed following TS and membrane separation. All three test
compounds reached the target basal epidermis in concentrations suggesting they would
be highly efficacious in reducing viral load. Furthermore, the data showed that each of
the test compounds would have a far superior performance than acyclovir. The
dermatomal site of viral replication during secondary infection the basal epidermis was
successfully targeted.

24. Inoue et al. (2005) the effect of CpG-oligodeoxynucleotide (CpG-ODN) on the immune
response to an antigen applied to tapestripped mouse skin was examined, by evaluating
the production of cytokines and Ig isotypes. Confocal laser scanning microscopy revealed
that the OVA (model antigen) and CpG-ODN easily penetrated the tape-stripped skin.
Co-administration of CpGODN and OVA to the disrupted skin elicited an
antigenspecific, Th1-predominant immune response, and enhanced the production of
Th1-type cytokines, IL-12 and IFN- type cytokine, IL-4, was drastically suppressed. In
terms of antigenspecific antibody production, the IgG2a level, which is regulated by IFN-
-ODN, but IgE production regulated by IL-4 was suppressed.
25. **Alvárez-Román et al. (2004)** whether encapsulation of lipophilic compounds in polymeric nanoparticles is able to improve topical delivery to the skin was determined. The penetration of caprolactone nanoparticles, into and across porcine ear skin *in vitro*, was investigated using TS. Quantification of OMC in the skin using TS demonstrated that nanoparticulate encapsulation produced a 3.4-fold increase in the level of OMC within the SC. Nanoparticulate encapsulation of OMC increased its “availability” within the SC.

26. **Olvera-Martínez et al. (2005)** polymeric nanocapsules (NCs) containing OMC and their *in vivo* distribution profile through the SC were determined by the TS technique was prepared. The penetration degree of OMC formulated in NCs was compared with that obtained for a nanoemulsion (NE) and a conventional oil-in-water (o/w) emulsion (EM). *In vivo* Percutaneous penetration, evaluated by the TS technique, demonstrated that NE increased the extent of OMC penetration relative to the penetration achieved by NCs or EM. Likewise, OMC accumulation in the skin was significantly greater with NE than with EM or NCs.

27. **Sarveiya et al. (2004)** a reverse HPLC assay to quantify four common sunscreen agents, namely, 2-hydroxy-4-methoxybenzophenone, 2-ethylhexyl-p-methoxycinnamate, octylsalicylate and salicylic acid 3,3,5-trimethylcyclohexyl ester in a range of biological matrices was developed. This assay was further applied to study skin penetration and systemic absorption of sunscreen filters after topical application to human volunteers. The results from the preliminary clinical study demonstrate a significant penetration of all sunscreen agents into the skin.

28. **Brian et al. (2007)** *In vitro* human skin permeation and distribution of geranyl nitrile (GN) were determined by Brian *et al.* using epidermal membranes, following application in 70% ethanol, under non-occlusive conditions, at maximum in-use concentration (1%). Levels of GN in the epidermis (plus any remaining in SC after TS), filter paper membrane support, and receptor fluid were combined to produce a total absorbed dose value of 4.72±0.32%. The systemic exposure resulting from the use of GN as a fragrance ingredient, under unoccluded conditions, would be low based on the currently reported use levels.

29. **Alberti et al. (2001)** using attenuated total reflectance Fourier transform infrared spectroscopy, the SC bioavailability of terbinafine (TBF) following topical treatment
with four different formulations, based on a vehicle consisting of 50% ethanol and 50% isopropyl myristate was evaluated. Three of these formulations included a percutaneous penetration enhancer: either 5% oleic acid, 10% 2-pyrrolidone or 1% urea. The SC concentration profile of TBF was measured by repeated infrared spectroscopic measurements while sequentially stripping off the layers of this barrier membrane with adhesive tape. TEWL measurements were also performed, to permit facile estimation of SC thickness.

30. **Kalia et al. (1996)** whether a structurally heterogeneous biomembrane, human SC, behaved as a homogeneous barrier to water transport was determined. Impedance spectra (IS) of the skin and measurements of the rate of TEWL were recorded sequentially in vivo in human subjects as layers of the SC were progressively removed by the serial application of adhesive tape strips. The low frequency impedance of skin was much more significantly affected by TS than the higher frequency values; removal of the outermost SC layer had the largest effect. In contrast, TEWL changed little as the outer SC layers were stripped off, but increased dramatically when 6-8 microns of the tissue had been removed. It follows that the two noninvasive techniques probe SC barrier integrity in somewhat different ways. After SC removal, recovery of barrier function, as assessed by increasing values of the low-frequency impedance, apparently proceeded faster than TEWL decreased to the pre-stripping control.

31. **Heba Abdulla et al. (2010)** Clindamycine Phosphate 1.2 % or Trtinoin 0.025 % gel, have been proven to be superior to clindamycine monotherapy in reducing acne lesion therapy. Topical clindamycin has been accepted as being effective, safe and well tolerated in the treatment of acne for decades. Topical clindamycin comes in various vehicles, including gel, lotion, solution and foam. Choosing the proper vehicle is dependent on patient preference, tolerability and application site.

32. **Kavitha Prabhu et al. (2011)** Clindamycin is kept as a reserve drug and is usually advocated in severe MRSA infections depending upon the antimicrobial susceptibility results. This study showed that D test should be used as a mandatory method in routine disc diffusion testing to detect inducible clindamycin resistance in Staphylococci for the optimum treatment of patients.