Chapter 1

Introduction
1. INTRODUCTION

Have we progressed in the past 2000 years? A little, but not much. When looking into the future the present is always a good starting point. For hundreds of years, Western physicians largely discounted traditional herbal remedies as little more than useless plants offering little more than a placebo effect for positively enhancing health. Today however, the scientific community is more apt to recognize these medicines as viable health alternatives.

Herbal technology has grown by leaps and bounds recently as the mainstream medical community has finally begun to recognize the healing benefits of many traditional medicines. Herbal remedies have gained attention as more sufferers of various ailments have turned to the natural solutions that herbs have to offer. Instead of risking the often-serious side effects of conventional pharmaceuticals, many individuals turn to herbs that contain relatively few side effects, if any.

Herbal technology historically has been limited, as most herbalists have simply ground the plants mechanically and then either ingested them whole, or boiled them to make tea. Though this method does offer many of the healing powers of the herbs, the human digestive tract often cannot break down the fibrous plant material and thus cannot extract the medicine.

Modern herbal technology delivers the herbs in a liquid extract form that allows the body to readily absorb all the nutrients and medicines the plant offers. The medicine is essentially
"pulled" from the plant and then either delivered in pure liquid form, suspended in an appropriate vehicle or as pharmaceutical formulations for easy usage.

The fundamentals of a successful pharmaceutical formulation are to enable delivery of active substance to the target organ at therapeutically relevant levels, with negligible discomfort and side effects to the patient. In this respect, the route of administration is of major influence. Topical administration offers several attractions compared to the traditional routes. The main limitation lies in the barrier function of the skin, which is considered one of the most impermeable epithelia of the human body to exogenous substances. Therefore, the major challenge for the topical formulations is to provide a sufficient increase in drug penetration into the skin, without inducing any significant irreversible alterations to the skin barrier function.

Skin is a complex entity consisting of a variety of cells and organelles, each of which has a particular function. Various factors influence the absorption of substances through the skin. Pathways by which the drug is absorbed and the role of vehicle on skin can be better understood if one is familiar with skin structure and function. It is imperative that a chemist be familiar with the fundamentals of the various factors that influence the absorption of substances through the skin before beginning bench work.

Almost since the introduction of modern scientific study of percutaneous absorption, workers have debated the relative importance of three potential routes of entry from the skin surface into the subepidermal tissue-through the hair follicles with their associated
sebaceous glands, via sweat ducts, or across the continuous stratum corneum between these appendages.

Heightened interest in the pilosebaceous unit as a potential drug delivery target lies in the fact that the etiologies of several dermatological diseases including acne, alopecia areata, androgenetic alopecia and some skin cancers relate to their hair follicle. Acne vulgaris is a disease of the pilosebaceous unit and is a clinical manifestation of excessive sebum production and accumulation of keratinized material in the follicular openings and sebaceous ducts.

In the past few decades, considerable attention has been focused on the development of New Drug Delivery System (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly it should deliver the drug at a rate directed by the needs of the body over period of treatment. Secondly, it should channel the active entity to the site of action. Topical novel delivery systems like liposomes, multiple emulsions, microemulsions, microspheres, nanoemulsions and nanoparticles, especially products designed for the face, have evolved into a technological spearhead during the past 20 years. As with any drug-delivery system, the physicochemical property of the drug and the vehicle or carrier determines the effectiveness of targeting the hair follicles and/or sebaceous glands.

For the treatment of pathologies like acne vulgaris associated with the sebaceous structures, it may be important to increase the distribution of certain drugs in the hair follicles. There
are several objectives of follicular targeting of drugs.

- Reducing or bypassing the transepidermal pathway.
- Decreasing the systemic toxicity.
- Increasing the drug concentration within the pilosebaceous units.
- Increasing the therapeutic index of certain drugs.
- Possibly reducing the applied dose of a drug and/or the frequency of its administration.

The quest never ends. From the very beginning of human race, the quests are going on for newer and better alternatives and in case of drugs it will continue; continue till we find a drug with maximum efficacy and no side effects. Herbal drug delivery targeting the follicular route may represent a promising and valuable therapeutic approach for pathologies like acne vulgaris associated with sebaceous structures. Finally medicaments, which provide more complete protection to patients thus helping them to overcome the inferiority complex and other secondary psychological effects, should be developed for treating this apparently normal life event.

RATIONAL

Acne vulgaris an inflammatory disease of the pilosebaceous unit is believed to be the commonest dermatologic disease in both black and white patients. It has been estimated that 50 million Americans are affected by some form of acne. This condition is a clinical manifestation of excessive sebum production and accumulation of keratinized material in the follicular openings and sebaceous ducts.
Melaleuca alternifolia, commonly known as tea tree is unique to Australia. Tea tree oil (TTO), obtained by steam distillation of the leaves of *M. alternifolia* is a pale yellow, viscous liquid with a distinctive pungent odour.

TTO is a popular component of skin preparations, and a number of its suggested uses imply an antimicrobial activity. A study comparing TTO gel to Benzoyl peroxide lotion demonstrated the efficacy of the oil for treating acne vulgaris (Bassett et al. 1990). *Propionibacterium acnes* and coagulase-negative staphylococci have been implicated in the aetiology of acne vulgaris and it is expected that the oil works by eradicating these microorganisms from acne lesions.

The aspects and factors in the aetiology and treatment of acne throw emphasis on the fact that no routine method is always successful. Added to this, we are seeing the development of increasing antibiotic resistance in *Propionibacterium acnes*, a problem exacerbated by long term and widespread use of often suboptimal doses of antibacterial agents.

Interest in the pilosebaceous structures arises due to a number of dermatological diseases including acne. The pilosebaceous unit consists of the sebaceous glands, the follicular canal and the squamous epithelium. Recent reports have suggested that in addition to the transepidermal route, hair follicles and sebaceous glands may contribute significantly to topical or transdermal delivery. The hair follicles and sebaceous glands contribute significantly to percutaneous absorption, which is complicated by the fact that the source of
the penetrating molecules may be extremely variable. Both are called shunt routes since they circumvent penetration across the continuous stratum corneum.

A major argument against the follicular delivery is the fact that the outer surface of the follicular orifices represents only 0.1% of the total skin surface. However, the hair follicle is an invagination of the epidermis deep into the dermis, providing a much greater actual area for potential absorption below the skin surface.

Further, the pH of the skin follows a sharp gradient across the stratum corneum (SC), which is expected to play an important role in controlling the enzymatic activities involved in cellular metabolism and renewal. The pH of some dermal products might influence the antimicrobial activity and also have detrimental effects on enzymatic process in the corneal layers. Such a process affects the natural defense mechanism of the skin, which plays a critical role in the efficacy of the product.

Therefore, improved skin care delivery systems are needed to deliver the medicament at the right pH within the follicles wherein lies the problem of excessive sebum production and hence microbial growth. Medicaments which provide more complete protection to patients thus helping them to overcome the inferiority complex and other secondary psychological effects need to be developed for treating this apparently normal life event. The need is therefore to develop new products and to improve currently existing products to address this cosmeceutical problem of the skin.
Keeping these in our mind, we planned to prepare and evaluate formulations containing TTO which would be effective against *S. aureus*, *S. epidermidis* and *P. acne* which are commonly implicated in acne vulgaris. These formulations were designed to deliver TTO into the sebaceous follicles where the oil can exert its activity.

Further, to study the effectiveness of the formulations prepared, it was decided to compare them with marketed formulations.