CHAPTER I. INTRODUCTION

The quest for inventions never ends; perhaps this is yet another feature which differentiates man from animals! Earlier man forgot to write down his discoveries or didn’t bother to disclose to others. Thus discoveries sometime become a standstill with that generation, a terrific lose for the next generation society. Slowly documentations, SOPs, technical writings etc. gained significance. Today in the modern era, we write down every step of what we do so that it can be retrieved later as well as archived by the scientific community in a rational way.

Thus, great strides have been made in the management of diseases through the intervention of drugs over the past five decades, as judged by the introduction and success of immunizing agents, antibiotics, steroids, tranquilizers and many other drugs. But alas, these accomplishments in drug development have not been matched by a similar growth in the area of drug delivery. It is well known that unless a drug can be delivered to its target area at a rate and concentration that both maximize the therapeutic effects and minimize the side effects, the drug will not be maximally beneficial to the patient. Thus the downside is a useful drug may be of little use.

For target tissues which are accessible, it is possible to titrate the patient by the pharmacological response and temporal administration is straight forward. However, most often the desired site of pharmacological action is quite away from the site of administration, thus localizing the API reaching the targets becomes more complicated. Adding to this problem, drug behavior in the dosage form and body proper, reliance on the patient to administer drug in the correct amount at the right time is quite challenging.

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery technologies are patent protected formulation technologies that modify drug release profile, absorption, distribution and
elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Compared to invasive route of administration, most common routes of administration preferred is non-invasive peroral (through the mouth), topical (skin), transmucosal (nasal, buccal/sublingual, vaginal, ocular and rectal) and inhalation routes.

A drug is defined as a substance/agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of diseases in humans or in the animals [1]. The product (form) in which drug substances are presented in market and can be administrated to a patient is called ‘dosage form/formulation’ [2].

Besides providing the mechanism for the safe and convenient delivery of accurate dose, dosage forms are needed for additional reasons

1. To protect from the destructive influences of atmospheric oxygen or humidity eg. Coated tablets, sealed ampoules.

2. To protect from the destructive influences of gastric acid after oral administration eg. Enteric coated tablets.

3. To conceal the bitter, salty or offensive taste or odour eg. Capsules, coated tablets, flavoured syrups.

4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle eg. Suspensions.

5. To provide clear liquid dosage forms of substances eg. Syrups, solutions.

6. To provide rate controlled drug action eg. Various controlled released tablets, capsules & suspensions.

7. To provide optimal drug action from topical administration sites eg. Ointments, creams, transdermal patches & ophthalmic, ear & nasal preparations.
Generations of Drug Delivery Systems (DDS)

First generation:

Tablets, Capsules, Ointments, Suspensions, Emulsions and Suppositories.

Second generation:

Repeat action tablets, Prolonged action tablets, Enteric coated tablets and Timed release tablets.

Third generation

Osmotic DDS, Swelling controlled systems and Diffusion controlled systems.

Fourth generation:

Targetted DDS, Modulated DDS and Self regulated DDS.

Fifth generation:

Gene theraphy and Undergoing various phases of development

Merits of herbal active pharmaceutical ingredient:

Herbal medicines have been developed and used by man for thousands of years [3]. Plants have formed the basis of sophisticated traditional medicine systems among which are ayurvedic [4], Arabic [5] and Chinese [6] amongst others. Many of the pharmaceuticals available to Western physicians today have a long history of use as herbal remedies, for example opium, aspirin, digitalis, quinine etc.

The use of herbs to treat disease is almost universal among non-industrialized societies.
In developing countries, as much as 80% of the indigenous populations depend on medicinal plants and traditional systems of medicine as their primary source of healthcare. Within the European community, herbal medicines account for an important share of the pharmaceutical market, with annual sales in the range of US$7 billion. In the US alone, the sale of herbal medicines exceeded $3.3 billion in 1997 [7]. The accurate scientific assessment of herbal medicine is a prerequisite for global harmonization of herbal health claims. In a recent World Health Organization (WHO) report (WHO Traditional Medicine Strategy 2002-2005) the following was high Directive [8].

“*The use of Traditional Medicine / Complementary and Alternative Medicine (TM/CAM) is increasing rapidly in developed countries. In many parts of the world, policy makers, health professionals and the public are wrestling with questions about the safety, quality, availability, preservation and further development of this type of health care. Although many TM/CAM therapies have promising potential, and are increasingly used, many of them are untested and their use not monitored. As a result, knowledge of their potential side-effects is limited. This makes identification of the safest and most effective therapies and promotion of their rational use more difficult. If TM/CAM is to be promoted as a source of healthcare, efforts must be made to promote its rational use, and identification of the safest and most effective therapies will be crucial.*”

In 1995, as part of its overall global strategy of “Health for All” and due to numerous requests from the member states, the Traditional Medicine Program of the WHO began the extensive task of reviewing the world’s scientific literature of commonly used herbal medicines. The WHO monographs published as a result of this work are technical reviews of the quality, safety and efficacy of commonly used herbal medicines and are intended primarily to standardize the proper use of herbal medicines throughout the world. The medicinal plant monographs divides the use of each botanical into one of three categories: use supported by clinical data; use described in pharmacopoeias and traditional systems of medicine; and use described in folk medicine and not supported by experimental or clinical data.
In March 2004, The Traditional Herbal Medicinal Products Directive (2004/24/EC) came into force in Europe with the aim to assure the quality, safety and efficacy (QSE.) of traditional herbal medicinal products. This led to the introduction of a simplified registration scheme for manufactured over-the-counter (OTC) traditional herbal remedies in the second half of 2005. However, herbal preparations that are prescribed to the patient after consultation of a medically trained herbal practitioner do not need to be registered under this Directive.

Under the terms of the Directive, a Committee for Herbal Medicinal Products has been established within the EMEA to manage tasks related to the simplified registration and authorization of traditional medicinal herbal products. Composed of experts in the field of herbal medicinal products, this Committee is also responsible for producing Community herbal monographs. Aided by these Community herbal monographs, harmonization will be promoted in the Member States as each registration of individual traditional herbal medicinal products is granted.

QUALITY

The safety problems emerging with herbal medicinal products reflect a growing market, largely unregulated, and arise due to lack of effective quality controls [9]. No such parallel exists with regulated pharmaceutical drug products. The quality aspect of the medicinal product is independent of its traditional use so that no derogation is made with regard to the necessary physico-chemical, biological and microbiological tests. Products should comply with quality standards in relevant European Pharmacopoeia monographs or those in the pharmacopoeia of a Member State.

The ingredients that make up herbal medicines are by nature complex mixtures and it is well documented that concentrations of plant constituents can vary considerably depending on environmental and genetic factors. Additionally, the constituents responsible for claimed therapeutic effects are frequently unknown or only partly understood. This precludes the level of control that can routinely be achieved with synthetic drug substances in conventional pharmaceuticals. The position is made even more difficult by the common traditional practice of
using combinations of herbal ingredients and it is not unusual to have up to five herbal ingredients in one product.

Reliable methods for the authentication of herbal ingredients have been developed [10], most notably those utilizing high-performance liquid chromatography (HPLC). One approach called similarity analysis, confirms the identity of an herbal medicine by comparing its unique chromatographic fingerprint to an already established chromatographic reference standard fingerprint [11]. By utilizing statistical algorithms, this technique not only allows samples of different origin to be clearly identified, but also allows confirmation of the same origin of separate samples. Similarity analysis offers a better differentiation of the similarity or difference between herbal ingredients compared to the established method of principal component analysis (PCA) for pharmaceutical ingredients.

Adulteration and substitution of herbal ingredients due to either genuine error or unscrupulous practices can be identified by means of reliable quality control methods. The levels of any microbial contamination, pesticides, fumigants or toxic metals can be also being evaluated and checked against accepted maximum limits.

Being able to ascertain the identity of herbal ingredients is only one aspect of establishing the quality of herbal medicinal products. There is also a requirement to assure the quality control of the herbal medicinal product through the application of standards [12] on: (1) herbal ingredient cultivation; and (2) manufacturing steps to produce the final product. In fact, recommendations have been made for developing and implementing Good Agricultural Practice (GAP) for herbal ingredients and Good Manufacturing Practice (GMP) specific to herbal medicinal products. Analytical standards for raw herbal materials could be established to aid reliable identification of herbal samples [13].

The European guideline 3AQ22 Quality of Herbal Remedies May 1989, [14] lists the documentation requirements on the composition, method of preparation; quality control measures used on the starting materials and the finished product, as well the stability and shelf-life data. On the latter point, it should be noted that because the chemical stability of herbal products is complex, determining the expiration date and shelf-life period is difficult.
SAFETY

The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible based on long-standing use and experience. Pre-clinical tests are not deemed necessary where the medicinal product proves not to be harmful in specified conditions from information gathered on its traditional use. However, even a long tradition of use does not exclude the possibility of adverse effects in a patient.

A common misconception about herbalism and the use of ‘natural’ products in general, is that ‘natural’ equals ‘safe to use’. Many plants have chemical defense mechanisms against predators that can have adverse or even lethal effects on humans. Examples include poison hemlock and nightshade. Herbs can also produce undesirable side-effects just as pharmaceutical products can. These problems are exacerbated by lack of control over the dosage and purity of the herbal product. Furthermore, if taken concomitantly with other medicinal drugs, there is danger of ‘summation’, where the herb and the drug have similar actions and add together to produce an overdose [15].

The concerns over the safety of herbal medicinal products have been expressed by a number of regulatory agencies. The UK Medicines Healthcare Regulatory Agency (MHRA) issued a report on the “Safety of herbal medicinal products” in July 2002. This report documented the known intrinsically toxic constituents of herbal ingredients together with any existing restrictions on toxic plant species.

The reported adverse effects of herbal remedies include allergic reactions, toxic reactions, adverse effects related to a herb’s desired pharmacological actions, possible mutagenic effects, drug interactions, drug contamination and even mistaken plant identities. The widely used herbal remedy for depression, St John’s Wort (Hypericum perforatum), can interact with HIV protease inhibitors, oral contraceptives and warfarin, resulting in a loss or reduction in the intended therapeutic effect of these prescribed medicines. The use of herbal products containing Aristolochia species has been associated with serious renal toxicity.
Evidence of substitution of certain ingredients in traditional Chinese medicine, has led to the publication of an EMEA position paper identifying the risks. Examples of developments to address these concerns include the compilation of a Chinese herbal medicine toxicology database [16]. This project set out to retrieve and evaluate scientific evidence on the toxicity of Chinese herbal medicine, to grade the toxicity of individual herbs and to summarize relevant herb data via a searchable electronic database. The resulting database and monographs should assist in promoting the safe and effective use of Chinese herbal medicines. Special precautions may be required when specific patient groups are concerned. Pregnant or breast-feeding mothers; children; babies; elderly and patients with heart conditions are all groups who may be more susceptible to experiencing adverse events linked to the use of herbal medicinal products. Herbs that contain volatile oils such as ground ivy and pennyroyal, are irritating to the genito-urinary tract and may induce uterine contractions if ingested in pregnancy. Some of these oils contain the terpenoid constituent, thujone, which is recognized to be abortifacient. Even the excessive consumption of herbal teas, in place of caffeine-containing teas and coffee, is not recommended in these susceptible patient groups owing to the pharmacologically active herbal components that may be present.

In comparison to conventional pharmaceutical drug products, pharmacovigilance for herbal medicines is still in its infancy. The associated safety risks for some herbal medicinal products are believed to be low but the collated knowledge on the relative safety of herbal medicines remains poor. Standard pharmacovigilance tools have additional limitations when applied to herbal medicines. For example, adverse effects may be reported as being attributed to a pharmaceutical drug even when it has been taken concomitantly with a herbal product. Inefficiencies in pharmacovigilance procedures will invariably lead to the relative underreporting of adverse effects due to herbal products [17].

**Efficacy**

The widespread availability and use of herbal medicines in today’s world indicates an increased need to evaluate objectively their effectiveness for specific conditions. Compared to conventional pharmaceutical drugs, there is a paucity of supporting scientific evidence for
the efficacy of herbal medicines. Fortunately, scientific evidence on the effectiveness of herbal medicines has grown rapidly in recent years, either in the form of randomized controlled trial data or systematic reviews. The efforts in this area have demonstrated how it is possible to evaluate herbal medicines in much the same way as for conventional pharmaceutical drugs. However, many herbal medicines still remain to be tested with one significant barrier to this being the shortage of supporting funds. Continuing with these lines of scientific investigation will help to establish which herbal medicines do have a beneficial effect for given illnesses and conditions [18].

Many of the herbal medicinal products in current use have the advantage of having been in use for a long time; in some cases, for hundreds of years. This history of traditional use is recognized in the current legislation within Europe. The European Traditional Herbal Medicinal Products Directive (2004/24/EC) has provisions for granting registration of a traditional herbal product on the basis of well-established medicinal use in the European Community. If the herbal medicine has recognized efficacy and acceptable safety profile, it can be registered without the need for preclinical data or clinical trials.

In the present work, a sincere effort was made to develop a wide spectra of topical dosage forms to target the melanocytes of the dermal layers of the skin in the treatment of vitiligo by piperine an alkaloid isolated from black pepper. A comparative extraction and isolation procedure was performed for piperine and standardized. The challenge was the drug should penetrate the tough stratum corneum, but should not reach the systemic circulation so that it will be localized at the dermis to replicate melanocytes and induces the formation of melanocytic dentrites. Thus an array of dosage forms was developed from conventional creams and ointments to novel drug delivery systems like phytosomes, transfersome and cubosomes. All the formulations were subjected to various analytical, characterization and evaluations. Evaluation reports of each formulation is documented separately. At the same time discussion part is done collectively so that there is a scope for comparative study.