Chapter 3 Research Envisaged
3.1 RATIONALE OF THE STUDY

A. THE ELDERLY - DEMOGRAPHY AND ARTHRITIS

The decline of fertility and mortality has added 20 years to the average life span. By 2030 the proportion of those over 60 will be one person in three and the median age will rise from 23.4 in 1950 to 31.1 in 2050. But more to the point, the major growth of the world's older population (half billion in 1990 to 1.5 billion in 2050) will be in developing countries, especially Asia. (Vestal, 1984)

Osteo-Arthritis is the most common of Rheumatic diseases, it is the principal source of pain and disability in the elderly and the overall disease prevalence increases with age. 10-20% of the population over 65 has the disease for the knee & hips. Currently over 50% of oral NSAIDs are written for Osteo-Arthritis. (Brooks and Day, 1991)

B. SAFETY ISSUES IN THE ELDERLY AND NSAIDs

Furthermore, increasing age is associated with an increased likelihood of adverse reactions after oral NSAID therapy, particularly with respect to peptic ulcer disease. The overall ratio for the risk of serious GI toxicity associated with oral NSAID administration is 2.74 [95% CI (Confidence interval) 2.54-2.97]: The risk assessed in people aged sixty years taking NSAID administration has been established to be 5.5 (95% CI: 4.6-6.6) (Gabriel et al.) Avoidance of GI tract should mitigate the common direct toxicities of acute mucosal lesions, nausea, vomiting, and dyspepsia, diarrhea acute mucosal lesions, which occur secondary to high local concentrations of NSAID in the alimentary tract. NSAID mediated toxicity is often dose related. Thus reduction in serum concentration should also lessen the risk of potentially serious systemic adverse effects secondary to NSAID induced prostaglandin inhibition viz. acute renal insufficiency, nephrotic syndrome, NSAID gastropathy, prolonged bleeding time and fluid retention.
The arthritic patients for whom these drugs are finally intended for, may be predisposed to gastrointestinal side effects because the disease causes the development of frail gastrointestinal mucosa with a decreased capacity to synthesize mucus, energy yielding molecules (adenosine triphosphate) and cytoprotective prostaglandin's. It reduces drug detoxification capacity and production of drug carrier proteins (albumin). Which may lead to abnormally high tissue concentrations of bioactive formulations of these drugs, impairment of liver metabolism and enhancement of adrenocortical activity. A few reports of cardiac failure associated with fluid retention have been described: this is particularly relevant for the elderly patients, who should be kept under strict medical supervision, which is impossible to perform since they frequently consume diuretics as a co-medication.

C. TRANSDERMAL DELIVERY OF NSAIDs - A POSSIBLE SOLUTION

Transdermal route of administration has been widely recognized as a better route of administration because it has the advantages over the intravenous therapy and it also overcomes the disadvantages associated with intravenous and oral routes. It also bypasses the first pass metabolism. It thus provides drug systemically at a predictable rate, and maintains the rate for extended periods of time. Diclofenac is indicated in rheumatoid arthritis, osteo- arthritis and other acute painful states. Ketorolac tromethamine is indicated for the short-term management of moderate to severe painful states. The two NSAIDs - Diclofenac and ketorolac were screened and evaluated for their skin permeation potential. Diclofenac is an anti-inflammatory analgesic, which is 450 times greater than aspirin. It has half-life of 1-2 hours, after oral administration and has high first pass effect. (40-50 % of the drug is destroyed in the liver due to first pass metabolism.) The predicted steady state plasma concentrations for diclofenac by transdermal route are considerably less than the therapeutic concentrations as predicted by the high ratio of therapeutic concentration (Ct) and the estimated plasma concentration (Css). (Ct/Css=825). (Cordero et al. in 1997) Ketorolac is an anti-inflammatory analgesic,
which has up to 800 times the potency of aspirin. Ketorolac has low intrinsic permeability and short lag time 1.2 h. Ketorolac has the pharmacological potency and appropriate pharmacokinetic profile and is the candidate of the series that has the potential for development as TTS using penetration enhancers. The predicted steady state plasma concentrations are considerably near to the therapeutic concentrations. (Ct/Css=26). In this background diclofenac and ketorolac were selected as the drug candidates for the development of transdermal systems for the NSAIDS. Diclofenac has low molecular weight, considerable first pass metabolism in the liver and short plasma half-life. Ketorolac has low molecular weight, low dosage, and tendency to cause gastrointestinal disturbances and hepatotoxicity.

D. PENETRATION ENHANCEMENT TO OVERCOME THE LOW INTRINSIC PERMEABILITY OF THE NSAIDs

Despite the identification of several very effective skin penetration enhancers such as dimethyl formamide, dimethyl acetamide, and azone their usefulness in commercial transdermal product is yet to be demonstrated. Toxicity and skin irritation has generally limited the practical application of these chemicals in transdermal drug delivery systems. Many established enhancers are synthetic compounds not yet approved by regulatory authorities for use with drugs. Therefore, the naturally occurring terpenes, which have been recognized as safe materials and have been assigned the designation of generally recognized as safe (GRAS) by the US FDA were screened as penetration enhancers for development of transdermal systems of diclofenac diethyl ammonium and ketorolac tromethamine. The terpenes tried were Chamomile oil, which is extracted from traditional medicinal plant, and is an expensive ingredient for pharmaceutical and cosmetic preparations The constituent α-bisabolol, which is present up to 50% in the essential oil, has anti-inflammatory property. It also reduces the duration of healing phase. Other terpenes that were tried are Eucalyptus oil, Geraniol, Mentha oil and
Thymol which have established uses in pharmaceutical and cosmetic industry for their medicinal value and fragrance.

3.2 OBJECTIVE OF THE STUDY

Transdermal drug delivery systems have been found to be effective means of drug delivery. Therefore it was proposed to develop transdermal delivery system of the NSAID’s diclofenac diethylammonium and ketorolac tromethamine using suitable polymers and penetration enhancers. Advantages of such a system would be

- Sustained antiarthritic, anti-inflammatory and analgesic activity hence, improvement in overall therapy of the antiarthritic condition and better management of pain and inflammation.
- Better patient compliance and good tolerability after prolonged treatment in the elderly patients.
- By pass “first-pass” metabolism.
- Suitable for effective therapy overnight.
- Allows, a strict medical control for the elderly patient as the drug delivery can be terminated any time by removing the patch. (Which is otherwise impossible to perform since they frequently consume diuretics, and co medication, and in patients with severe renal failure the pharmacokinetic parameters of the drug are markedly influenced.

3.3 PLAN OF WORK

It is the aim of the present investigation to prepare pressure sensitive adhesive matrix patches for transdermal delivery of NSAIDs - Diclofenac diethylammonium and Ketorolac tromethamine and thus provide adhesive matrix patches and methods of use
that are compatible with hydrophilic salt forms of above mentioned drugs for transdermal delivery.

Formulation of a pressure sensitive adhesive matrix patch involves a device comprising a drug-containing adhesive matrix layer of polymeric adhesive which dissolves an effective amount of the hydrophilic salt form of the drug, and optionally an effective amount of a penetration enhancer, a proximal surface of the layer adapted to adhere to the skin and a distal surface of the layer adapted to adhere to a backing layer, and a backing layer that is substantially impermeable to the drug laminated to the distal surface.

Preferred water-based adhesives include acrylic and polyisobutylene adhesives, and preferred drugs include Diclofenac diethylammonium, ketorolac tromethamine and the preferred penetration enhancers include the terpenes. Present work encompasses

A. Selection of a suitable NSAID to be fabricated as transdermal drug delivery system.

A single daily dose of non-steroidal anti-inflammatory drug is widely recognized as the best dose regimen in chronic diseases such as degenerative osteoarthropathy, inflammatory afflictions of skeletal muscles etc. For several years biomedical research has been involved in the development of anti-inflammatory and antirheumatic compound to be used in these chronic conditions. These drugs should posses-

A rapid and long-lasting analgesic effect, a sustained anti-inflammatory and antiarthritic activity,

Good tolerability even after prolonged treatment in the elderly patients

and Easy dose schedule and possibly one single daily administration.

In this background Diclofenac and Ketorolac were selected as the drug candidates for the development of transdermal systems for the NSAIDS. Diclofenac has low molecular weight, considerable first pass metabolism in the liver and short plasma half-life.
Ketorolac has low molecular weight, low dosage, and tendency to cause gastrointestinal disturbances and hepatotoxicity.

B. Selection of a suitable penetration enhancer of natural origin
Terpenes were tried as penetration enhancers. The terpenes tried were mentha oil, Lemon oil, eucalyptus oil, and Geraniol, Thymol and Chamomile oil. Terpenes have been given the designation of generally recognized as safe (GRAS) by the US FDA.

C. Selection of suitable pressure sensitive adhesives
The adhesive properties of transdermal delivery system are fundamental to transdermal treatment. It has been demonstrated that when the patch fails to adhere the ratio cost effectiveness increases. In the present investigation acrylates, silicones and polyisobutylene pressure sensitive adhesives were considered.

D. Fabrication of the TDDS

E. Evaluation of physico-chemical properties of the TDDS.

F. In vitro evaluation TDDS

G. Stability studies on the selected formulations.

H. Pharmacodynamic evaluation:
- Skin irritation studies,
- Analgesic and anti-inflammatory activity and
- Comparative effectiveness of transdermal versus oral formulation in human volunteers and the residual amount in TDD after transdermal delivery.

I. In vivo evaluation of the selected transdermal formulation in rabbits

J. In vivo evaluation of selected transdermal formulations in human volunteers.