1. Introduction
Topical administration of drugs for the treatment of dermatological diseases is a logical and long established part of medical therapy. Equally, the transcutaneous route of drug delivery has been used to alleviate pain, in particular, in the underlying tissues, with the obvious advantage of reduced systemic exposure. Transdermal drug administration is, however, more sophisticated, achieving central pharmacological effects. Seven drugs are currently approved in USA for transdermal delivery viz. scopolamine, nitroglycerine, clonidine, estradiol, fentanyl, nicotine and testosterone; with many products on the market (Cleary, 1993).

Although the first approved transdermal system appeared over fifteen years ago, the range of molecules suitable for this means of delivery remains limited. This is due to the excellent barrier function of skin, in particular the superficial layer, the stratum corneum. The stratum corneum is a remarkable feat of bioengineering, both from structural and compositional viewpoint, and provides a uniquely impressive resistance to molecular transport both from and into the body (Guy, 1996). This is the reason that transdermal delivery requires potent drugs. One simply cannot transfer many micrograms of any compound across a small area in a period of few hours. Because the principal function of the skin is to minimise transepidermal water loss, the stratum corneum is predominantly a lipophilic barrier that is particularly impermeable in a passive sense to hydrophilic drugs including charged species. It follows that successful transdermal delivery is limited only to potent drugs of low molecular weight and appropriate partition coefficient.

The diffusional resistance of the stratum corneum is a challenge that has been accepted by the pharmaceutical scientist and considerable activity has been directed towards percutaneous enhancement technologies. Currently, there are three approaches to circumvent the stratum corneum barrier viz. chemical, biological and physical approach (Panchangula, 1997). The chemical approach involves the use of chemicals or combination of chemicals that can act as penetration enhancers while biological approach involves the use of skin metabolism inhibitors or synthesis of bio-convertible pro-drugs. The practical utility of these two approaches is limited by local irritation or local inflammatory response associated with their use. The use of chemical/ biological enhancers also concerns the issue of control "allotted" to the delivery system. This means it is rather difficult to control the permeability of the penetrants depending on individual needs.
Perturbation of the skin permeability with the aid of physical means such as electric current (iontophoresis and electroporation), ultrasound waves (sonophoresis), thermal energy (hyperthermia) or pressure (PowderJects®) are gaining interest since they promote effective and non-invasive delivery of wide array of drugs ranging from smaller to high molecular weight compounds both ionic and non-ionic (Tyle, 1986; Meidan et al., 1995; Oharo et al., 1994; Sarphie et al., 1997).

**Iontophoresis** uses an electrode of the same polarity as the charge on the drug to drive ionic (charged) drugs into the body (Tyle, 1986; Banga and Chien, 1988; Green et al., 1993; Banga et al., 1999). The potential of this technique is being rediscovered for transdermal systemic delivery of ionic drugs including peptides and oligonucleotides, which are normally difficult to administer except, by parenteral route. The technique has been observed to enhance the transdermal permeation of ionic drugs several fold and this can expand the horizon of transdermal controlled drug delivery for systemic medication. Besides the typical advantages of transdermal delivery, iontophoresis presents a unique opportunity to provide programmable drug delivery. This is because the drug is delivered in proportion to the current which can be readily adjusted. Such dependence on current may also make drug absorption via iontophoresis less dependent on biological variables unlike most other drug delivery systems.

**Sonophoresis** (Phonophoresis or Ultrasonophoresis) is the application of acoustic waves in the frequency range above 20 KHz (i.e. above the audible threshold for the humans) for transdermal drug enhancement (Tyle and Agrawala, 1989; Kassan et al., 1996). Sonophoresis differs from iontophoresis in that it enhances the transdermal transport of non-ionic drugs in addition to ionic drugs. Moreover, ultrasonic waves penetrate upto 5 cm below the skin, while iontophoresis penetrates only to an approximate depth of 1 cm (Tyle and Agrawala, 1989).

In case of sonophoresis, the increase in permeability is attributed to transient heating, radiation pressure and cavitational effects on skin. Sonophoresis has been shown to enhance the transdermal permeation of charged as well as uncharged molecules of high molecular weight (Meidan et al., 1995; Mitragotri et al., 1996).
Hyperthermia refers to the application of heat to promote transdermal delivery of drugs (Sasaki et al., 1987; Ohara et al., 1994; Peck et al., 1995). Heat can be applied with the help of water bath, microwaves, infrared waves or other thermo-couple type of devices. Application of hyperthermia leading to enhanced percutaneous drug absorption has been attributed to the change in the structure or function of the skin, especially the peripheral blood flow, and also to an increase in fluidity of lipids in the skin with temperature. Application of hyperthermia either alone or in combination with chemical enhancer d-limonene has been shown to enhance the transdermal permeation of polar/ionic or non-polar drugs (Peck et al., 1995; Ohara et al., 1995).

From drug delivery point of view, temperature sensitive liposomes, which would release the drug only to heated area (localised hyperthermia) can also be prepared. This is an important approach for the targeted delivery of cytotoxic drugs to localised tumours (Yatvin et al., 1978; Weinstein et al., 1980; Tacker and Anderson, 1982; Iga et al., 1991).

The present study explores the possibility of employing the above mentioned novel physical parameters for enhancing the transdermal penetration of ketorolac tromethamine, a non-steroidal anti-inflammatory agent. The study was also aimed at formulating thermosensitive liposomes of few anticancer drugs and evaluating the formulation in combination with hyperthermia as a bimodality approach for cancer management in suitable animal models.

Objectives of the work: The main objectives of the present study are;

- To develop an ‘indigenous’ and cost effective iontophoresis unit.
- To use the developed unit for investigating in vitro iontophoretic transport of ketorolac tromethamine (a non-steroidal anti-inflammatory agent) across synthetic and excised skin membranes and to identify electrical (current type and density, frequency etc.) and physical parameters (drug concentration, pH, ionic strength etc.) affecting delivery rate.
- To conduct in vivo iontophoresis studies in suitable animal models.
- To study the effect of ultrasound and hyperthermia on transdermal transport of ketorolac using excised skin membrane.
• To explore the possibility of utilising techniques of iontophoresis and sonophoresis in clinical setup.

• To formulate thermosensitive liposomes of antitumour agents plumbagin and bleomycin for targeted delivery to the tumour and evaluate the formulation in combination with hyperthermia (43 °C) in mice bearing tumour.