INTRODUCTION
The success in the field of transdermal drug delivery systems over the past few years depends on the ability of the drug molecules to penetrate the skin and reach the circulatory system in sufficient quantities for them to be of therapeutic value. This is in spite of the inherent protective function of the stratum corneum, the outer most layers of the skin epidermis, which is considered to form a primary rate-limiting barrier to the permeation of the drug molecules across the skin (Hadgraft, 1999). The remarkable achievements of pharmaceutical technologists have made the transdermal delivery systems as the most successful non-oral systemic drug delivery system, and several drugs have been administered via this system viz. nitroglycerine (Hadgraft et al., 1993; Good, 1983), scopolamine (Shaw, 1983), nicotine (Ho and Chien, 1993), testosterone (Kim et al., 2001) and clonidine (Toon et al., 1989).

Despite the obvious interference of stratum corneum, transdermal drug delivery systems provides rate controlled continuous supply of the drug during a predetermined time interval and drug so delivered diffuses through the skin and enters the systemic circulation, bypassing the liver (Cleary, 1984).

The skin is structured in three layers, namely the epidermis, the dermis and the subcutaneous layer. The outer layer of the epidermis, the stratum corneum (SC), covers the entire outside of the body and it is composed of dense layers of dead flattened cells filled with the fibrous protein, keratin, which is embedded in lipid matrix (Barry et al., 1987). It impedes the evaporation of water from the tissue beneath and acts as a barrier to large amounts of water and foreign substances (including drugs), with which the skin comes in contact.
As a consequence there has been intensive research into the development of strategies to increase, in a controlled and reversible fashion, the permeability of the barrier (Mao-Qiang et al., 1993). These include physical penetration enhancement and passive penetration enhancement. The physical penetration enhancement techniques include iontophoresis, electrophoresis and sonophoresis (Naik et al., 2000; Tashiro et al., 2000). The passive penetration enhancement strategies include the use of supersaturated drug solutions (Davis & Hadgraft, 1993), submicronemulsions (Friedman et al., 1995), liposomes (Touiton et al., 1994), prodrugs (McMahon et al., 1988), chemical enhancers (Hadgraft, 1999).

Combined physical and chemical penetration enhancement could have the distinct advantage that it could permit iontophoretic drug delivery under milder conditions of electrical potential and current density, thereby minimizing side effects such as skin damage. Chemical penetration enhancement refers to the process whereby chemical agents are used to modify the barrier properties of the stratum corneum and ultimately enhance the transdermal delivery of drug substance. Penetration enhancers may be applied to the skin prior to application of drug, co-applied with the drug or used in the vehicle matrix (Goodman & Barry, 1989; Aungst et al., 1990). Ideally, the effects of the penetration enhancer on the skin should be reversible; it should be non-toxic, non-allergenic and non-irritant. Many enhancers exhibit many of these attributes, and they have been tested in clinics or in research laboratories. These include azone and its analogues (Michniak et al., 1993), fatty acids (Aungst et al., 1990), alcohols (Takahashi et al., 1991), pyrrolidones (Southwell & Barry, 1983; Sasaki et al., 1988), sulfoxides (Choi et al., 1991), urea and its analogues and terpenes (Williams & Barry, 1991).
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Terpenes have been utilized for a number of therapeutic purposes, such as antispasmodics, carminatives, perfumery, and others, but a few reports also suggest their potential as percutaneous absorption enhancers of both hydrophilic (Zhao & Singh, 1999) and lipophilic drugs (Kobayashi et al., 1993) due to their low cutaneous irritancy.

The effect of d-limonene, the active constituent of lemon oil as a penetration enhancer was also reported in the literature. Thus, these were used as penetration enhancers in the present study for increasing the permeability of a lipophilic drug such as flurbiprofen.

Thus, the effect of turpentine oil and lemon oil as penetration enhancer of the lipophilic drug flurbiprofen was investigated in the present study. An attempt was also made to investigate the potential of NA-102 as a transdermal permeation enhancer.

Flurbiprofen is a chiral non-steroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class. Flurbiprofen, one of the most potent inhibitors of platelet aggregation currently available, is used to treat gout, osteoarthritis, rheumatoid arthritis, and sunburn (Adams, 1977). Upon oral administration, the most frequently reported side effects of flurbiprofen are abdominal discomfort along with other gastrointestinal effects. Also, it has a short elimination half life of 3.9 h and requires frequent dosing (Chalmers et al., 1977). Long-term percutaneous absorption of flurbiprofen at a controlled rate is needed. Minnesota Mining and Manufacturing (3M, USA) has patented an adhesive transdermal delivery device for the topical application of flurbiprofen (Effing et al., 1997). The device was found to
demonstrate good skin adhesion and to penetrate moderately as determined using mouse and human skin.

The inherent barrier properties of the skin, and the fact that flurbiprofen is one of the least-permeable drugs across skin among a series of lipophilic drugs (Chi et al., 1995), has inspired us to design the present study, which implies the development of transdermal therapeutic system for flurbiprofen that could provide a predetermined constant drug delivery and the use of chemical penetration enhancers to modulate skin permeation of flurbiprofen which would be beneficial for an effective and safe therapy.