CHAPTER I
INTRODUCTION

Osteoarthritis is the most common joint disease in the elderly, affecting nearly 50% of those over 65 years of age and almost all individuals over the age of 75. Osteoarthritis also ranks second for causing chronic disability, making this condition of significant importance to public health. Appreciation of the human and economic costs of this disease has prompted advances, in etiology and treatment. Osteoarthritis affects primarily the weight bearing joints of the axial and peripheral skeleton, causing pain, limitation of joint movement, deformity, progressive disability and decreased quality of life. The major goals of osteoarthritis therapy are to educate the patient, alleviate pain and other symptoms, and improve function. Pharmacologic therapy begins with non-opioid analgesics such as acetaminophen, followed by nonsteroidal anti-inflamatory drugs (NSAIDs), inhibitors specific for the cycloxygenase-2 (cox-2) enzyme, topical analgesic creams, intra-articular glucocorticoid or hyaluronic acid injections, opioid analgesics and nutrition supplements, such as glucosamine (Hansen and Elliott, 2005).

Glucosamine is the natural aminomonosaccharide, which is physiological presence in the human body. Glucosamine plays an important role in the biochemistry of cartilage. In pharmacological studies it was shown that when glucosamine enters into the biosynthesis of glycosaminoglycans, it stimulates proteoglycan synthesis. In clinical trials glucosamine has been proven to modify symptoms in osteoarthritis. Therefore, glucosamine is classified as symptoms-modifying drug in osteoarthritis. Glucosamine has also been found to significantly reduce the progression of joint-space narrowing in patients with knee osteoarthritis, and has been suggested, it may be a possible disease-modifying agent (Piperno et al., 2000).

There are now many products commercially available that contain glucosamine such as injection, tablet, capsule, powder, solution, cream, gel and transdermal patch dosage form (htpp:\\www.glucosamine-artritis.urg/glucosamine/glucosamine-product-guide.html). However, glucosamine products in oral dosage form have disadvantages, due to poor oral bioavailability and extensive degradation in

the digestive tract, only 2.2% of the administered dose available in the body (http:/www.skin_forum.org.uk/abstracts/ismaiel-tekko.php). Because of side effects such as epigastric pain, heartburn, diarrhea and increased blood sugar level in DM patient (Henrotin, Sanchez and Baligand, 2004) and low patient compliance when injection dosage form is used, transdermal drug delivery system would be an alternative dosage form to overcome the problems of conventional delivery.

Transdermal drug delivery system is a method of delivery that is convenient, easy to use and has high patient compliance. However, transdermal delivery of glucosamine, has problems with permeability of the drug through skin, which is low, because of the physicochemical propertie of glucosamine, as it is a hydrophilic drug (http:/www.glucosamine-arthritis.org/glucosamine/glucosamine-cream.html).

In previous studies concerning transdermal delivery of glucosamine, it has been reported, that in rat skin, the permeation rate was determined to be 13.27 mcg/cm^2/h at 5% concentration of glucosamine sulfate solution (Kanwischer et al., 2005). When the bioequivalence of glucosamine sulfate oral dosage form and cream was compared, it was found that glucosamine orally fed to the mice at 0.4 g/kg body weight gave a plasma level of glucosamine that was hardly detectable even at 6 hours post feed. In contrast, topical application of the same dose resulted in an initial surge of glucosamine in the blood within the first 30 minutes post application. Thereafter, it subsided to a level of approximately 160 mcg/ml and sustained at this concentration for beyond 6 hours post feed (http:/www.lynk Bio Technologies 2002.htm). The studies above, show that glucosamine can permeate through the skin, but is not adequate.

There are many reports about the study of solvent, lipid and drug delivery system to enhance drugs permeation through skin. In the solvent systems such as study of fluoxetine, the permeation of fluoxetine free base was significantly enhanced from a vehicle system consisting of 65% v/v ethanol (Parikh and Ghush, 2005). In the permeation study of ketorolac tromethamine it was shown that, when isopropyl myristate is added to the binary mixture of isopropyl alcohol and water, a significant increase in the skin flux of drug can be observed (Roy and Manoukian, 1995). And in microemulsion system, their ability to enhance permeation of many drugs, including hydrophilic and hydrophobic drugs (Malmesten, 2002) for example, aceclofenac (Lee

et al., 2005), celecoxib (Subramanian, Ghosal and Moulik, 2005), progesterone, indomethacin (Nandi, Bari and Joshi, 2003), 5-fluorouracil (Gupta, Jain and Varshney, 2005) and estradiol (Peltola et al., 2003) was reported.

The effect of formulation dosage form and components on the permeation across the pig ear skin of glucosamine is of interest. The investigated dosage forms were solution, hydroalcoholic solution, gel and microemulsion, respectively. The objectives are :

1. To determine the effect of the transdermal dosage forms and their components on permeation of glucosamine hydrochloride across pig ear skin.
2. To study the physical properties of the transdermal dosage forms of glucosamine hydrochloride.