Chapter 1

INTRODUCTION

1.1 Introduction

Arthritis is a general term used to indicate any disease that causes pain, stiffness, swelling, and/or inflammation of a joint. It is not one disease but a group of more than 100 diseases whose common threads cause limited movement of the joints. Arthritis literally means "bone/joint inflammation;" but it is joint pain, rather than inflammation, that is the most important characteristic.

Arthritis is not a new disease. Archeologists have found evidence of it in Egyptian mummies. Paleontologists discovered it in skeletons of early man, dating back half a million years. It affects more adults than cancer, heart disease, respiratory conditions and spinal cord trauma—having a serious impact on quality of life. Some forms of arthritis can lead to disfigurement or even reduced life expectancy. Arthritis is the number one cause of disability in the United States. It limits daily activities such as dressing, climbing stairs, opening a door, or even holding a fork. As the leading cause of disability in Canada today, more than 600,000 Canadians with arthritis are unable to work.

The magnitude of the spread of arthritis can be imagined from the statistics which says that about 1% of the world population is suffering from arthritis. Until fairly recently, arthritis was thought of as a sign of aging. Today, we know that it can affect any one at any age. In the UK, about 20 million people suffer from the disease. Osteoarthritis accounts for about five million while about one million suffer from rheumatoid arthritis. Some 15,000 children are affected, with more girls (86%) than boys suffering from a juvenile form of the disease. In the US, one in seven is affected with the arthritis, with estimates ranging between 40 and 60 million people. Of this total, 23 million are women. About 16 million are affected with osteoarthritis and over two million with rheumatoid arthritis. In Canada, four million people suffer from arthritis; about one in seven like the US. In other countries, where similar statistics are available, the proportions are proving

to be about the same. A survey of the prevalence of major diseases suggests that about 10% of the U.S. population of all ages suffer from some form of arthritis, most commonly, osteoarthritis, rheumatoid arthritis, or gout. Arthritis and other rheumatic conditions are among the most common disabilities in the U.S. and by year 2020 are predicted to affect about 59 million (~18% of all) people in this country. Arthritis is not only associated with physical impairment of the patient, but also has a psychological, social and economic impact on the sufferer.

The most commonly used drugs in the treatment of arthritis are the Non-steroidal anti-inflammatory drugs (NSAIDs). With a total of 97 million prescriptions per year in Germany alone, NSAIDs are the foremost medication in terms of frequency of use. Every day they are taken by more than 30 million people worldwide; of these, 40% of consumers are older than 60. Population studies have shown that 10-20% of all people who are 65 years or older either are currently receiving or have recently received a prescription for NSAID. NSAIDs act by inhibition of the enzyme cyclo-oxygenase which converts arachidonic acid to prostaglandins which are responsible for causing pain and inflammation. Due to the fact that Non-steroidal anti-inflammatory drugs inhibit both the forms (COX-1 and COX-2) of enzyme cyclo-oxygenase throughout the body, they are associated with a wide range of side effects. The most common and severe side effect is the gastrointestinal bleeding and ulcers, which may be sometimes life threatening. Due to the severity of the side effects associated with the use of NSAIDs, much research was focused on the development of selective cyclo-oxygenase-2 inhibitors which, the researchers thought, would reduce the gastro-intestinal side effects of NSAIDs. Thus, selective COX-2 inhibitors like celecoxib, rofecoxib, valdecoxib, etoricoxib etc were developed and used extensively. These drugs are associated with a significantly lower gastro-intestinal toxicity but are not totally devoid of side effects. Thus, celecoxib is

associated with cardiovascular (Bing et al, 2003) and renal side effects (Brater, 1999, Taconelli et al, 2004, Perazella & Eras, 2000), rofecoxib is associated with increased incidences of myocardial infarction (Whelton, 2002) and valdecoxib is associated with toxic epidermal necrolysis (Glasser & Burroughs 2003). The severity of cardiotoxicity of rofecoxib led to its ban in the United States recently. Thus, it has become absolutely necessary to develop a drug or its delivery system which can reduce the side effects. Targeting the drug to the arthritic joint while minimizing its distribution to other organs is expected to reduce the side effects associated with the drug.

Thus in this investigation we tried to develop the targeted drug delivery system for anti-arthritic drugs celecoxib, rofecoxib and valdecoxib. The aim was to reduce the distribution of the drug to organs other than the arthritic joint. One approach used was to inject the microspheres containing the drug intra-articularly and study the retention of the plain drug with that of the microspheres in the joint cavity. The second approach was to investigate whether the intra-venously administered formulations are able to reach selectively the inflamed synovium of the rat or not.

There are many factors that play role in the initiation of arthritis; of particular importance is the relation between active collagenase and arthritis. The normally inhibited matrix metalloproteinases or collagenase in articular structures is activated in the joints of patients of rheumatoid arthritis and osteoarthritis (Arican et al, 2000). It is this increased collagenase activity that is responsible for irreparable cartilage destruction in osteoarthritis and rheumatoid arthritis. Cross-linked microspheres of polymers like gelatin (Tabata et al, 1989), albumin (Willmot et al, 1989) or chitosan are reported to degrade in the presence of proteolytic enzymes such as pepsin, papain or proteases such as matrix metalloprotease (collagenase) and release the drug at a rate dependent on the cross-linking density. So it was hypothesized that the cross-linked microspheres of these

polymers containing the anti-arthritic drug, if injected intra-articularly, would degrade the microspheres and release the drug at a rate dependent on the cross-linking density. These polymers are bio-degradable, bio-compatible and non-toxic and are easily available. So the microspheres of the drugs celecoxib, rofecoxib and valdecoxib were prepared using these polymers.

Recently, the use of solid lipid nanoparticles in formulations of therapeutic drug delivery systems has gained widespread application due to their advantage of being biodegradable and non-toxic, stable against coalescence, drug leakage and hydrolysis. They also have the advantages of low cost of ingredients, ease of preparation and scale up, high entrapment efficiencies of hydrophobic drug and controlled particle size (Utreja and Jain, 2001). There are no reports on the use of solid lipid nanoparticles for intra-articular drug delivery. As reported by previous workers (Brown et al, 1998), the principal requirement of an ideal intra-articular drug carrier system is to retain the active substance in the joint until it is taken up by the phagocytic cells of the inflamed synovium. Solid lipid nanoparticles being hydrophobic in nature are prone to be taken up by the phagocytes of the inflamed synovium. Thus, it was hypothesized that intra-articular injection of the drug incorporated into the solid lipid nanoparticles would lead to its phagocytosis by the macrophages of the inflamed synovium leading to enhanced retention at the inflamed site. SLNs containing celecoxib were prepared and the various factors affecting the characteristics of the microspheres were studied.

1.2 Proposed plan

The proposed plan of the work is as under:

1. Literature review
2. Preparation of microspheres of celecoxib, rofecoxib and valdecoxib using the polymers

   a. Gelatin

   b. Chitosan

   c. Bovine serum albumin
3. Preparation of solid lipid nanoparticles containing celecoxib
4. Characterization of the prepared formulation for
   a) Entrapment efficiency
   b) Particle size
   c) In-vitro drug release
   d) Surface morphology
   e) FTIR studies
5. Application of factorial design for optimization of the formulation
6. Radiolabelling of the drug and the formulations
7. In-vivo studies
   a) Pharmacokinetic and bio-distribution studies of the radiolabelled drug and formulations after intra-articular injection.
   b) Evaluation of arthritis by γ-scintigraphy
   c) Pharmacokinetic and bio-distribution studies of the radiolabelled drug and selected formulations after intra-venous injection.
   d) Evaluation of the bio-compatibility of the formulation

1.3 References

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bovine synovial fluids. J. vet. Med. A. Physiol. Pathol. Clin. Med., 2000; 47: 449-456.

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