CHAPTER 3

AIMS AND OBJECTIVES

3.1 Aims of the study

A wide variety of newer drug delivery systems are being designed and evaluated in the recent years in order to overcome the limitations of conventional drug therapy. The oral controlled/sustained release dosage forms are the most commonly used products in the treatment of acute disease conditions. They offer once daily or twice daily dosing reduces frequency of adverse effects and are cost effective to manufacturing. These products are able to maintain study drug plasma level for extended periods of time. As a result, peak-to through variations of the drug level in the blood is prevented and also dose related side effects are minimized. This is particularly important when medications are delivered for chronic conditions or where constant levels of the drug are required to achieve optimal therapy, as for example in the therapeutic management of pain and inflammation.

Oral drug delivery products lead the world wide drug delivery market as they are the most convenient to administer, cost effective to manufacture and the most preferred by patients. In 1998, the world wide drug delivery market was worth approximately 30 billion US-dollars, of which 15 billion accounted for oral drug delivery products. If the prediction of the industry experts proves right the market for the oral drug delivery systems will likely to reach over 34 billion US- dollars by 2001, 50 billion US dollars by 2005 and expecting 80 billion US dollars by 2014.

The conventional NSAIDs are generally poor aqueous solubility, poor permeability in the biological membrane and a short biological half-life. Due to this reason multiple dosing is necessary to maintain the constant drug in plasma for long
therapy which leads to reduce the patient compliance. The clear relationship between the drug half-life and therapeutic response could be necessary administered at regular frequency of dose in order to maintain the concentration of dose within a therapeutic range. Moreover, the higher doses administered frequently will result in fluctuation of plasma concentration above therapeutic range precipitates the toxic effects commonly gastric irritation. A new trend in NSAIDs development has been to improve therapeutic efficacy and reduce the dose related adverse effects through altering the dosage forms by modifying the drug release, using certain novel drug delivery techniques\textsuperscript{131}.

In the present research work, therefore to develop oral sustained release products of aceclofenac sodium and dexibuprofen microbeads by microencapsulation ionotropic gelation technique, using sodium alginate as release modifier, natural clay as adsorbent and calcium chloride as crosslinking agent. When drug loaded sodium alginate dispersion is added drop wise to a solution of calcium chloride and forms a spherical gel with regular shape and size, also known as microspheres or microbeads. The formed calcium alginate beads have nontoxic orally, better physiologic compatibility and scarcely reswell in acidic environment but increases in swelling at neutral environment. Thus, they are good carriers for acid sensitive drugs protected from gastric juice\textsuperscript{132}

The proposed research methodology was extended to develop oral sustained / controlled release matrix tablets. Matrix systems are also called as monoliths since the drug is homogeneously dissolved or dispersed throughout a soluble hydrophilic or insoluble erodible or non-swellable hydrophobic rate controlling materials. Matrix system is commonly used to developing an oral controlled release formulation manufactured by direct compression or wet-granulation techniques admixed of active
drug, retardants and other additives to form tablets. The release of the drug from the tablets by dissolution controlled as well as diffusion/erosion controlled mechanisms. In the present study, the selection of hydroxypropylmethylcellulose, locust bean gum and Kollidon SR (polyvinyl acetate & povidone) used as drug release retardants in matrix formulations because of their advantages such as binding, gelling properties, swellability, biocompatibility, biodegradability, ease of availability and low cost.

3.2 Objective(s) of the project

At present more than 200 oral sustained/controlled/extended/modified release formulations are available in the global market. In India however, only limited products are commercially available. Taking a step ahead from manufacturing conventional dosage forms, development of oral sustained/controlled drug delivery systems can meet the following benefits;

i) It will reduce the frequency of drug administration and improve patient compliance. As the drug blood level oscillations are minimized, it is possible to reduce the dose related adverse effects, dose intake and cost of the drug therapy.

ii) The applications of new methods of drug delivery will have the added benefits of extending the patent period of older drugs. Since the reformulation of a drug by new techniques or excipients/polymers, constitute a new drug product in eyes of regulatory authorities.

iii) It can lead to improved pharmacokinetics, bio-distribution and ultimately improve the therapeutic indices for drugs that are currently have clinical approval.
iv) It will also provide an opportunity for the Indian pharmaceutical industries to compete with global drug delivery market as it has advantage for materialize, maintenance, improve the quality standards according to regulatory authorities.

v) It will enable to optimize and scale-up of the product from the F&D level to industrial scale.

3.3 Plan of work

Aceclofenac sodium and Dexibuprofen, the two NSAIDs are being used in the therapeutic management of inflammation and pain with dose range 100 to 200mg (aceclofenac sodium) and 200 to 600mg (dexibuprofen) in divided doses a day. Due to their shorter biological half-lives of 2-3 hours, they required multiple dosing (2-3 times a day). Multiple dosing leads to fluctuation in the drug-blood levels and dose related adverse effects. Multiple dosing also often results in poor compliance and inefficient therapy

It was proposed, therefore, to develop sustained release oral products of aceclofenac sodium and dexibuprofen namely microbeads and matrix tablets by using suitable polymers and evaluate their physicochemical characteristics, *in-vitro* drug release potential and stability studies at different temperature and humidity conditions as per ICH guidelines to optimize the products feasible for further scaling up and clinical studies. The study was proposed to be carried out in the following stages:

**Stage 1 Preformulation studies**

1.1 To develop calibration curves for the drugs namely, aceclofenac sodium and dexibuprofen by UV-Visible spectrophotometry.
1.2 Compatibility of the drugs and the selected excipients by FT-IR, DSC and XRD.

**Stage 2 Formulation and evaluation of physicochemical properties**

2.1 Formulation and evaluation of aceclofenac sodium microbeads.

2.2 Formulation and evaluation of dexibuprofen microbeads.

2.3 Formulation and evaluation of aceclofenac sodium matrix tablets by wet granulation technique.

2.4 Formulation and evaluation of dexibuprofen matrix tablets by direct compression technique.

2.5 In-vitro matching approach with the innovators product.

**Stage 3 Stability studies**

3.1 Stability analysis of aceclofenac sodium and dexibuprofen microbeads.

3.2 Conventional stability analysis of aceclofenac sodium and dexibuprofen matrix tablets.

3.3 Development of stability by HPLC method for matrix tablets.

**Stage 4 Compilation of data and submission report**