CHAPTER I

INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and potential compliance. Controlled release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible.

Polymers which are used as release-retarding materials in the design of Controlled release drug delivery systems play a vital role in controlling the delivery of drug from the systems. The success of Controlled drug delivery systems depends on how well the polymer regulates the release of drug from the system. Though a wide range of polymers and other release retarding polymers are available, there is a continued need to develop new and more efficient release retarding polymers for controlled release. The major objective of the present study is to develop a new release – retarding and rate controlling polymers for controlled release.

A survey of the literature revealed that modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. The controlled release properties of modified starches generally based on solvent-activation have been intensively investigated. For example, pre-gelatinized starch1, cross
linked amylose\textsuperscript{2}, substituted amylose\textsuperscript{3}, short-chained amylose (i.e. amylodextrin)\textsuperscript{4,5} and calcium starch\textsuperscript{6,7}, all have retarded drug release from matrix tablets.

In the present investigation starch-urea cross-linked with calcium, a new modified starch polymer was synthesized and evaluated for its application in controlled release. Starch reacts with urea to form starch carbamate, a starch urea polymer. Khalil \textit{et al.}\textsuperscript{8} investigated the reactions between starch and urea resulting in the formation of starch – urea polymer. No reports are available on the pharmaceutical applications of starch urea. In the present study, starch urea and starch urea cross–linked with calcium were evaluated for their applications in controlled release.

The formation of cross-linked starches with calcium salts is known in polymer chemistry. As the cross-linked polymers generally swell in water and aqueous fluids and form gelatinous matrices suitable for controlled release, it is thought worthwhile to investigate starch urea cross-linked with calcium chloride for its application in controlled release.

Among the various approaches, preparation of drug embedded matrix tablets is one of the least complicated techniques for controlled release and is widely used in industry. This technique was selected for the design of controlled release drug delivery systems employing starch urea and starch urea cross–linked with calcium.

Two medicaments namely diclofenac and aceclofenac (anti-inflammatory and analgesic drugs), which require controlled release formulation are included in the study to develop controlled release formulations of these drugs employing starch urea and cross–linked starch urea.
Diclofenac sodium is a widely used non-steroidal anti-inflammatory analgesic and anti-pyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half life\textsuperscript{9} of 2.0 h. The drug also causes\textsuperscript{10} gastrointestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

Aceclofenac is a relatively new and widely prescribed NSAID drug. Aceclofenac is a potent inhibitor of cyclo – oxygenase enzyme (COX – 2 inhibitor). The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Controlled release formulation is needed for aceclofenac because of its short biological half life of 4.0 h, low and variable oral bioavailability due its poor aqueous solubility and also to minimize the g.i. disturbances such as peptic ulceration with bleeding, if present in large concentration in g.i. tract\textsuperscript{10}.

The specific objectives of the investigation are as follows:

1. To prepare and characterize starch urea cross–linked with calcium, a new modified starch polymer by microscopy, chemical and physical tests and also by DSC and FTIR spectra.

2. To evaluate starch urea cross linked with calcium as a new release retarding and rate controlling polymer for controlled release application and to develop cross-linked starch urea matrix tablets for controlled release.
3. To design controlled release drug delivery systems in the form of matrix tablets of diclofenac and aceclofenac (anti-inflammatory and analgesic drugs) for once-a-day (24 hours) administration.

4. To evaluate the compatibility of cross–linked starch urea with selected drugs by FTIR spectral studies.

5. To evaluate the kinetics and mechanism of drug release from matrix tablets formulated employing cross–linked starch urea.

6. To make a comparative evaluation of release retarding and rate controlling efficiency of cross – linked starch urea with various other polymers such as sodium CMC, methyl cellulose, sodium alginate and HPMC used in matrix tablets for controlled release.

7. Pharmacokinetic evaluation of selected controlled release formulations developed employing cross–linked starch urea.

8. To evaluate the stability of release rates of selected controlled release formulations developed employing cross–linked starch urea.

Extensive experimentation, both in vitro and in vivo has been carried out to fulfill the objectives of the investigation and the studies carried out and the results obtained are described in the subsequent chapters.
REFERENCES


