CHAPTER X
SUMMARY AND CONCLUSIONS

The thesis describes studies carried out on “Preparation and evaluation of cross-linked starch urea, a new modified starch for oral controlled release of diclofenac and aceclofenac”. Introduction and objectives of the investigation are described in Chapter I.

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. 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. 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. Starch reacts with urea to form starch carbamate, a starch urea polymer. 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.

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.

The specific objectives include (i) 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, (ii) 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, (iii) 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, (iv) 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 and (v) Pharmacokinetic evaluation of selected controlled release formulations developed employing cross–linked starch urea.

Literature on controlled release is reviewed in Chapter II. Modified starches and their applications in controlled release are described in Chapter III. Drug profiles, need and past work on controlled release of diclofenac and aceclofenac are given in Chapter IV. Analytical methods used and their validation are described in Chapter V. UV – spectrophotometric methods were used for the estimation of diclofenac and aceclofenac in the *in vitro* studies. A known HPLC method was used for the estimation of diclofenac in plasma samples.
Studies carried out on the preparation and characterization of cross-linked starch urea are described in Chapter VI. Starch urea cross-linked with calcium was prepared by gelatinizing potato starch in the presence of urea and calcium chloride. The crosslinked starch urea was found to be fine, hard and free flowing crystalline powder. It gave a positive iodine test indicating the presence of α-amylose. When tested for melting point, crosslinked starch urea charred at 210°C. Microscopic examination indicated that crosslinked starch urea consists of rectangular, transparent crystals. It was insoluble in water, aqueous fluids of acidic and alkaline pHs. Crosslinked starch urea exhibited good swelling in water. The swelling index was 630.2%. As crosslinked starch urea is insoluble in aqueous fluids of acidic and alkaline pHs and has good swelling property in water, it is considered suitable as release retarding and rate controlling polymer in matrix tablets for obtaining controlled release.

Studies carried out on the formulation and evaluation of controlled release tablets of diclofenac and aceclofenac employing cross-linked starch urea are discussed in Chapter VII. Matrix tablets of (i) Diclofenac (100mg) and (ii) Aceclofenac (100mg) were prepared employing (i) starch-urea (ii) cross-linked starch-urea in different proportions (33, 50, and 66 strengths in the formulae) by wet granulation method.

All the prepared tablets were evaluated for content of active ingredient, hardness, friability, disintegration time and drug release characteristics. All the tablets were found to be non-disintegrating in water, aqueous acidic (pH 1.2) and alkaline (pH 6.8 and 7.4) fluids. Matrix tablets of diclofenac and aceclofenac prepared were of good quality with regard to drug content, hardness and friability. Diclofenac release from the matrix tablets prepared was studied in phosphate buffer of pH 7.4. For comparison, diclofenac release from one commercial SR brand (Reactin SR tablets) was also studied. Aceclofenac release from the matrix tablets prepared was studied in phosphate buffer of pH 6.8. The
drug release data were analyzed as per zero order, first order, Higuchi, and Peppas equation models. For comparison, aceclofenac release from one commercial SR brand (Hifenac SR tablets) was also studied.

Diclofenac matrix tablets, DF3 formulated employing 50 % cross linked starch urea and aceclofenac matrix tablets, AF3 formulated employing 50 % cross linked starch urea were subjected to stability testing. In each case the tablets were packed in screw capped HDPE bottles and were stored at 40° ± 2°C and 75 % RH for 6 months. After storage for 6 months, the products were tested for drug content and drug release rate.

From the results obtained the following conclusions are drawn.

1. Cross-linked starch-urea was more suitable than starch-urea for the design of controlled release tablets of diclofenac and aceclofenac.
2. Drug release from the matrix tablets formulated employing cross-linked starch-urea was slow and spread over 24 h and depended on percent polymer in the tablets with both diclofenac and aceclofenac.
3. Drug release from the matrix tablets formulated employing cross linked starch – urea was diffusion controlled and followed zero order kinetics.
4. Non – Fickian diffusion was the drug release mechanism from the matrix tablets formulated employing starch-urea and cross linked starch-urea with both the drugs diclofenac and aceclofenac.
5. A good linear relationship was observed between percent polymer in the tablets and release rate in both the cases (i.e. diclofenac and aceclofenac).
6. Some of the tablets formulated employing cross linked starch –urea gave release over 24 h and similar to that from commercial SR tablets in each case.
7. Diclofenac CR and Aceclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

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8. FTIR spectral studies indicated no interaction between the polymer (cross-linked starch urea) and the drugs studied (diclofenac and aceclofenac).

9. Drug content and drug release rate of the matrix tablets formulated employing cross linked starch urea were quite stable during stability studies carried out at 40° ± 2°C and 75 ± 5 % RH for 6 months. The controlled release characteristics of the matrix tablets remained unaltered.

Studies on a comparative evaluation of release retarding and rate controlling efficiency of cross-linked starch urea and other known polymers are described in Chapter VIII. Matrix tablets of (i) diclofenac and (ii) aceclofenac were prepared by wet granulation method employing cross-linked starch-urea and other polymers such as methyl cellulose (MC), hydroxypropyl methyl cellulose (HPMC, K15M), sodium carboxymethyl cellulose (Sodium CMC) and sodium alginate (SA) at 1:1 ratio of drug: polymer. All the matrix tablets prepared were evaluated for drug release kinetics and suitability for controlled release. All the tablets were found to be non-disintegrating in water, aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. All the prepared matrix tablets of diclofenac and aceclofenac were of good quality with regard to drug content, hardness and friability.

From the results of drug release studies the following conclusions are drawn.

1. Drug release from the matrix tablets of diclofenac and aceclofenac formulated employing cross-linked starch-urea and various other polymers was slow, spread over 24 h and depended on the polymer used.

2. Non–Fickian diffusion was the drug release mechanism from all the matrix tablets formulated employing various polymers except aceclofenac tablets formulated with sodium alginate which gave rapid release of aceclofenac following Fickian diffusion.

3. The order of increasing release retarding effect observed with various polymers was HPMC > cross-linked starch-urea > MC > sodium CMC > sodium alginate in the
case of diclofenac and cross-linked starch-urea > HPMC > Sodium CMC > Sodium alginate > MC in the case of aceclofenac.

4. Cross-linked starch urea was found to be a better release-retarding polymer than Sodium CMC, Methyl cellulose and Sodium alginate and it is comparable to HPMC (K15M).

5. Overall, cross-linked starch urea and HPMC (K15M) were found more suitable for the design of controlled release tablets of diclofenac and aceclofenac.

Studies carried out on pharmacokinetic evaluation of diclofenac matrix tablets formulated employing cross-linked starch urea are described in Chapter IX. For evaluating the release retarding and rate controlling efficiency of cross linked starch urea in vivo, pharmacokinetic evaluation was done on diclofenac matrix tablets formulated employing cross linked starch urea in comparison to diclofenac pure drug in rabbits.

The study was conducted as a cross over RBD in healthy rabbits of either sex (n = 6) with a washout period of one month. The in vivo protocols were approved by Institutional Animal Ethics Committee (Regd. No. 516/01/a/CPSEA).

Pharmacokinetic evaluation indicated slow absorption of diclofenac from the matrix tablets formulated employing cross-linked starch urea when compared to pure drug. The absorption rate (Ka) was 0.152 h⁻¹ in the case of matrix tablets, whereas in the case of diclofenac pure drug it was 0.8172 h⁻¹. A C_max of 4.7 ± 1.4 µg/ml was observed at 3.0 h in the case of diclofenac pure drug; whereas a C_max of 2.9 ± 0.6 µg/ml was observed at 6 hr in the case of matrix tablets. The MTR increased from 9.68 h for diclofenac pure drug to 14.05 h with the matrix tablets. The relative bioavailability of diclofenac from matrix tablets was 124.9% when compared to diclofenac pure drug (100%).

The pharmacokinetic evaluation indicated that diclofenac from the matrix tablets formulated employing cross-linked starch urea was released slowly and absorbed slowly.
over longer periods of time *in vivo* resulting in the maintenance of plasma concentrations within a narrow range over longer periods of time. Cross-linked starch urea exhibited good release retarding and rate controlling effect *in vivo* in the pharmacokinetic evaluation.

The results of the investigation, thus, indicated that starch urea cross-linked with calcium chloride is a promising matrix former for controlled release. Matrix tablets of (i) diclofenac and (ii) aceclofenac formulated employing cross-linked starch urea provided slow and controlled drug release over 24h. Matrix tablets of diclofenac also exhibited good release retarding effect *in vivo*. Drug release from these tablets was by non-fickian diffusion. Cross-linked starch urea is a better release retarding polymer than sodium CMC, methyl cellulose, sodium alginate and is comparable to HPMC K15M. Matrix tablets formulated employing cross-linked starch urea are quite stable during short time accelerated stability testing. Their controlled release characteristics remained unaltered. The present investigation, thus, resulted in the development of a new release retarding and rate controlling polymer for controlled release.