SUMMARY AND CONCLUSIONS

Controlled drug delivery is a topic of current interest in pharmacy and biotechnology. Development of controlled release drug delivery systems is receiving increasing attention in recent years in pharmaceutical industry. These are the systems designed to release one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Drug release from these systems should be at a desired, predictable and reproducible rate. Oral route is the most convenient and common mode of administration of controlled release systems. Though oral controlled drug delivery is the most widely utilized route of administration it suffers with a major limitation of short residence time of the drug delivery system in the g.i. tract. Among the various approaches developed to prolong residence time of the dosage form in the g. i. Tract, the principle of mucoadhesion and design of mucoadhesive systems was very successful.

Drug delivery systems formulated employing mucoadhesive polymers prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage forms with the underlying absorption surface and thus contribute to improved or better bioavailability and therapeutic performance of drugs.

The objective of the present investigation is to design mucoadhesive tablets for oral controlled release of selected medicaments (Diltiazem, Glipizide, Diclofenac and Indomethacin) which require controlled release
formulation and to develop technology for this type of new drug delivery systems.

Four medicaments namely diltiazem (an anti anginal and antihypertensive drug), glipizide (an antidiabetic drug), diclofenac (an analgesic and anti-inflammatory drug and indomethacin (an analgesic and anti-inflammatory drug) which require controlled release formulation because of their short biological half-lives, low oral bioavailabilities and gastric disturbances if present in larger concentration in g. i. Tract are included in the study. Mucoadhesive polymers such as HPMC (50 cps and 500 cps), hydroxy propyl cellulose (HPC), carbopol 934 P and sodium carboxy methyl cellulose (sodium CMC) with and without added excipients like ethyl cellulose, mannitol were utilized in the design of mucoadhesive tablets.

A review of the relevant literature is given in Chapters I to IV. The analytical methods used are described in Chapter V. UV spectrophotometric methods were used for the estimation of the drugs in the products and in the dissolution rate studies. All the methods were validated for linearity, accuracy and precision. A known HPLC method was used for the estimation of diclofenac in serum samples.

Studies carried out on the design and evaluation of mucoadhesive tablets of diltiazem are described in Chapter VI. Matrix tablets each containing 90 mg of diltiazem were prepared employing HPMC (50 cps), HPC, carbopol 934 P and sodium CMC alone and with ethyl cellulose in different proportions. All the batches of tablets prepared were of good quality with regard to hardness,
The matrix tablets were found to be non-disintegrating in water, acidic (0.1N HCl) and alkaline (pH 7.4) fluids and were found suitable for oral controlled release.

Diltiazem release from the tablets was slow and extended over longer periods of time and depended on the polymer used. Relatively rapid release was observed with sodium CMC and slow release with carbopol. The order of increasing release - retarding effect of various polymers was carbopol > HPMC > HPC > sodium CMC. As the release was complete in 6 – 8 h with all polymers except with carbopol, ethyl cellulose was incorporated in the tablets to further retard the drug release from the tablets. When ethyl cellulose was incorporated the tablets remained intact and provided slow release of diltiazem for over 12 h. Drug release from tablets formulated employing carbopol, sodium CMC and HPMC followed zero order kinetics. Whereas release from HPC tablets followed first order kinetics. Analysis of release data as per Peppas equation and Higuchi equation indicated non-Fickian (anamolous) diffusion as the release mechanism from all the tablets. Overall, formulation formulations F3 (HPMC + 5% EC), F9 (carbopol alone), F10 (carbopol + 2% EC) and F15 (sodium CMC + 5% EC). These matrix tablets were found suitable for the maintenance portion of oral controlled release tablets as release from these tablets was slow, gradual and complete in 12 h.

Initial, maintenance and total doses and the desired release rate (K,0) needed for diltiazem were evaluated based on its pharmacokinetics. Oral CR tablets each containing 90 mg of diltiazem were designed as two - layered
tablets with an immediately releasing layer consisting of diltiazem (30 mg) and AC – Di – Sol, a super disintegrant and a matrix having composition similar to formulations F3, F9, F10 and F15 and containing diltiazem (60 mg) as second layer. The two – layered CR tablets of diltiazem designed gave release profiles close to the theoretical SR needed and diltiazem release from these formulated tablets was also better than that of commercial SR tablets.

Studies carried out on the design and evaluation of mucoadhesive tablets of glipizide for oral controlled release are described in Chapter VII. Matrix tablets each containing 10 mg of glipizide were prepared employing HPMC (50 cps), HPC, carbopol 934 P and sodium CMC alone and with ethyl cellulose in different proportions. All the batches of the tablets prepared were of good quality with regard to hardness, friability and drug content. The matrix tablets were found to be non – disintegrating in water, acidic (0.1N HCl) and alkaline (pH 7.4) fluids and as such are suitable for controlled release.

Glipizide release from all the tablets prepared was slow and extended over longer periods of time and depended on the polymer used. Relatively rapid release was observed with HPC and sodium CMC and slow release with HPMC and carbopol. The order of increasing release - retarding effect of various polymers was carbopol > HPMC > sodium CMC > HPC. Incorporation of ethyl cellulose resulted in a further decrease in drug release with all the polymers, glipizide release from majority of the formulations followed zero order kinetics. Analysis of release data as per Peppas equation and Higuchi equation indicated non-Fickian (anamolous) diffusion as the release mechanism.
from all the tablets prepared. Drug release from formulations F3 (HPMC + 5% EC), F8 (HPC + 10% EC), F13 (sodium CMC alone) and F14 (sodium CMC + 2% EC) was slow, gradual and complete over a period of 12 h and these formulations were found suitable for the maintenance portion of oral CR products.

Initial, maintenance and total doses and the desired release rate ($K_o$) needed for glipizide were evaluated based on its pharmacokinetics. Oral CR tablets each containing 10 mg of glipizide were designed as two-layered tablets with an immediately releasing layer consisting of glipizide (2.5 mg) and AC-Di-Sol and a matrix having composition similar to formulations F3, F8 and F13 and containing glipizide (7.5 mg) as a second maintenance layer. The two-layered CR tablets of glipizide designed gave release profiles close to the theoretical SR needed and glipizide from these tablets was also better than that of commercial SR tablets of glipizide.

Hence the two-layered tablets of diltiazem and glipizide designed employing mucoadhesive polymers HPMC (50 cps), HPC, sodium CMC and carbopol along with EC (2-5%) are considered as good oral controlled release tablets for twice a day administration. The drug release profiles of these two-layered tablets are comparable and better than those of commercial SR tablets of these drugs.

Studies carried out on the design and evaluation of mucoadhesive tablets of diclofenac are described in chapter VIII. Attempts were made to design mucoadhesive tablets of diclofenac for once a day administration. For this
purpose HPMC (500 cps) and carbopol 934 P were tried with and without mannitol, a hydrophilic, slow dissolving tablet excipient with good compressibility character. Matrix tablets each containing 100 mg of diclofenac sodium were prepared employing HPMC and carbopol 934 P alone and in combination with mannitol. The tablets prepared were of good quality with respect to hardness, friability and drug content. All the tablets except those prepared with mannitol alone, were found to be non-disintegrating in water and aqueous fluids of acidic and alkaline pHs. Diclofenac release from matrix tablets formulated with mannitol alone was very rapid and complete within 1 to 2 h. Matrix tablets formulated employing HPMC (500 cps) and carbopol alone gave very slow release of diclofenac. The release from these tablets was only 75 – 80% in 24 h. The release was incomplete in 24 h and hence these tablets are considered not suitable for oral controlled release. Incorporation of mannitol has improved the drug release from the HPMC and carbopol matrix tablets. As the proportion of mannitol was increased, the drug release from the matrix tablets was also increased. Overall formulations F3 (HPMC and mannitol in 2:1 ratio as matrix) and F8 (Carbopol and mannitol in 2:1 ratio as matrix) provided slow, controlled and complete release of diclofenac over 24 h. The drug release from these tablets was comparable and similar to the drug release from Voveran SR tablets, a commercial diclofenac SR tablets for once a day administration. Hence these formulations (F3 and F8) are considered as good oral CR products of diclofenac for once a day administration.
Analysis of release data as per Peppas and Higuchi equations indicated non – Fickian (anamolous) diffusion as the release mechanism from all the tablets formulated with HPMC and carbopol along with mannitol.

Studies carried out on the design and evaluation of mucoadhesive tablets of indomethacin are described in Chapter IX. Mucoadhesive tablets each containing 75 mg of indomethacin were formulated employing HPMC (500 cps) and carbopol 934 P alone and in combination with mannitol with a view to achieve controlled release over 24 h. All the tablets prepared were of good quality with regard to hardness, friability and drug content. All the tablets formulated with HPMC and carbopol with and without mannitol were found to be non – disintegrating in water and aqueous fluids of acidic and alkaline pHs. Indomethacin release from the matrix tablets formulated with mannitol alone was very rapid and complete within 1 – 1.5 h. Matrix tablets formulated with HPMC (500 cps) and carbopol 934 P alone gave very slow release of indomethacin and the release was incomplete, about 60 – 75% in 24 h. Incorporation of mannitol has considerably improved the drug release from HPMC and carbopol matrix tablets. As the proportion of mannitol was increased, drug release from the matrix tablets was also increased. Overall, formulations F3 ( HPMC and mannitol in 2:1 ratio as matrix) and F8 ( carbopol and mannitol in 2:1 as matrix) provided slow, controlled and complete release of indomethacin over 24 h.

Indomethacin extended release capsules are official in USP 24. As per official (USP 24) drug release test – I, these capsules should provide a release
between 10 – 25% in 1 h, 20 – 40% in 2 h; 35 – 55% in 4 h; 45 – 65% in 6 h; 60 – 80% 12 h and not less than 80% in 24 h. Indomethacin release from the formulations F3 and F8 designed was in good agreement with the above official (USP 24) drug release requirement. Hence these formulations (F3 and F8) are considered as good oral CR products of indomethacin for once a day administration. Analysis of release data as per Higuchi and Peppas equations indicated non – Fickian (anamolous) diffusion as the release mechanism from the indomethacin tablets formulated with HPMC, carbopol with and without mannitol.

Studies on pharmacokinetic evaluation of diclofenac CR tablets formulated and commercial products are described in chapter X. in vivo pharmacokinetic studies were carried out on (i) diclofenac enteric coated tablets (ii) Voveran SR tablets (iii) Formulation F3 and (iv) Formulation F8. The study was carried out in healthy volunteers (n = 4) as per a cross over LSD.

Serum concentrations of diclofenac were determined by a known HPLC method. From the time vs serum concentration data various pharmacokinetic parameters such as $K_a$, $K_e$, $t_{1/2}$, AUC, MRT were calculated. The serum concentrations of diclofenac were stabilized and maintained within a narrow range for over longer period of time with formulated CR products. MRT was increased from 2.82 h for enteric coated tablets to 11.42 and 12.68 h with formulations F3 and F8 respectively. MRT of commercial Voveran SR tablets was 7.0 h. Diclofenac from the formulated CR tablets was released and
absorbed slowly over longer periods of time which in turn maintained the serum concentrations within a narrow range over 20 – 24 h. Hence these formulations of diclofenac (F3 & F8) are considered suitable for once a day administration.

Studies carried out to evaluate the stability of drug release rate of selected formulated tablets are described in Chapter XI. Stability studies were carried out 40±2°C and 75±5% RH for 3 months. Drug release characteristics of

(i) Formulation DSR I (two – layered diltiazem CR tablets based on HPMC and EC).
(ii) Formulation GSR III (two- layered glipizide CR tablets based on sodium CMC).
(iii) Formulation F3 (matrix tablets of diclofenac based on HPMC and EC).
(iv) Formulation F8 (matrix tablets of indomethacin based on carbopol and EC).

were evaluated before and after storage for 3 months. The controlled release characteristics of all the formulated tablets tested remained unaltered during storage.

CONCLUSIONS AND ACHIEVEMENTS

Thus, the study resulted in the development of mucoadhesive tablets of diltiazem, glipizide, diclofenac and indomethacin for oral controlled release with the following major conclusions.
A combination of mucoadhesive polymers (HPMC 50 cps, HPC, sodium CMC) and ethyl cellulose is more suitable for the design of matrix tablets for controlled release. Matrix tablets containing the above mentioned mucoadhesive polymers alone exhibited rapid and complete drug release due to erosion of polymers in 6 – 8 h. Incorporation of ethyl cellulose along with mucoadhesive polymer provided an intact matrix and slow release of the contained medicament over 12 h.

Drug release from these matrix tablets was by non – Fickian (anamolous) diffusion mechanism.

Matrix tablets formulated employing mucoadhesive polymer and ethyl cellulose are suitable only for the maintenance portion of oral CR products as the initial release from these matrix tablets was small.

Controlled release products of diltiazem and glipizide are designed as two – layered tablets. Two – layered tablets are designed with an immediately releasing layer consisting of drug, lactose and a super disintegrant agent (Ac – Di – Sol ) and a slow releasing matrix consisting of drug in mucoadhesive polymer and ethyl cellulose (2-5%) as second layer. Drug release from these two – layered tablets was spread over 12 h and very close to the theoretical SR needed for the drug (diltiazem/glipizide) based on its pharmacokinetics. The
release profiles of the two-layered tablets are comparable and better than those of commercial SR products of the drugs.

(v) The two-layered CR tablets of diltiazem and glipizide are suitable for twice a day administration.

(vi) The design of mucoadhesive two-layered tablets for oral controlled release employing HPMC (50 cps), HPC and sodium CMC is suitable for both soluble drugs such as diltiazem and poorly soluble drugs such as glipizide.

(vii) Mucoadhesive polymers, HPMC (500 cps) and carbopol 934 P are suitable for the design of controlled release products for once a day administration (24 h). Once a day controlled release products (tablets) of (i) diclofenac and (ii) indomethacin are designed employing HPMC (500 cps), carbopol 934 P and mannitol.

(viii) A combination of mucoadhesive polymer, HPMC (500 cps) or carbopol 934 P and a hydrophilic excipient mannitol is more suitable to formulate diclofenac and indomethacin CR tablets for once a day i.e. 24 h controlled release, which was not possible either with the HPMC or carbopol alone or mannitol alone.

(ix) Drug release from these matrix tablets was by non-Fickian (anamolous) diffusion mechanism.

(x) Matrix tablets formulated employing a combination of mucoadhesive polymer and ethyl cellulose (2-5%) and a combination of
mucoadhesive polymer and mannitol (2:1) exhibited good mucoadhesive property in the in vivo.

(xi) Drug release characteristics of the mucoadhesive CR tablets designed are quite stable.

(xii) In the in vivo pharmacokinetic evaluations, diclofenac CR tablets designed exhibited good sustained serum concentrations of diclofenac over 20 – 24 h. The MRT was also increased from 2.82 h h for enteric coated tablets to 11.42 – 12.68 h with diclofenac CR tablets designed. Thus, the objectives of the investigation are fulfilled.