CHAPTER XI

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS


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. Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of activity and targeting 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 dosage forms play a vital role in controlling the delivery of drug from these dosage forms. Though a wide range of polymers and other release retarding materials are available, there is a continued need to develop new, safe and effective release retarding 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 acetates are novel modified starches that are produced by acetyling native starch. They are reported to have direct compressible matrix forming properties. Starch acetate is also having good potential for coating because of its film forming properties. Though starch acetate has good film forming property, it has not been
investigated thoroughly in microencapsulation for controlled release application. In the present investigation studies were carried out on microencapsulation by starch acetate (a new modified starch) with an objective of evaluating, by in vitro and in vivo methods, starch acetate as a new release retarding and rate controlling coat polymer in microencapsulation for controlled release of glipizide. Glipizide was also microencapsulated with ethylene vinyl acetate copolymer (EVA) with an objective of making a comparative evaluation of the permeability and drug release characteristics of starch acetate and EVA microcapsules. Another objective of the investigation is to design controlled release microcapsules of glipizide employing starch acetate for once a day (24 h) administration. Preparation of drug embedded matrix tablets is another least complicated technique for controlled release and is widely used in industry. This technique was also selected for the design of controlled release drug delivery systems employing Starch Acetate and EVA.

Glipizide, an effective anti-diabetic drug was selected for formulation into controlled release drug delivery system employing starch acetate and EVA. Glipizide, an effective anti-diabetic requires controlled release formulation owing to its short biological half-life of 3.4 ± 0.7 h and is rapidly eliminated. Controlled release formulation is needed for glipizide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce g.i. disturbances and to enhance patient compliance. A few controlled release formulations of glipizide are available commercially.
Literature on controlled release drug delivery systems (microcapsules and matrix tablets) is reviewed in Chapter II. Chapter III contains literature on role of polymers in controlled release and polymers investigated. Literature on glipizide along with past research work on this drug is described in Chapter IV.

Studies on the preparation and characterization of starch acetate are described in Chapter V. Starch acetate (SA) was prepared by acetylation of potato starch with acetic anhydride in alkaline medium. The percent acetylation in the starch acetate prepared was 42.38 % and the degree of substitution was 2.75. The IR spectrum of starch acetate showed the acetyl carbonyl stretching at 1749 cm\(^{-1}\), which was absent in the IR spectrum of potato starch indicating the acetylation of the native starch. It is freely soluble in chloroform. Starch acetate exhibited good film forming properties when dried from a solution in chloroform.

Pre-formulation studies carried out are described in Chapter VI. An UV spectrophotometric method based on the measurement of absorbance at 223 nm in phosphate buffer of pH 7.4 was used for the estimation of glipizide in \textit{in vitro} studies. The method was validated for linearity, accuracy and precision. Drug – excipient compatibility was evaluated by IR, DSC, and XRD. FT-IR and DSC spectra indicated no interaction between glipizide and starch acetate polymer investigated for controlled release application. XRD spectra indicated the presence of drug (glipizide) in amorphous form in the microcapsules prepared.
Studies on preparation and evaluation of starch acetate and EVA microcapsules of glipizide for controlled release are described in Chapter VII. Glipizide which requires controlled release formulation was microencapsulated by (i) Starch Acetate and (ii) EVA. An emulsification solvent evaporation method was tried to prepare the microcapsules. In each case different proportions of core: coat were used to prepare microcapsules with different wall thickness. All the starch acetate and EVA microcapsules prepared were evaluated for size and size distribution, drug content, microencapsulation efficiency, wall thickness, drug release kinetics and mechanisms. From the results obtained the following conclusions are drawn.

1. Starch acetate and EVA microcapsules of glipizide could be prepared by the emulsification-solvent evaporation method developed employing chloroform as solvent for starch acetate and EVA. The method of preparation of microcapsules was reproducible with regard to size and size distribution of microcapsules.

2. The microcapsules prepared were discrete, spherical and free flowing and were of multinucleate and monolithic type with both starch acetate and EVA.

3. The sizes in a batch of microcapsules could be separated by sieving and a more uniform size range of microcapsules could readily be obtained. Size analysis showed that a large proportion of microcapsules in a batch were in the size range of -20+30 (715 µm) and -30 +50 (443 µm) mesh with both starch acetate and EVA.

4. The drug content was uniform in each batch of microcapsules. The microencapsulation efficiency was nearly the same with both SA and EVA and was in the range 99.86 - 101.71 % and 100.60 – 100.86 % respectively in the case
of starch acetate and EVA microcapsules. Microcapsules prepared with various ratios of core: coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

5. Drug release from the microcapsules was slow and spread over a period of 24 hr and depended on core: coat ratio, wall thickness and size of microcapsules with both starch acetate and EVA.

6. Drug release from the microcapsules was diffusion controlled and followed first order kinetics with both starch acetate and EVA.

7. Glipizide release from all starch acetate microcapsules was by Fickian diffusion except microcapsules SAGM3 (Size 20/30). In the case of microcapsules SAGM3 (Size 20/30) which provided very slow release of glipizide, the release was by non-fickian (anomalous) diffusion.

8. Glipizide release from all EVA microcapsules was also by Fickian diffusion except microcapsules EVAGM2 (Size 20/30) and EVAGM3 (Size 20/30). In the case of microcapsules EVAGM2 (Size 20/30) and EVAGM3 (Size 20/30) which provided very slow release of glipizide, the release was by non-fickian (anomalous) diffusion.

9. When the release was relatively fast it was by fickian diffusion. Whereas when the release was relatively slow it was by non-fickian diffusion both starch acetate and EVA. Smaller microcapsules gave higher release rates with both starch acetate and EVA.

10. Good linear relationships were observed between wall thickness of the microcapsules and release rate ($K_t$) with both starch acetate and EVA.
11. Drug release mechanism from the microcapsules prepared was diffusion controlled. As both starch acetate and EVA are insoluble in both the acidic and alkaline fluids the mechanism of dissolution and erosion of the coat are not applicable.

12. A comparative evaluation of drug release and permeability of glipizide microcapsules prepared employing starch acetate and EVA was made. The permeability constant \((P_m)\) of various microcapsules was calculated from release data. The microcapsules prepared employing SA as coat polymer have shown lower permeability constants than those of EVA microcapsules. The order of increasing permeability of the microcapsules prepared was EVA>SA. With very low permeability starch acetate microcapsules were found to be more suitable for the design of controlled release drug delivery systems than EVA.

13. Glipizide release from starch acetate microcapsules SAGM3 (Size 20/30) was similar to that Glytop SR tablets (A commercial SR tablet formulation of Glipizide). Hence these starch acetate microcapsules, are considered as the best controlled release formulation developed suitable for controlled release of glipizide over 24 h.

14. Studies on formulation and evaluation of matrix tablets of glipizide employing starch acetate and EVA are described in Chapter VIII. Matrix tablets of glipizide were formulated employing (i) Starch acetate and (ii) EVA in different proportions of drug and polymers and the tablets were evaluated for drug release kinetics and mechanism. From the results obtained the following conclusion are drawn.
15. Matrix tablets of glipizide could be prepared employing different proportions of Starch acetate, a new modified starch and EVA by conventional wet granulation method.

16. All the matrix tablets prepared were found to be non-disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such they are considered suitable for oral controlled release.

17. Glipizide release from the matrix tablets formulated was slow and spread over 24 h and depended on the concentration (%) of polymer (i.e. starch acetate and EVA) in the matrix tablets and nature/type of diluent used.

18. As the concentration of polymer (i.e. starch acetate and EVA) in the matrix tablets was increased, drug release was decreased.

19. Release was relatively faster with water soluble diluent lactose when compared to water insoluble diluent DCP at all concentrations of starch acetate and EVA.

20. Glipizide release from the matrix tablets prepared was diffusion controlled and followed first order kinetic.

21. Good linear relationships were observed between percent polymer and release rate with both SA and EVA. Drug release from the matrix tablets could be controlled by varying the proportion of drug: polymer in the matrix.

22. Glipizide release from matrix tablets (TSAF2) formulated employing 5 % starch acetate was similar to that Glynase XL tablets (A commercial SR tablet formulation of Glipizide). Hence these starch acetate matrix tablets are considered as the best controlled release matrix tablet formulation developed suitable for controlled release of glipizide over 24 h.
23. Stability studies described in Chapter IX indicated that the drug content and drug release rate of the starch acetate microcapsules and matrix tablets of glipizide were quite stable and remained unaltered when subjected to accelerated stability testing at $40^\circ C \pm 2^\circ C$ and $75\%$ RH $\pm 5\%$ for 6 months. Studies on Biochemical, Pharmacokinetic and Pharmacodynamic evaluation of starch acetate microcapsules of glipizide are described in Chapter X. Pharmacokinetic and pharmacodynamic evaluation was done on starch acetate microcapsules of glipizide SAGM3 (Size 20/30) in comparison to glipizide pure drug with a view to evaluate the release retarding and rate controlling efficiency of starch acetate in vivo. From the results obtained the following conclusions are drawn,

24. Biochemical studies indicated no change in the body weight, blood glucose levels, protein, TG and cholesterol level following treatment with SA microcapsules is comparable to that of pure glipizide.

25. The absorption of glipizide from SA microcapsules was slow over longer periods of time in vivo with a $K_a$ of $0.158 \pm 0.22\ h^{-1}$. Whereas the absorption was relatively rapid in the case of glipizide pure drug with a $K_a$ of $0.8164 \pm 0.19\ h^{-1}$.

26. A $C_{max}$ of $4.92 \pm 0.24\ \mu g/ml$ was observed at 3 h after oral administration of glipizide pure drug. In the case of SA microcapsules a $C_{max}$ of $2.88 \pm 0.16\ \mu g/ml$ was observed at 6 h following the administration indicating slow absorption of glipizide from SA microcapsules.

27. The MRT was increased from $10.24 \pm 0.25\ h$ for glipizide pure drug to $14.75 \pm 0.34\ h$ with the SA microcapsules.
28. The relative bioavailability of glipizide from SA microcapsules was 110.3 ± 0.48 % when compared to glipizide pure drug (100 ± 1.06 %).

29. A rapid reduction in blood glucose levels was observed when glipizide was administered. A maximum reduction of 57.2 ± 0.8 % was observed at 1 h after administration of glipizide. The reduced glucose levels were recovered rapidly to normal levels within 6 – 8 h in the case of glipizide.

30. A significant hypoglycemic effect was maintained during the period from 0.5 to 6 h following the administration of glipizide.

31. When starch acetate microcapsules of glipizide were administered at the same dose, reduction in blood glucose occurred slowly and percent reduction in blood glucose values was lower than those observed with pure drug. The reduced glucose levels were sustained over longer periods of time with the SA microcapsules. The significant hypoglycemic effect was maintained during the period from 4 to 24 h with starch acetate microcapsules.

32. Starch acetate exhibited good release retarding and rate controlling effect *in vivo* in both pharmacokinetic and pharmacodynamic evaluation.
11.1. SIGNIFICANT CONTRIBUTIONS AND RECOMMENDATIONS

The present investigation resulted in the development of starch acetate (SA) as an effective and efficient release retarding and rate controlling coat polymer in microencapsulation and in matrix tablets for obtaining controlled release. SA microcapsules of glipizide exhibited good controlled release characteristics in vitro and in vivo and were found suitable for oral controlled release for 24 h. The plasma concentrations of glipizide as well as hypoglycemic effect were sustained over longer periods of time up to 24 h with the SA microcapsules. With low permeability and slow and controlled drug release characteristics SA microcapsules are more suitable for controlled release than EVA microcapsules. The drug release characteristics of SA microcapsules and matrix tablets were quite stable during accelerated stability testing.

Hence Starch acetate, a new modified starch is recommended as a new efficient release retarding and rate controlling coat polymer in microencapsulation and in matrix tablets for obtaining controlled release.