CHAPTER – XIII

SUMMARY AND CONCLUSIONS
SUMMARY AND CONCLUSIONS

Controlled drug delivery is a topic of current interest in pharmaceutical technology. In recent years, considerable attention has been focused on the development of new drug delivery systems known as controlled release drug delivery systems. Such interest is based largely on the fact that the controlled release products have established and retained a place in the market based on their uniqueness and their clinical advantages in the practices of medicine. 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 dosage forms play a vital role in controlling the delivery of drug from these dosage forms.

In the present investigation tamarind kernel gum, a new natural based polymer was prepared and evaluated for its application in controlled release. The specific objectives of the investigation are (i) to prepare and characterize tamarind kernel gum, chemical and physical tests and also by X-ray and FTIR spectra, (ii) to evaluate tamarind kernel gum as a new release retarding and rate controlling polymer for controlled release application and (iii) to develop
tamarind kernel gum matrix tablets for controlled release and to design controlled release drug delivery systems in the form of matrix tablets of prednisolone (poorly soluble drug) and diclofenac (water soluble drug) for twice-a-day (12 hours) administration and to evaluate them by *in vitro* and *in vivo* methods.

The tamarind kernel gum obtained from the seed kernel of plant *Tamarindus indica* is light brown coloured granular powder which is amorphous in nature. It slightly soluble in water, practically insoluble in alcohol, chloroform and acetone and forms thick gel which can control the drug release.

For evaluation of tamarind kernel gum as a new release retarding and rate controlling polymer for controlled release, matrix tablets of two drugs namely prednisolone (40 mg), and diclofenac (50 mg) were prepared employing tamarind kernel gum in different proportions in each case by conventional wet granulation method in diclofenac case and direct compression in the case of prednisolone employing its solid dispersions. All these matrix tablets prepared were evaluated for drug content, hardness, friability, disintegration time and kinetics and mechanism of drug release from the matrix tablets. The release data were analyzed as per zero order, first order, Higuchi and Peppas equation models. The release retarding and rate controlling efficiency of tamarind kernel gum was compared with that of other polymers commonly used in matrix tablets such as sodium CMC HPMC. In each case
(i.e with diclofenac, and prednisolone) matrix tablets were prepared employing tamarind kernel gum and the above mentioned other polymers and the matrix tablets were evaluated. Selected best controlled release product formulated employing tamarind kernel gum were subjected to accelerated stability testing as per ICH guidelines. Pharmacokinetic evaluation was done on prednisolone matrix tablets formulated employing tamarind kernel gum in comparison to prednisolone pure drug in rabbits with a view to evaluate the release retarding and rate controlling efficiency of tamarind kernel gum in vivo. From the results obtained the following conclusions are drawn:

**Conclusions from solid dispersions:**

1. The results obtained from the dissolution studies of drug: PEG solid dispersions, it is concluded that PEG in the ratio 1:3, is better than other ratios 1:1, 1:2 and 1:5. In case of 1:5, the viscosity of the dissolution medium might be increased significantly, which had lead to decrease in dissolution of Prednisolone. The dissolution efficiency was increased significantly by 3.91 times than the pure drug in the case of physical mixing of drug and polymer in the ratio 1:3. In both dissolution media i.e. in pH 1.2 and pH 6.8, the same was observed. When compared to pH 1.2 dissolution medium, in pH 6.8 the dissolution efficiency was more. As in case of pH 1.2 the dissolution medium, the dissolution efficiency increased significantly by 3.91 times of the pure drug, where as in pH 6.8, the dissolution medium, the dissolution efficiency
increased significantly by 5 times of the pure drug in the case of PEG physical mixing.

2. In co-grinding method by using PEG, the ratio 1:3 showed better dissolution when compared to other ratios. Co-grind solid dispersions showed better dissolution in pH 6.8 when compared to pH 1.2. As the dissolution efficiency was increased significantly 7.1 times than the pure drug in the pH 6.8, the co-grind solid dispersions of drug: PEG in the ratio of 1:3 was conducted the dissolution studies. In the case of pH 1.2 the dissolution efficiency was only 5.66 times greater than pure drug.

3. In solvent evaporation method also the same results as that of the physical mixing and co-grinding were found i.e. 1:3 ratio of drug: PEG enhanced the dissolution to a greater extent, when compared to other ratios. The dissolution rate was enhanced significantly in pH 6.8, when compared to pH 1.2, as the dissolution efficiency was enhanced significantly by 7.1 times of pure drug in pH 6.8 and it was only 5.91 times of pure drug in pH 1.2 dissolution medium.

4. Of all the methods, physical mixing, co-grinding and solvent evaporation, solvent evaporation or co-precipitation is the best method as the dissolution efficiency was enhanced significantly to a greater extent in case of solvent evaporation than the physical mixing and co-
grinding method, when PEG was used an hydrophilic polymer to enhance the dissolution rate of Prednisolone.

5. The results obtained from dissolution studies of drug: PVP solid dispersions, it is concluded that PVP in the ratio of 1:3, is better than other ratios 1:1, 1:2 and 1:5. In case of 1:5, the viscosity of the dissolution medium might be increased, which had lead to decrease in dissolution of Prednisolone. The dissolution efficiency was increased by 5.8 times than the pure drug in the case of physical mixing of drug and polymer in the ratio 1:3. In both dissolution media i.e. in pH 1.2 and pH 6.8, the same was observed. When compared to pH 1.2 dissolution medium, in pH 6.8 the dissolution efficiency was more. As in case of pH 1.2 the dissolution medium, the dissolution efficiency increased significantly by 5.8 times of the pure drug, where as in pH 6.8, the dissolution medium, the dissolution efficiency increased significantly by 7.8 times of the pure drug in the case of PVP physical mixing.

6. In co-grinding method by using PVP, the ratio 1:3 showed better dissolution when compared to other ratios. Co-grind solid dispersions showed better dissolution in pH 6.8 when compared to pH 1.2. As the dissolution efficiency was 7.2 times the pure drug in the pH 6.8, the co-grind solid dispersions of drug: PVP in the ratio of 1:3 was conducted the dissolution studies. In the case of pH 1.2 the dissolution efficiency was only 5.93 times greater than pure drug.
7. In solvent evaporation method also the same results as that of the physical mixing and co-grinding were found i.e. 1:3 ratio of drug: PVP enhanced the dissolution to a greater extent, when compared to other ratios. The dissolution rate was enhanced more in pH 6.8, when compared to pH 1.2, as the dissolution efficiency was enhanced significantly by 11 times of pure drug in pH 6.8 and it was only 6.16 times of pure drug in pH 1.2 dissolution medium.

8. Of all the methods, physical mixing, co-grinding and solvent evaporation, solvent evaporation or co-precipitation is the best method as the dissolution efficiency was enhanced to a greater extent in case of solvent evaporation than the physical mixing and co-grinding method, when PVP was used an hydrophilic polymer to enhance the dissolution rate of Prednisolone.

9. All the matrix tablets formulated employing tamarind kernel gum were of good quality with regard to drug content, hardness and friability and fulfilled the official (IP/USP) requirements of compressed tablets with regard to the above mentioned physical properties.

10. With all the two medicaments (Prednisolone and diclofenac,) drug release from the matrix tablets formulated employing tamarind kernel gum was slow and spread over more than 12 hours and depended on the percentage strength of tamarind kernel gum in the tablets. The release
of two drugs from the matrix tablets was non-diffusion controlled and followed zero order kinetics.

11. With the two drugs as the polymer (tamarind kernel gum) strength in the matrix tablets was increased the release rate was decreased. Overall, tamarind kernel gum was found to be a better release retarding polymer than HPMC and sodium CMC with the two drugs and hence it could be used in the formulation of matrix tablets to provide controlled release of the contained drug for 12 hours.

12. The absorption of Prednisolone from the tamarind kernel gum matrix tablets was slow over longer periods of time \textit{in vivo} with a $K_a$ of 0.553 h$^{-1}$. Whereas the absorption was relatively rapid in the case of Prednisolone pure drug with a $K_a$ of 0.667 h$^{-1}$.

13. A $C_{\text{max}}$ of 0.45 $\mu$g/ml was observed at 4 h after oral administration of Prednisolone pure drug. In the case of tamarind kernel gum matrix tablets, a $C_{\text{max}}$ of 1.56 $\mu$g/ml was observed at 2 hr following the administration, indicating slow significant (P<0.05) absorption of Prednisolone from tamarind kernel gum matrix tablets.

14. The MRT was increased from 3.06 hr for Prednisolone pure drug to 4.011 hr with the matrix tablets. The relative bioavailability of Prednisolone from tamarind kernel gum matrix tablets was 236 % when compared to Prednisolone pure drug (100 %).
15. The sustained effect observed with the matrix tablets is due to the slow release and absorption of the contained drug from the matrix tablets over a longer period of time.

16. Drug release characteristics of the matrix tablets formulated employing tamarind kernel gum were quite stable and remained unaltered when subjected to accelerated stability testing at $40^0 \pm 2^0$ C and 75 % RH for 6 months.

Significant Contributions and Recommendations:

The present investigation resulted in the development of tamarind kernel gum as an effective and efficient release retarding and rate controlling polymer in matrix tablets for obtaining controlled release. Matrix tablets of two drugs (prednisolone and diclofenac) formulated employing tamarind kernel gum exhibited good controlled release characteristics in vitro and in vivo (taking prednisolone formulation as model) and were found suitable for oral controlled release for 12 hours. Hence tamarind kernel gum is recommended as a new release retarding and rate controlling polymer in matrix tablets for obtaining controlled release. So it can be used in the controlled released formulations of both poorly soluble drugs and water soluble drugs. Ours is the first work done on enhancing the dissolution rate of Prednisolone and formulating it into controlled release matrix tablets employing tamarind Kernel gum and also formulation of controlled release matrix tablets of Diclofenac employing tamarind kernel gum.
Further scope of work:

- Tamarind kernel gum can be evaluated as a microencapsulating polymer for micro encapsulation.
- Tamarind kernel gum can be evaluated as an enteric coating polymer.
- Tamarind kernel gum can be evaluated as gastro retentive polymer.