CHAPTER 7

SUMMARY

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma and maintains the desired drug concentration constantly for the entire duration of treatment. This is possible through administration of dosage forms in a particular dose by repeated administration at particular frequency. The dosing intervals depend upon the biological half-life of the drugs. The multiple dosing leads to fluctuation in the drug blood levels and precipitates the dose related adverse effects.

The most common NSAIDs such as aceclofenac sodium and dexibuprofen are being used in the therapeutic management of inflammation and pain with dose range 100 to 200mg (aceclofenac sodium) and 200 to 600mg (dexibuprofen) in divided doses a day. Due to their shorter biological half-lives of 2-3 hours, repeated administration 3 to 4 times a day is necessary to maintaining the steady state concentration for entire duration of treatment. This leads to patient non-compliance and also fluctuation in drug blood level. However, due to this reason and also numerous clinical reports, post-marketing surveillance studies have revealed that NSAIDs are associated with extensive side effects like gastric-irritation, peptic ulceration, esophagitis, constipation, sodium and water retention, chronic intestinal nephritis.

The great therapeutic value of these drugs has made necessary to develop strategies for avoiding the gastrointestinal risks. The oral sustained drug delivery systems namely microbeads and matrix tablets are developed to minimize their dose related side effects and improve the pharmacotherapy of inflammation and pain.
This thesis deals with the investigations carried out the objective of developing oral sustained release formulations through microbeads and matrix tablets for widely used novel non-steroidal anti-inflammatory drugs (NSAIDs) like aceclofenac sodium, dexibuprofen and to evaluate their sustained release potential in various gastrointestinal pH environment.

The first chapter of the thesis deals with a brief background of the research problems associated with oral conventional dosage formulations over sustained/controlled drug delivery. Further, it explains brief background history of certain new techniques such as microencapsulation and polymeric matrix systems involved in the formulation of NSAIDs to minimize dose related adverse effects and improve the pharmacotherapy of arthritis.

The second chapter of the thesis explains the fast research work reported in various national and international journals on oral sustained/controlled release dosage forms by adopting microencapsulation techniques and matrix systems using natural or synthetic polymers. It also reviews the physicochemical properties of drugs such as aceclofenac sodium, dexibuprofen and polymers involved in the present research work.

The third chapter of the thesis reveals the aim and objective of the present investigation and designing the suitable drug delivery systems for the drug candidates selected in the present research investigation.

The fourth chapter of the thesis explains in detail the experimental procedures that are involved in the research work, such as preformulation studies (solubility of drugs, drug and polymer compatibility by FTIR, DSC, and XRD) formulation of dosage forms like microbeads and sustained release matrix tablets. Further, it explains
the effects of various manufacturing variables on physicochemical properties and in-vitro drug release behaviors in various physiological pH environments and investigates the stability of optimized formulations by HPLC technique.

The fifth and sixth chapters of the thesis deals with the results obtained in the preformulation work, formulation variables and effects on physicochemical properties of formulated products namely microbeads and matrix tablets along with detailed discussion. Some of the important findings of the present investigation are listed below;

8.1 Preformulation studies

FTIR spectral data indicates that the major peaks of drugs are present in the formulations show nearer value to pure drug; there were no considerable changes in IR peaks in all physical mixtures of drug and polymer.

The DSC thermograms explain that there were no appreciable changes in the melting endothermic peaks and thermal behavior of drug in the manufacturing process and the drug was molecularly dispersed in different hydrogel matrices.

The XRPD patterns reveal that the decrease in the degree of crystallinity is due to partial amorphization of the drug in the polymeric matrix. Thus, there were no appreciable changes in the crystallinity of drug during the manufacturing process.

7.2 Aceclofenac sodium microbeads

The aceclofenac sodium microbeads were prepared by ionotropic external gelation technique by using sodium alginate and calcium chloride as cross-linking agent. The effects of different variables such as drug-polymer ratios, concentration of cross-linking agent, stirring speed and cross-linking time were evaluated on mean
particle size, drug content, swelling properties, drug entrapment efficiency and drug release potential.

The rheological properties of drug loaded microbeads such as angle of repose, bulk and tapped density, Carr’s index and hausner’s ratio were found in an acceptable range. It indicates that the formulated microbeads are having good flowability and packability.

SEM photographs indicated that the microbeads were discrete, nearly spherical shape and the small cracks, pores; large polymeric bridges were observed which influence the swelling and drug release.

By increasing the drug to polymer ratio the actual drug content, entrapment efficiency, mean particle size increases significantly. The swelling behavior of microbeads was high by increasing the drug to polymer ratio and the beads swell in acidic media scarcely and maximum at higher pH level.

The effect of drug to polymer ratio on in-vitro drug release behavior was significant. The drug release from the microbeads was pH dependent, very negligible drug release in pH 1.2 (< 10%) and maximum amount of aceclofenac sodium release (>70 % w/w) in pH 6.8 PBS at 6 hours was observed and followed by sustaining in pH 7.4 PBS up to 12 hours.

In general the increase in the polymer ratio retards the drug release to a greater extent due to maximum swelling of microbeads in higher pH level.

By increasing the concentration of calcium chloride in curing media during the manufacturing process decreases the mean particle size, swelling behavior and drug release.
Increase in the crosslinking time and stirring speed decreases the mean particles size, drug entrapment efficiency but increases the sphericity of microbeads.

The kinetic data was best fitted to Korsmeyer and Peppa’s model and good regression co-efficient values in the range of 0.91624 to 0.97772 and diffusion coefficient (n) values are 1.6448 to 1.7552 indicating the drug release from the microbeads exhibited zero-order kinetics followed by super case-II transport.

The formulated microbeads were stable at 25°C / 60% RH for 6 months, more than 6 months slightly change their physical nature and flow properties

7.3 Dexibuprofen solid microemulsion microbeads

The oral sustained release solid microemulsion microbeads of dexibuprofen were prepared by using Labrafac PG as oil, Labrasol surfactant and Tween 80 co-surfactant, sodium alginate as gelling agent and clay as absorbent. Initially homogenous microemulsion was formulated and converted into solid spheres by using sodium alginate/clay and calcium chloride as cross-linking agent.

To study the effects of various formulation and process variables, each time one variable was varied, fixed others constant and examined the effects of drug-polymer ratio, concentration of cross-linking agent, clay (HAS) on mean particle size, distribution patterns, drug entrapment efficiency, mechanical strength and in-vitro drug release potential of the product.

The rheological properties of drug loaded microbeads such as angle of repose, bulk and tapped density, Carr’s index and hausner’s ratio were in acceptable range. It indicates that the formulated microbeads are having good flowability and packability.

The effect of drug to polymer ratio on in-vitro drug release behavior of dexibuprofen microbeads was significant. The percentage of drug release from the
microbeads was observed in pH 1.2 for initial 2 hours in the range of 44.25 to 28.15; pH 6.8 PBS at 6 hours was 64.83 to 50.79 and in pH 7.4 PBS at the end of 12 hours was found 98.65 to 88.40. This indicates that the maximum drug release was observed in pH 6.8 PBS followed by sustaining up to 12 hours due to the relaxation of polymer net-work at higher pH level.

By increasing the concentration of clay (HAS) significantly decreases the particle size and increases the drug entrapment efficiency, swelling behaviors of sodium alginate microbeads.

The concentration of clay (HAS) influence on in-vitro drug release of sodium alginate microbeads explains that the concentration of clay increases the initial burst release of the beads and decreases significantly in SGF pH 1.2 due to formation of SA/clay dense matrix. The percentage of drug release from SA-clay (HAS) composite beads at 6 hours in pH 6.8 PBS and pH 7.4 PBS at the end of 12 hours was decreased from 58.11 to 44.72 and 93.52 to 80.96 respectively. It has been stated; that the drug diffusivity of the composite gel is affected by the denser matrix structure and created by the interaction between SA and clay (HAS). The denser matrix structure had higher tortuosity, resulting slower drug diffusion through water filled channels in the clay/alginate gel at higher pH level.

The kinetic release mechanism of sodium alginate microbeads shows first order release followed by huguchi matrix and sodium alginate/clay composite microbeads show the mechanism of drug release followed nearer to zero-order and huguchi matrix kinetics. The diffusion co-efficient values were in the range of 0.9166 to 1.1779. This indicates that the drug release from microbeads by both diffusion and erosion mechanisms followed by super case-II transport is due to control of swelling and diffusion of sodium alginate/clay (HAS) matrices.
The concentration of clay also influences the stability of sodium alginate microbeads. The alginate-clay composite microbeads (M8) are very stable at higher temperature and humidity condition; there were no significant changes in drug potency because the addition of clay increases the stability.

7.4 Matrix tablets of aceclofenac sodium and dexibuprofen

The polymer and diluent proportion seems to have a significant effect on physicochemical properties such as granular bulk and tapped density, flow behaviors, average weight, hardness, content uniformity and drug release profiles of formulated sustained release matrix tablets of aceclofenac sodium and dexibuprofen.

All the micromeritic properties of the granules and powder blends show acceptable range that is free flowing during the compression of tablets. The compressed tablet properties such as percentage of drug content, hardness, average weight and weight variation obtained an acceptable range and the values meet pharmacopeias limits.

The swelling behaviors of formulated tablets remarkably increase with optimum proportion of polymer and diluent level. In the present research work, higher level of diluent and lower level of polymer decreases the swelling and increases the erosion at alkaline pH. The increase in the polymer proportion controls the erosion due to the swelling nature of polymer. The optimum proportion of HPMC K15M and Pharmatose shows the gradual swelling behavior and gives a great contribution to sustain the drug release for extended period of time.

The in-vitro drug release significantly decreases with variable concentration of polymer and diluent ratio. The formulated drug loaded matrix tablets in SGF pH 1.2 show less than 20% w/w of drug release due to hydrophobicity of drugs, but
maximum amount of drug release (>60 %w/w) in pH 7.4 at 6 hours followed by sustaining up to 12 hours due to formation of thick hydrodynamic polymer gel layer by swelling of hydrophilic layer, that takes time to diffuse the drug in to bulk of the dissolution media. Thus the results, clearly explain that the polymer and diluent ratio modify the release in a sustained manner.

The kinetic drug release mechanism of formulated aceclofenac sodium and dexibuprofen matrix tablets was found to be linear and close correlation with huguchi matrix diffusion followed to Korsmeyer and Peppa’s model and good regression co-efficient was observed due to diffusion and erosion mechanism of polymeric chains.

The stability study of formulated matrix tablets with respect to their physical characteristics such as hardness, weight variation and drug content over a period of six months, stored at different temperature and humidity condition was observed. Based on these observations, the developed formulations of aceclofenac sodium and dexibuprofen matrix tablets are physically and chemically stable and retain their pharmaceutical properties at various temperature and humidity conditions over a period of 6 months.

Stability studies of aceclofenac sodium and dexibuprofen matrix tablets were conducted by HPLC technique. By comparing the chromatographs of pure aceclofenac sodium and formulated matrix tablets, the retention time, peak height, theoretical levels, tail factor and resolution factors are almost identical. On the other hand, asymmetry value obtained below 2.0 and recovery of drug in the formulation slightly decreases. The results indicate that the formulated matrix tablets are stable but slightly retain their active drug potency in the formulation after 6 months.
By comparing the chromatographs of pure dexibuprofen and formulated matrix tablets the retention time, peak height, theoretical levels, tail factor and resolution factors are almost identical. On the other hand, asymmetry value of pure drug below 2.0 and recovery of drug content about 99.32 mg. In the formulated tablets, the asymmetry value above 2.0 and the content of dexibuprofen decreases significantly about 83.07 mg. The results indicate that the formulated matrix tablets are not stable because some amount of active drug degraded in the formulation after 6 months.