REVIEW OF LITERATURE
B. N. Nalluri et al developed tablet formulations of nimesulide-β-cyclodextrin (NI-β-CD) and meloxicam-γ- cyclodextrin (ME-γ-CD) binary systems. The tablet formulations containing drug-CD binary systems prepared by the wet granulation and direct compression methods showed superior dissolution properties when compared with the formulations of the corresponding pure drug formulations. Overall, the dissolution properties of tablet formulations prepared by the direct compression method were superior to those of tablets prepared by the wet granulation method. Drug-CD binary systems are useful in developing tablet formulations of nimesulide and meloxicam with improved dissolution properties1.

M. C. Gohel et al develop a novel dosage form of rifampicin and isoniazid to minimize degradation of rifampicin in acidic medium and to modulate the release of rifampicin in the stomach and isoniazid in the intestine. Gastroretentive tablets of rifampicin (150 mg) were prepared by the wet granulation method using hydroxypropyl methylcellulose, calcium carbonate, and polyethylene glycol 4000. Study revealed that a substantial amount of rifampicin was degraded from the immediate release capsule containing rifampicin and isoniazid powder owing to drug accumulation in the dissolution vessel and also to the presence of isoniazid. Authors concluded that the problem of rifampicin degradation can be alleviated to a certain extent by this novel dosage form2.

S Jamzad et al described dissolution quality assessments, in the evaluation of the rate of dissolution for 2 low solubility drugs, glipizide and fenofibrate. The influence of formulation, sink conditions, surfactant type, and medium pH on their dissolution behavior and discriminatory effect of dissolution testing has been presented. Saturation solubility of fenofibrate and glipizide in different media were determined. Solubility of fenofibrate increased directly with SLS concentration3.

V Kotwal et al developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. The in vitro drug release study revealed that HPMC K100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (F2) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release4.

M.Chavanpatil et al developed sustained release gastroretentive drug delivery system for ofloxacin and carried out in vitro and in vivo evaluation. Authors found that HPMC K100M increases the dimensional stability of the formulation, which is necessary in case of once daily formulations. Betacyclodextrin proved to be a very good channeling agent. The formulation was bioequivalent to the marketed product5.

A.K.Srivastava et al studied oral sustained delivery of Atenolol from floating matrix tablets. Authors found that by varying the amount of effervescent and using different polymer combinations, a lesser floating lag time and prolonged floating duration could be achieved. Polymer swelling was crucial in determination of drug release and floating ability of the dosage form6.

S.C. Basak et al designed floatable gastroretentive tablets of Metformin hydrochloride and found that gas generating agents can be used to achieve floating dosage forms in combination with gel forming agents like HPMC K4M. A prolonged drug release was obtained for a period of 8 h. Authors found that increase in concentration of polymers decrease drug release from the formulation7.
M.A. Solinis et al studied the release of Ketoprofen enantiomers from HPMC K100M matrices and diffusion process. They found that the amount and mechanism of the release of racemic Ketoprofen from formulation elaborated are conditioned mainly by the pH of the matrix. The release of the drug was governed by diffusion process.

H. Mehrghan et al studied the release behavior and kinetic evaluation of Diltiazem HCl form various hydrophilic and plastic based matrices. HPMC polymer in concentration of 35-45% was found to be successful to retard the drug release form the matrices for 12 h period. The drug release mechanism was governed by diffusion process. (Diffusion exponent= 0.46-0.59).

A.O. Nur developed Captopril floating tablets and evaluated release kinetics. Polymers employed were HPMC K4M, HPMC K15M and Carbopol 934P. The drug retardation was achieved for 24 h period. The release of drug was governed by diffusion process. (Diffusion exponent= 0.41-0.51). Hardness of the tablets was crucial in drug release study.

J. Siepmann and N.A. Peppas studied modeling of the drug release form delivery systems based on hydroxypropyl methylcellulose (HPMC). Authors explored various kinetic models to study drug release from matrices. They found that diffusion, swelling and erosion are the most important rate controlling mechanisms of controlled release products. For HPMC tablets, the drug diffusion coefficients are strongly dependent on the water content of system. Polymer dissolution depends on degree of substitution and chain length of the HPMC type used.

A. Miranda et al studied the critical points of HPMC hydrophilic matrices for controlled drug delivery. The application of the percolation theory explained the changes in the release and hydration kinetics of swellable matrix type controlled delivery system. The critical points observed in dissolution and water uptake studies can be attributed to the excipient percolation threshold, being this threshold one of the main factors governing the gel-layer formation and consequently, the drug release control from hydrophilic matrices.

S. Kiil and K.D. Johansen studied controlled drug delivery from swellable hydroxypropylmethylcellulose matrices: model based analysis of observed radial front movements. Authors explored various zones i.e. glassy, diffusion, swelling and erosion in drug release process from matrices. They also studied concept of glass transition temperature and swelling of polymer. Authors found that accurate modeling of drug delivery from cylindrical HPMC matrices involve both axial and radial diffusion.

X. C. Fu et al studied prediction of the drug release from HPMC matrices with respect to effect of physicochemical properties of drug and polymer concentration. Authors studied various drugs with different solubilities and HPMC K4 M as polymer. They found that more soluble drugs usually have less diffusional exponent values may be because of smaller molecular volumes.

E. Verhoeven et al explored the use of xanthan gum to tailor drug release of sustained release ethylcellulose mini-matrices prepared via hot-melt extrusion. Authors used various grades of xanthan gum like XG 75, XG 180 and XG 11 K in 10-30% concentration. Ibuprofen was used as model drug. They found that increasing xanthan gum concentration yielded a faster drug release, higher liquid uptake, swelling and erosion rate. Diffusion was not the only mechanism controlling drug release but it was also dependent on the swelling of hydrated polymer mass. In vivo studies showed that XG/EC formulation was able to sustain plasma levels in dogs.

Y. Machida et al formulated and evaluated intragastric buoyant preparations of Cinnarizine. Buoyancy of the tablets was confirmed by Roentgenography using x-ray grade barium sulphate. The tablet remained buoyant in stomach for 3 hours, where as in vitro buoyancy was more than 5 hours. This could be due to the escape of carbon di oxide gas from the tablet.
M.M. Talukdar et al studied in vivo evaluation of xanthan gum as a potential excipient for oral controlled release matrix tablet formulation. Authors showed that the common pharmacokinetic parameters of the drug from XG matrices are statistically equal to those from a marketed controlled release product, indicating XG as a potential excipient for formulation of oral controlled release tablets17.

Z. Rahman et al designed and evaluated bilayer floating tablets of Captopril. Authors employed HPMC K15 M, HPMC K4 M, HPMC K100 M, PVP-K30 and Carbopol 934P as polymers, alone and in combination. Citric acid and sodium bicarbonate were used to impart floating ability to the formulation. The polymers retarded the drug release for 24 hours with a floating duration of 40 hours. During this time of floating, tablets maintained very good matrix integrity. In vivo (x ray) studies showed that tablet remained buoyant for 6 hours in abdomen18.

I.S. Ahmed et al studied bioavailability of Riboflavin from a gastric retention formulation. Authors found that the formulation released the drug in zero order fashion for 24 hours. The formulation remained buoyant for more than 9 hours. The bioavailability of riboflavin from a large size GRP was more than triple than measured after administration of an immediate release formulation. In vivo studies in dogs indicated that large size GRF stayed in stomach for about 15 hours19.

Z. Wei et al designed and evaluated two-layer floating tablet for gastric retention using Cisapride as model drug. One layer was floating layer consisting HPMC K100 M, NaHCO3 and starch-1500 and other layer was drug loading layer consisting HPMC K15 MCR as polymer. Tablet remained buoyant for 8 hours and retarded the drug release. Authors also studied effect of rpm on release of drug from tablet. Higher the rpm, greater was the drug release. Zero order drug release was obtained when compared with conventional slow release tablet20.

L. Whitehead et al developed floating dosage form and carried out in vitro study for buoyancy. Gamma-Scientigraphy was used to study in vivo buoyancy of beads. Sodium alginate was used to prepare beads. Freeze drying method was employed for the preparation of beads. Gamma-Scientigraphy studies showed that beads remained buoyant for 540 min. Presence of food did not affect the duration of gastro retention21.

H. Yieqiao et al developed floating matrix dosage form for Phenoporlamine hydrochloride using gas generating agent. Authors carried out in vitro and in vivo evaluation in healthy volunteers. Polymers employed were HPMC K4M and Carbopol 971P. The drug release mechanism was non-fickian diffusion. The tablets remained buoyant for more than 6 hours. In vivo experiments showed that keeping the amount of Carbopol 971P NF at a higher concentration effectively increased the relative bioavailability of drug22.

J. T. Fell et al explored the use of citric acid to prolong the in vivo gastro retention of a floating dosage in the fasted state. The results of the study revealed that prolonged gastric retention was achieved when the dosage form was administered with citric acid solution as compared to retention in the absence of citric acid. Citric acid has the potential to delay the gastric emptying of the calcium alginate beads when administered to the fasted volunteers23.

J. Kristl et al optimized and evaluated floating matrix tablets. HPMC K4 M was used as polymer. Pentoxyfilline was taken as model drug. The tablets containing gas generating agent floated for 24 hours where as tablets without gas generating agent did not float. Crushing force played crucial role in floating studies. The drug release mechanism was non fickian diffusion. In vivo experiments for determination of buoyancy were carried out in fasted state in beagle dogs. The gastric residence time for fasted tablets was 240 min24.
REFERENCES

OUTLINE OF THESIS

> Experimental part of the thesis is divided into four parts.

- Part I- Formulation, Optimization, Stability Studies of Regioselective Drug Delivery System of Lovastatin and Diltiazem HCl
- Part II- Formulation, Optimization, Stability Studies of Regioselective Drug Delivery System of Lovastatin and Atenolol
- Part III- Formulation, Optimization, Stability Studies of Regioselective Drug Delivery System of Lovastatin and Propranolol HCl
- Part IV- Analytical Profile Development.
  - Part IV A- Analytical Profile Development of Formulation Containing Lovastatin and Diltiazem HCl
  - Part IV B- Analytical Profile Development of Formulation Containing Lovastatin and Atenolol
  - Part IV A- Analytical Profile Development of Formulation Containing Lovastatin and Propranolol HCl

* Materials and Methods for Part I, Part II and Part III are explained initially under Materials and Methods heading.

* Results and Discussion is explained separately for Part I, Part II and Part III under Part I, Part II and Part III headings.