CHAPTER 2
REVIEW OF LITERATURE

2.1 LITERATURE REVIEW ON REPAGLINIDE

Megha Sharma et al., formulated floating microspheres for repaglinide by ESD (emulsion solvent diffusion) technique and studied the effect of independent variables on selected responses. Particle size of repaglinide microspheres was observed in the range of 181.1 µm and 248 µm. Formulation containing low viscosity (5 cps) HPMC shown maximum drug release of 83.20% in contrast HPMC (100 cps). In vivo studies affirms the buoyancy of optimized formulation [constituting EC: HPMC (5 cps) in the ratio of [1:2] for about 6 h [49].

Gujar et al., formulated mucoadhesive nanoparticles of repaglinide by utilising natural polymers like chitosan and sodium alginate (SA). Compatibility between drug and polymers was confirmed by FTIR and DSC studies. Concentrations of polymers were altered in order to achieve maximum entrapment efficacy (EE) with finest particle size. Optimised formulation revealed admirable mucoadhesive properties as noticeable from bioadhesive strength. Drug release was in controlled manner up to 12 h [50].

Wei He et al., developed repaglinide sustained release tablets by direct compression method to lengthen its therapeutic action. Sustained drug release profile was observed over 10 h and a diminished impact of medium pHs on drug release was confirmed. Furthermore optimised formulation was studied for hypoglycemic activity and pharmacokinetics in dogs. In conclusion, sustain release of repaglinide was seen with prepared formulations, which consequently provide a promising formulation for type II diabetic patients [51].

Vijayan et al., studied on biodegradable nanoparticles of repaglinide by solvent extraction technique by employing PLA and PCL. The particles were found to be spherical in shape with sizes of 108.6±3.4 nm to 220.6±1.2 nm and PDI was ranging in between 0.06 to 0.44. In addition, optimized nanoparticles were loaded in methocel transdermal patches. The in vitro release kinetics reveals that release was almost independent of drug concentration. Bioavailability parameters confirms that, transdermal patch containing nanoparticles shown 76 fold efficient than conventional oral formulation [52].
Patel et al., explored about buccal tablets of repaglinide using chitosan as a mucoadhesive polymer, HPMC K15M as a sustained release polymer and ethyl cellulose (EC) as an impermeable backing layer. Three factors at two different levels were studies to optimize the formulation. Formulation with chitosan and HPMC K 15 M in the proportion of 1:1 shown highest drug release. F2 batch was identified as optimum on basis of strong bioadhesive strength of 17.86 ±0.51 g and maximum similarity factor (64.43). Drug release from optimum batch followed non-Fickian diffusion mechanism. Stability study confirms that tablets were stable even at accelerated conditions [53].

Imran et al., designed repaglinide floating tablets to contemplate the impact of several natural polymers on gastric residence time and drug release rate. All the formulations were assessed for in vitro evaluation parameters. Hardness of all the prepared batches was found to be in range of 4.0-5.0 kg/cm². Among all these formulations F3 was selected as best formulation which has shown desired controlled release up to 5 h with minimum floating time of 79 sec [54].

Meina Liu et al., fabricated inclusion complex of repaglinide by lyophilization method. The prepared complexation was characterized by DSC, XRD, NMR spectroscopy and evaluated for drug release rate. All the characterization information affirmed the formation of RPG-HP-β-CD complex. The in vivo studies in beagle dogs by LC–MS/MS technique shown that C_max and AUC_0-t of RPG-HP-β-CD were 2.5 and 2 times eminent than physical mixture. These outcomes proposed that inclusion complex remarkably enhances bioavailability of repaglinide in contrast to physical mixture [55].

Dhana Lakshmi et al., attempted to prepare and characterize PMMA nanoparticles loaded with repaglinide. FTIR, DSC and TGA confirms the compatibility between drug and polymer. The particle size (PS) of best formulation was observed as 108.3 nm and shown desired in vitro drug release. Toxicity study in albino rats shown, there is no significant changes in pathological and biochemical examinations. Therefore, formulated system could probably beneficial in terms of extended release, shortened dose frequency and improved patient compliance [56].

Sunil K et al., aimed at assessing gastric residence and pharmacokinetic parameters of prepared floating microspheres. Best formulation (RgFMCS4) shown
desired floating and drug release characters. Stability test of 99mTc-labeled formulations were done by utilizing suitable buffer solutions of pH 2.0, 6.8 and 7.4. Labeling efficacy of microspheres with 99mTc was measured by organ distribution study in albino rats. Transit RgFMCS4 and RgNFM in GIT was monitored by gamma scintigraphy study. Microspheres with calcium silicate shown enhanced GRT up to 6 h. The relative bioavailability floating microspheres was increased about 3.17 times with reference to marketed conventional formulation [57].

Gajanan Shinde et al., optimized repaglinide nanocrystal formulations by high pressure homogenization. Optimization of polymer concentration, number of cycles and HPH pressure was done by using Taguchi design. Formulations were evaluated for mean PS, PDI (Polydispersity index), zeta potential and drug release. NC 3 formulation was identified as optimized formulation on basis of desired particle size (187 nm), zeta potential (-29.4 mV) and controlled drug release subsequently used for further studies. ANOVA study confirms the significant effect of selected variables on desired responses. Surface morphology study shown aggregation of nanocrystals of drug. Slight change in the crystallinity was observed in DSC thermogram of optimized formulation. Formulation was stable interms of particle size and zeta potential throughout the stability study period of 3 months [58].

2.2 LITERATURE REVIEW ON FLOATING DRUG DELIVERY SYSTEM

M V Srikanth et al., applied statistical design to explore the impact of formulation variables on buoyancy and drug release properties of formulated floating delivery system. Selected variables shown significant effect on selected responses, as evident form p value. Drug release from optimized formulation followed non-Fickian mechanism. In vivo buoyancy studies of optimized formulation in human volunteers confirms the enhancement in GRT in the fed than in fasted state [59].

Rajani Shakya et al., formulated hydrophilic matrix based gastro retentive drug delivery system by utilizing Box-Behnken statistical design with three factors at three different levels and total of fifteen experimental trials. Optimized formulation shown desired controlled in drug release for about 12 h and admirable buoyancy characters (floating lag time <1 min, floating duration >16 h). In vivo studies in twelve healthy human volunteers was performed. Observed pharmacokinetic parameters were compared with the marketed formulation (Zanocin OD) [60].
**B K Nanjwade et al.,** performed studies on effervescent technology based gastro retentive drug delivery system of poorly soluble drug, glipizide. Floating tablets were formulated by two different grades of HPMC (K15M, K100M) and carbopol 940P. Effervescent combination of anhydrous citric acid and sodium bicarbonate were added to facilitate the floating efficacy. F7 formulation shown drug release of 98.60% by the end of 24 h, whereas floating lag time was found to be 140 sec. Drug release followed non-Fickian mechanism [61].

**Lifang Yina et al.,** attempted to prepare and optimize floating tablets of to extend GRT an major absorption sites by using sodium bicarbonate and HPMC K100M. Prepared tablets were evaluated for floating lag time, total floating duration and drug release. Additionally, bioavailability studies were performed in beagle dogs in both fed and fasted state. Desired sustained release was observed from the floating tablets in both *in vitro* and *in vivo* conditions, with needed pharmacokinetic properties. [62].

**Peter Dio et al.,** investigated the effect L-HPC 11 (low substituted hydroxy propyl cellulose) and L-HPC B1 in enhancement of floating in gastro retentive tablets. Effect of variables were studied by using central composite design. Amount of L-HPC (X2) and sodium alginate (X1) were identified as numerical factors. Mixture of L-HPCs at 1:1 proportion was included as a categorical factor (X3). Paracetamol was used as model drug. Floating lag time, floating duration, *in vitro* drug release and swelling index were studied as responses. Less water uptake and floatability was observed with L-HPC 11 compared to L-HPC B1. Total floating duration was less with L-HPC 11 and L-HPC mixtures with 0.5% SA. Assessing drug release and swelling index shown the correlation, which will be helpful to understand the impact of L-HPCs in the designing of GRDDS [63].

**Liandong Hu et al.,** performed studies on sustained release formulations of dextromethorphan HBr (DMB-SR) tablets to extend the gastric residence time. Consequently, their pharmacokinetic behaviour was compared with conventional sustained release tablets. Floating tablets of DMB-SR were prepared using NaHCO₃ as effervescent agent, HPMC as hydrophilic gel material and hexadecanol as floating enhancer. Optimization of formulation was done by employing orthogonal experiment design. All the trail batches were evaluated for weight variation, friability, drug
content, floating behaviour, *in vitro* release and bioavailability studies. Optimized concentrations of HPMC K4M, sodium bicarbonate and hexadecanol were found to be 25 mg, 20 mg and 18 mg respectively. Floating lag time was less than 3 min and remain buoyant for more than 24 h. All the physical parameters were found to be within the limits. Drug release at the end of 12 h was about 85%. All these results rendered floating tablets as a feasible approach for the drugs which having narrow absorption window in upper region of GIT [64].

**Mina Ibrahim et al.,** attempted to develop controlled release system with desired swelling, floating and adhesive properties. Formulations were prepared by using different concentrations of HPMC K15M and/or SA as release-retarding polymer(s). Sodium bicarbonate (NaHCO₃) and calcium carbonate (CaCO₃) were used as effervescent agents. Swelling index, floating activity, adhesion period and *in vitro* drug release studies were performed in 0.1 N HCl (pH 1.2) buffer at 37 ± 0.5°C. Drug release from all the formulations followed non-Fickian mechanism. Formulation Optimized formulation shown admirable floating properties, prolonged adhesion times and sustained drug release. X-ray studies of best formulation (loaded with barium sulphate) in six healthy volunteers, revealed 5.50 ± 0.77 h as mean GRT [65].

**Saisivam et al.,** developed floating drug delivery system using different concentrations of HPMC-K4M and karaya gum. All the prepared batches were evaluated for pre compression, post compression, *in vitro* release parameter. *In vivo* X-ray studies were conducted in rabbits. All the formulations shown admirable drug release up to 16 h. Drug release from F9 (optimized formulation) followed non-Fickian mechanism. X-ray photograph of optimized formulation shown that, it was remain buoyant for more than 12 h in the stomach region of the rabbit. These results concluded that formulated drug delivery system enhanced the bioavailability of losartan potassium [66].

**Sasa Baumgartner et al.,** carried a research to develop floating tablets to extend the gastric residence time, thereby increasing bioavailability and lessen the side effects of some irritating drugs. The exploration shows that composition of formulation and hardness have furthermore effect on floating behaviour and *in vitro* drug release. Addition of gas-generating agent along with MCC, enhanced floating characters (floating lag time -30 s; floating duration - 8 h) along with drug content.
Drug release was sufficiently sustained for more than 8 h with non-Fickian mechanism. Radiographic studies confirms that prepared floating tablets remained buoyant without adhering to gastric mucosa for about 4 h [67].

2.3 LITERATURE REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM

V Senthil et al., planned to formulate and evaluate theophylline gastroretentive mucoadhesive tablets by direct compression method. Natural gums (locust bean gum, carrageenan gum), natural polymer (chitosan) and synthetic polymer (carbopol) were used at different concentrations alone/in combination to formulate gastro retentive tablets. Formulation with the locust bean gum and chitosan in the proportions of 4.5:3, demonstrated more prominent mucoadhesive strength, greater swelling index and desired drug release in contrast to other formulations with single gum and other gum combinations. Radiographic studies in rabbits shown that the tablets remain adhesive to gastric mucous membrane for about 10 h [68].

Sharad et al., fabricated furosemide loaded bi layer polymeric films made up of controlled (CR) and immediate release (IR) layers. These films were folded into empty hard gelatin capsule. Unfolding and swelling of the film causes for bioadhesion to the gastric mucosa. Incorporation of hydroxy propyl β-cyclodextrin in both CR, IR layers and Carbopols 971P NF in only CR layer, results for optimum drug release, desired bioadhesion and mechanical properties. The film to unfold and swell under acidic conditions and IR of the drug over 1 h and CR for about 12 h in acidic medium. DSC, XRD and SEM revealed uniform dispersion of furosemide in the formulated polymeric matrices. The outcomes indicates that the dosage form is gastro retentive and can control the release of medicament [69].

Anilkumar et al., studied the impact of HPMC K4M and sodium alginate concentrations on gastric residence and sustained behaviour of dosage form. Different proportions of HPMC K4M, Sodium alginate (1:1, 1:1.5, 1:2) and drug to Polymer ratio were used to prepare mucoadhesive tablets by direct compression. Among all formulations F 3 formulation shown highest mucoadhesive strength of 26.35 ± 1.15 mg. Gastric residence time and drug content was found to be > 7.5 h, and 98.75 ± 0.05 % correspondingly. Drug release at the end of 12 h was observe as 75.71%. Drug
release from best formulation followed super case II transport and fits well for zero order kinetics [70].

Mayur Chordiya et al., developed propafenone HCl gastroretentive system with mucoadhesive properties. Different grades of HPMC (E5, K100M) were used as controlled release polymers and sodium CMC as a mucoadhesive polymer. All the evaluated parameters for prepared tablets, were found to be within satisfactory limits. Mucoadhesive strength, shown greater detachment force up to 12 h. M11 formulation posses good dimensional stability, highest mucoadhesion and controlled drug release even up to the end of 12 h in comparison to other formulations [71].

Hitendra S Mahajan et al., attempted to improve bioadhesive strength of xyloglucan (XG) by thiolation. Thiolated xyloglucan (TXG) was synthesised by esterification of xyloglucan with TGA (thioglycolic acid). TXG was characterized by DSC and XRD analysis. Mucoadhesive property of TXG and XG was compared by formulating ondansetron in situ gel system, using sheep nasal mucosa. This evaluation revealed superior bioadhesion time of TXG in contrast to XG. This can be credited to the formation of strong disulfide bonds between mucus and TXG. Improved drug permeation was observed for TXG while conducting ex vivo permeation study in sheep nasal mucosa. In conclusion, TXG results in enhanced bioadhesion and drug permeation but doesn't shown any impact on resultant properties of gel [72].

Rimple Sharma et al., tried to enhance the mucoadhesive strength of pectin by thiolation with TGA. Characterization of TP (Thiolated pectin) was done by FTIR, XRD, DSC and SEM. Relative assessment of mucoadhesive property pectin and TP was done by formulating metformin-loaded gelled beads by ionotropic method. Wash off test using goat gastric mucosa confirms the higher bioadhesion time of TP in comparison to unmodified pectin. Comparable drug release profile was noticed from both pectin and TP formulated beads in phosphate buffer (pH 6.8) [73].

Shikha Yadav et al., synthesized gellan–thioglycollic acid conjugate, with the goal to enhance mucoadhesive potential. Thiolation was affirmed by thiol stretch in the FTIR spectra at 2571 cm⁻¹. Quantification of thiol groups by Ellman's method reports 13.92 mM of thiol groups/g of the conjugate were present. As a result of thiolation, slight increase in the crystallinity and decreased sensitivity to Ca²⁺ induced gelation was observed. Mucoadhesion strength of metronidazole gels formulated by
using gellan TGA was increased by 1.82 folds than gellan gum contained formulations. Drug release from gels contained gellan and gellan TGA followed first order and Higuchi's kinetics respectively [74].

Harmanmeet Kaur et al., synthesized thiolated tamarind seed mucilage (TSP) by esterification of tamarind seed mucilage (TSP) with thioglycolic acid. Thiolation was confirmed by -SH stretch in FTIR spectra at 2586 cm\(^{-1}\). DSC and XRD studies indicates increase in the crystallinity. Polymer compacts made-up of thiolated TSP shown higher mucoadesion strength by 6.85 folds than that of TSP. Gels formulated with TSP released drug by following first-order kinetics with Fickian diffusion mechanism, whereas drug release from thiolated TSP followed Higuchi’s square root release kinetics with Fickian diffusion mechanism [75].

### 2.4 LITERATURE REVIEW ON OKRA GUM

Gurpreet Kaur et al., examined mucoadhesive potential of okra polymer (OP). Mucoadhesive films were prepared by solvent casting method using three different concentrations of OP (2.0%, 2.5%, 3.0% w/v) and glycerol (0.25%, 0.50%, 0.75% v/v). On basis of desired mechanical characters formulation (containing 3% OP and 0.5% glycerol) was identified optimum. Subsequently, optimized formulation was loaded with zolmitriptan and evaluated for different in vitro evaluation parameters. In vitro and ex vivo drug release studies confirms the controlled release of zolmitriptan up to 8 h in salivary fluid. Thus, OP can be used as a promising polymer in designing of CDDS [76].

Priyanka Sinha et al., used extracted okra gum (OG) as a control release polymer along with SA to formulate glibenclamide beads for oral route. FTIR studies confirms the compatability between drug and polymers. Prepared beads shown EE and particle size in the range of 64.19 ± 2.02 to 91.86 ± 3.24% and 1.12 ± 0.11 to 1.28 ± 0.15 mm correspondingly. Drug release was sustained over an extended period of 8 h and fits well for zero order kinetics [77].

ND Zaharuddin et al., formulated propranolol hydrochloride tablets to compare the binder efficacy of okra gum with HPMC and SA. Formulations were evaluated for all in vitro parameters. Formulations contained okra gum were shown highest mechanical strength and prolonged drug release (for about 24 h) in
comparison to other formulations. As a result, okra gum was affirmed as an effective binder to formulate the tablets with good tensile and crushing strength [78].

Newton et al., used different natural polymers such a tamarind gum, okra gum and chitosan to develop colon targeted chronotherapeutic to treat early morning signs in blood pressure. Direct compression technique was used to prepare the tablets and evaluated for different in vitro parameters. Drug release and physicochemical characters were modified by using carbopol 940. Drug release studies were initialy performed in 0.1 N HCl for about 1.5 h, followed by phosphate buffer of pH 6.8 (for 2 h) and pH 7.4 phosphate buffer till maximum release of propanolol. Tamarind gum contained formulations shown an admirable compression parameters along with desirable drug release in comparison to other polymer based formulations [79].

Uzma Farooq et al., developed controlled multi-particulate drug delivery system by using okra mucilage. Microspheres were prepared by using different concentrated solutions of okra mucilage and SA. Formulated microspheres demonstrated maximum swelling characteristics in intestinal fluid. Rate and extent of drug release was decreased significantly with increase of concentration of polymers and crosslinking agent (Calcium chloride). Prolonged drug release was observed even after 6 h with F-6 formulation [80].

Patel VI et al., searched for cost-effective and proficient natural excipient that can be used as a feasible choice for the formulation of pharmaceutical dosage forms. Okra mucilage was extracted from fresh fruits of Abelmoschus esculentus and subjected to various preformulation studies for assessment of safety and appropriateness for its use as a binder. Different concentrations (1-5% w/v) of okra mucilage were employed to prepare the tablets. The properties of tablets in terms of hardness, uniformity of weight, friability and disintegration time were evaluated as per USP. Studies concludes that depending on its binding capability and stability of formulations, okra mucilage can be used as a binder at 4-5 % w/v [81].

Kalu et al., revealed utilization of plant gum in the preparation of paracetamol controlled release drug delivery system in comparison with sodium carboxymethyl cellulose (NaCMC) and HPMC. Prepared tablets were assessed for drug release in stimulated gastric fluid. Kinetics attained from dissolution data shown controlled release of paracetamol even at the end of 6 h and followed zero order kinetics [82].
Kotadiya et al., fabricated coated tablets of diclofenac by $3^2$ full factorial design. Concentration of okra gum and guar gum were selected as independent variables. Formulations were evaluated for various in vitro parameters and in vivo pharmacokinetic study. Formulation consisting of okra gum and guar gum was most expected to give colonic delivery. Enhanced pharmacokinetic profile was observed in rabbits, in contrast to marketed formulation of diclofenac [83].

Edukondalu et al., reported on optimization of okra gum and HPMC K 100 M as retarding agents in the preparation of gastro retentive tablets of atenolol to prolong the gastric residence time. Sodium bicarbonate was used as a gas generating agent. The prepared atenolol tablets were evaluated for physicochemical parameters and found to be within acceptable range. The concentration of okra gum with a gas generating agent was optimized. The optimized formulation has better release rate [84].