2. LITERATURE SURVEY:

There has been an increased interest in recent years in the development and marketing of prolonged action or controlled release dosage forms. Pharmaceutical research in this regard has progressed by providing various novel alternatives to the conventional dosage system. Simultaneously new polymers and other materials have been introduced which are constantly upgrading the drug delivery system to impart its benefits to patients. Also, there has been exponential growth in the investigations related to the use of different pharmaceutical technology for oral drug delivery system as controlled drug delivery matrices because of possessing several attractive features such as reduction in dose frequency, patient compliance, ease of preparation and economy.

Extensive research is directed towards achievement of prolonged action drug forms due to better understanding of the mechanism of drug absorption.

Gastro retentive drug delivery system (GRDD) is one such system which is a promising approach for oral controlled drug delivery which allows the drug to be retained in the stomach and release it in more reproducible and predictable manner. Various types of drugs with absorption window in stomach and small intestine have been evaluated in developing such delivery system. The use of gastro retentive drug delivery system for various diseases for drug delivery is a part of ever growing research. With the recent scientific and technological advancements research has progressed and developed in the rate controlled oral drug delivery systems by overcoming physiological adversities such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT including floating drug delivery systems (FDDS), also known as hydro-dynamically balanced systems (HBS), swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices.

In order to develop an effective, modified release drug delivery system with prolonged residence time in stomach and which can act locally in stomach, has an absorption window in stomach and upper small intestine and has low solubility at higher pH values,
with reduced frequency of administration and which can improve patient compliance; the literature available was studied and reviewed in 3 categories as:

Category I: Research papers and Review articles on GRDD systems and formulations of GRDD using various polymers.

Category II: Research articles on *In-vitro* and *In vivo* study.

Category III: Articles published on work done on Drug Mosapride.

### 2.1 Category I: Research papers and review articles on GRDD systems and formulations of GRDD using various polymers:

- **Sunil Kumar et al** reviewed the features and facts of gastro retentive drug delivery system. They compiled the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, they summarized important factors controlling gastric retention. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus gastro retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage forms can be achieved by the mechanisms of floatation, muco-adhesion, sedimentation, expansion or by modified shaped systems.

- **Garima Chawla et al** studied the control of gastrointestinal transit of orally administered dosage forms using gastro retentive drug delivery systems which can improve the bioavailability of drugs that exhibit site specific absorption. Prolonged gastric retention can be achieved by using floating, swelling, bio-adhesive or high density systems. The article reviewed the concept of the absorption window and described the performance evaluation of GRDDS, including *in-vitro-In vivo* correlation studies and potential use.

- **Parakh S.R. et al** studied and reported a novel method for study of water absorption rates by swellable matrices. Swellable matrices represent the most popular oral drug
delivery system that has temporal control of the drug release. The rate at which water is absorbed by the system decides the pattern of drug release, therefore, the study of water absorption kinetics, play a vital role in predicting and explaining the drug release pattern. The authors developed a novel method to study the water absorption rate. The method allowed for the study of accurate actual water content determination. The results obtained in the study showed a good correlation with swelling behavior of the matrices. The authors observed that the rate of water absorption depends on ratio of polymer: hydrophilic excipient and polymer viscosity. 

✓ **Dave Brijesh S. et al** studied the formulation and *In-vitro* evaluation of gastro retentive drug delivery system of Ranitidine Hydrochloride. They used guargum, xanthanum gum and Hydroxypropyl methyl cellulose and evaluated them for gel forming properties. Sodiumbicarbonate was used as gas generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. Addition of stearic acid reduced the drug dissolution due to its hydrophobic nature. A $3^2$ full factorial design was applied to systemically optimize the drug release profile. The result of the full factorial design indicated that a low amount of citric acid and high amount of stearic acid favours sustained release of Ranitidine Hydrochloride from a gastro retentive formulation. Similarity factor was applied between the factorial design and theoretical dissolution profile. No significant difference was observed between the desired release profile and factorial designed batches indicating that proper balance between release enhancer and release rate retardant can produce drug dissolution profile similar to a theoretical dissolution profile. 

✓ **Klausner Eytan A. et al** gave a review of expandable gastro retentive dosage forms. These expandable gastro retentive dosage forms were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDF are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention. After drug release their dimensions are minimized with subsequent evacuation from the stomach. Gastro retention is enhanced by the combination of substantial dimensions with high rigidity of dosage form to withstand the peristalsis
and mechanical contractility of the stomach. Narrow absorption window drugs compounded in such systems have improved *In vivo* absorption properties. The expandable GRDF\(^5\) reported in the article describes the physiological basis of their design. Dog was used as preclinical model prior to human studies, relevant imaging techniques and pharmacokinetic and pharmacodynamic aspects of such delivery systems were also studied by the authors\(^5\).

✔ **Arora Shweta et al** gave the review of floating drug delivery systems. They combined the recent literature then available with special focus on the principal mechanism of floatation to achieve gastric retention. The physiological and formulation variables affecting gastric retention, approaches to design single unit and multiple unit floating systems, their classification and formulation aspects were covered in detail. They also summarized the in vitro techniques, *In vivo* studies to evaluate the performance and application of these floating systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form as reported by them\(^6\).

✔ **Afargan Michel et al** reviewed the controlled release gastric retention and reasons for formulating GRDD preparation explaining the importance of GI absorption for oral drugs, the effect of fasted and fed states and care to be taken while designing GRDD formulation, the various gastric retention systems and clinical trials with the accordion like expandable dosage form. Finally they concluded the drugs that would benefit from gastric retention\(^7\).

✔ **Davis Stanley S.** reviewed the formulation strategies for absorption windows. Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of control release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are discussed in this review. Two main approaches are presently being explored i) Bio-adhesive microspheres that have slow intestinal transit and the gastro retentive dosage systems which is based on multi particulates or large single unit systems.

He concluded that the transit of a drug formulation through the GI tract will determine how long a compound will be in contact with its preferred absorption site.
A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of drug delivery systems that will have clinical benefit\(^8\).

- **Gambhire M. et al** developed floating drug delivery system of Diltiazem hydrochloride using Methocel K100M and Compitrol 888 ATO as rate retardant polymers. Floating matrix tablet of Diltiazem hydrochloride was prepared by direct compression method. The effect of tablet hardness on release profile was also studied. Sodium bicarbonate was used as gas generating agent. The study showed the effect of excipient on release profile of drug and use of floating controlled drug delivery\(^9\).

- **Kristl J. et al** developed floating matrix tablet of pentoxyfilline to increase its bioavailability and diminish the side effects. The importance of the composition optimization; the technological process development for the preparation of the floating tablets with high dose of freely soluble drug and characterization of tablet properties such as crushing force, floating properties, *in-vitro* and *in vivo* drug release was examined. The investigation shows that tablet composition and mechanical strength have great influence on the floating properties and drug release\(^10\).

- **Patel G. et al** prepared gastro retentive drug delivery system using HPMC K4M and Carbopol 934P. Floating tablets of Glipizide was prepared by direct compression method. A \(3^2\) full factorial design was applied to systemically optimize the drug release profile. The HPMC K4M and Carbopol 934P were evaluated for gel forming properties\(^11\).

- **Oth M. et al** developed bilayer floating dosage unit to achieve local delivery of Misoprostol. The system was capsule consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content and drug layer formulated to act as a sustained delivery system. The differential design of the two layers allows the optimization of both floating capability and drug release profile\(^12\).

- **Yiqiao H. et al** developed floating matrix dosage form for Phenoporlamine hydrochloride based on gas forming agent and its *in-vitro* and *In vivo* evaluation in healthy volunteers. Three floating matrix formulations of Phenoporlamine hydrochloride based on gas forming agent were prepared. Hydroxy propylmethylcellulose K4M and Carbopol 971P NF were used in formulating the
hydrogel drug delivery system. The dissolution profiles of all tablets showed Non-Fickian diffusion in simulated gastric fluid. Data obtained in-vivo studies demonstrated that the floating matrix tablet containing more Carbopol was capable of sustained delivery of the drug for longer periods with increased bioavailability.

✓ **Bodmeier R. et al** prepared floating matrix tablet based on low density foam powder and studied the effect of formulation and processing parameters on drug release. The highly porous foam powder provided low density and an excellent in-vitro floating behavior of the tablets. Different types of matrix forming polymers were studied. The release rate could effectively be modified by varying the matrix forming polymer/foam powder ratio, the initial drug loading, the tablet geometry (radius and height), the type of matrix forming polymer, the use of polymer blends and the addition of water-soluble or water-insoluble fillers such as lactose or microcrystalline cellulose. The floating behaviour of the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns.

✓ **Chueh H. et al** developed a novel extended release Sotalol hydrochloride tablet formulation which possesses a unique combination of flotation and bio-adhesion for prolonged residence in the stomach. Tablets were produced by direct compression. A two factorial, central, composite Box-Wilson experimental design was employed to develop and optimize the tablet formulation containing 240mg Sotalol hydrochloride. The ratio of two major bioadhesive agents, sodium carboxymethylcellulose (NaCMC) to hydroxypropylmethylcellulose (HPMC), and the ratio of two direct compressible diluents, ethylcellulose (EC) to cross povidone, were used as formulation variables (independent variables) for optimizing tablets response parameters, such as dissolution bio-adhesive capability, tablet density and required compression force. An optimum direct compression, bio-adhesive and floating tablet formulation of Sotalol hydrochloride was achieved by considering the dissolution characteristic as primary objective and using required compression force, bio-adhesive capability as constraints within the experimental region.

✓ **Mamoru F. Et al** studied to investigate the influence of sodium bicarbonate on the physicochemical properties of controlled release hot melt extruded (HME) tablets containing Eudragit RS PO and/or Eudragit E PO. Acetohydroxamic acid and
2. Literature Survey

Chlorpheniramine Maleate were used as model drugs. Sodium bicarbonate was incorporated into the tablet formulations and the drug release properties and buoyancy in media for HME tablets and directly compressed (DC) tablets were investigated. The HME tablets prepared from the powder blend containing both Eudragit\textsuperscript{R} RS PO and sodium bicarbonate exhibited sustained release properties and the tablets floated on the surface of the media for 24hrs\textsuperscript{16}.

✓ **Ali J. et al** developed a hydro dynamically balanced system of Metformin as a single unit floating capsule. Various grades of low density polymers were used for the formulation of this system. They were prepared by physical blending of Metformin and the polymers in varying ratios. The formulation was optimized on the basis of *in-vitro* buoyancy and *in-vitro* release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0). Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethylcellulose gave the best *in-vitro* percentage release and was taken as the optimized formulation. *In-vivo* studies were carried out in rabbits to assess the buoyancy, as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy\textsuperscript{17}.

✓ **Zhang J. et al** developed floating tablets of Captopril using HPMC K4M and K15M and Carbopol934P. Study was concluded that buoyancy of tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet\textsuperscript{18}.

✓ **Atyabi F. et al** developed a floating system which consisted ion exchange resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome rapid loss of carbon dioxide. Upon coming in contact with gastric content exchange of chloride and bicarbonate took place, resulted in release of carbon dioxide thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads\textsuperscript{19}.

✓ **Joseph N. et al** developed floating, hollow polycarbonate microspheres of piroxicam by solvent evaporation technique. Encapsulation efficiency of \~95\% was achieved. It was capable of sustained delivery of the drug over a prolonged period\textsuperscript{20}.
Whitehead L. et al prepared multi unit dosage form by dropping a sodium alginate solution into aqueous calcium solution. After internal gelation was complete, beads were separated and freeze dried. The results of these beads maintained a positive force for over 12hrs\textsuperscript{21}.

Kawashima Y. et al prepared multiple unit hollow microspheres by emulsion solvent diffusion technique. Drug and acrylic polymer were dissolved in an ethanol-dichloromethane mixture and poured into aqueous solution of PVA with stirring to form emulsion droplet. The latter gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microspheres of the polymer with the drug. In vitro polymer floated for 12hrs. In aqueous media and radio-graphical studies provided that it remains in upper part of stomach for 3hrs\textsuperscript{22}.

El-Kamel et al designed sustained release system for Ketoprofen to increase its residence time in the stomach without contact with the mucosa, which was achieved through the preparation of floating micro-particles by the emulsion solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating micro-particles. The results indicated that drug retained in the floating micro-particles decreased with increase in ERL content\textsuperscript{23}.

Patel V. et al developed intra-gastric drug delivery system for Cefuroxime Axetil. A full factorial design was employed to evaluate contribution of HPMC-K4M / HPMC-K100LV ratio (polymer blend) and sodium lauryl sulfate (SLS) on drug release from HPMC matrices. Multiple regression analysis was performed for factorial design batches to evaluate the response. The study concluded that all formulations had floating lag times below 2 minutes and constantly floated on dissolution medium for more than 8hrs\textsuperscript{24}.

Narendra C. et al developed and optimized gastric floating drug delivery system containing Metoprolol tartarate as a model drug by the optimization technique. A factorial design was employed in formulation with total polymer drug ratio, polymer-polymer ratio, and different viscosity grades of hydroxypropyl methylcellulose (HPMC) as independent variables. Four dependent variables considered were percentage of drug release at 8 hrs. t\textsubscript{50}%, diffusion coefficient, and floating time. The
main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that polymer-drug ratio and polymer-polymer ratio significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was not significant. 

**Shimpi S. et al** explored the application of Gelucire 43/01 for the design of multiunit floating systems of a highly water soluble drug Diltiazem HCL. Diltiazem hydrochloride Gelucire 43/01 granules were prepared by melt granulation technique. The granules were evaluated for *in vitro* and *In vivo* floating ability, surface topography, and *in vitro* drug release. The results suggest that granules were retained in stomach at least for 6hrs. approximately 65% to 80% of drug was released over 6hrs. with initial fast release from the surface.

**US Patent No. 4814179** describes the floating sustained release therapeutic compositions. Non compressed sustained release floating tablets comprising of hydrocolloid gelling agent, therapeutically acceptable inert oil, the selected therapeutic agent and water was described. Non compressed tablet with sufficient mechanical strength with bulk density less than1 was prepared which were capable to float on the gastric fluid and deliver the therapeutic agent over extended period of time.

**US Patent No. 5443843** describes gastric retention system for controlled drug release. This gastric retentive system consists of a non continuous compressible element and an attached controlled release device and which in expanded form resists gastrointestinal transit; and a modular system for use there in comprising a non continuous compressible element and an attached receptacle means for receiving and holding a drug containing orally administrable controlled release device and which in the expanded form resists gastric transit.

**US Patent No. 20033064101A** explains the floating osmotic device for controlled release of drug. This invention provides a novel floating osmotic device that is capable of delivering a first active agent in an outer coat immediately followed by continuous controlled delivery of second active agent from the osmotic core while the dosage form floats in the fluid environment. Controlled delivery of drugs over extended period of time can be achieved using these floating osmotic devices.
US Patent no. 2003021845A12 disclosed pharmaceutical gastro retentive drug delivery systems for the controlled release of an active agent in G.I. tract which comprises of a single or multiple layered matrix containing hydrophilic, enteric or hydrophobic and/or mixture thereof. The polymer used was both degradable and non degradable type consisting of drug where the matrix was retained in the stomach for 3-24hrs\textsuperscript{30}.

2.2 Category II: Research Articles on \textit{In vitro} and \textit{In vivo} study

Chavan Patil Mahesh et al reported the development of sustained release gastro retentive drug delivery system for Ofloxacin and its \textit{In vitro} and \textit{In vivo} evaluation. A new strategy was proposed for the development of gastro retentive dosage forms for Ofloxacin preferably once daily. The design was based on sustained release formulation with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as Psyllium husk, HPMC K100M, Cross povidone and its combinations were tried in order to get the desired sustained release profile over a period of 24hrs. Various formulations were evaluated for buoyancy lag time, duration of buoyancy dimensional stability, drug content and \textit{In vitro} drug release profile. The dimensional stability of the formulation increased with the increasing psyllium husk concentration. In vitro drug release rate increased with increasing amount of cross povidone due to increased water uptake and increased driving force for drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. \textit{In vivo} studies were carried out for optimized formulation in 24 healthy human volunteers and pharmacokinetic parameters of developed formulations were compared with the marketed, once daily (Zanocin) formulation. The \textit{In-vivo} performance in parallel study design in healthy subjects showed promise to be bioequivalent to the marketed product (Zanocin). The \% relative bioavailability of developed formulation was found to be 97.55\textsuperscript{31}.

Dorkoosh F.A. et al reported the feasibility study on the retention of super-porous hydro-gel composite polymer in the intestinal tract of man using scintigraphy. Many complex oral drug delivery systems have been developed using various polymers in
order to achieve better drug targeting and drug absorption in the intestinal tract. Super-porous hydro-gel and SPH composite (SPHC) based drug delivery systems were developed for the targeted delivery of peptide drugs into the intestinal tract. The authors studied the retention time of SPHC polymers in man using the scintigraphy technique. The SPHC polymers were radio-labeled with TC-99m and administered orally in an enteric coated gelatin capsule. The location of the radio-labeled polymer was monitored in five healthy volunteers while the subjects were sitting in front of a large field of view of gamma camera. They found that the enteric coated capsules remained in the stomach for 75 to 50 minutes after oral administration to fasted volunteers and that the SPHC polymers thereafter attached to the upper part of the small intestine for at least 45 to 60 minutes due to their mechanical fixation properties. No discomfort was observed indicating that the polymers are safe for oral administration.

✓ **Sakkinen Mia et al** carried out *In vivo* studies in human volunteers to evaluate the microcrystalline (Mcch) chitosan granules for gastro retentive drug delivery of Furosemide which is site specifically absorbed from the upper G.I tract. The rate of release of Furosemide *in-vitro* could be prolonged by increasing molecular weight or amount of Mcch in the granules and also by addition of acidic excipients to the formulations. No marked changes in the *In vivo* absorption rate were noted but the amount of Furosemide absorbed decreased as the *in vitro* release rate decreased. It was found that the gastric retention time of the granules is too short in relation to the release rate and a large amount of drug passes its ‘absorption window’ before being released. The *In vivo* study produced no evidence that the chitosan formulations studied can be used as muco-adhesive gastro retentive drug delivery systems. The results of *In vitro* muco-adhesion studies did not predict the results of *In vivo* studies.

✓ **Beattie D.T. et al** studied the *In vivo* gastrointestinal activity of TD-5108, a selective 5-HT4 receptor with high intrinsic activity and compared to that of clinically studied gastrointestinal pro-kinetic agents Tegaserod, Cisapride and Mosapride. They evaluated the activity of TD-5108 in guinea pig colonic transit, rat oesophageal relaxation and dog gastrointestinal smooth muscle contractility models. The
subcutaneous administration increased guinea pig colonic transit (rank order of potencies: TD-5108>Tegasorod>Cisapride>Mosapride). Following intravenous and intra-duodenal dosing, TD-5108, Tegasorod, Cisapride and Mosapride produced dose dependent relaxation of the rat esophagus. Orally dosed TD-5108 increased the contractility of the canine antrum, duodenum & jejunum with higher potency than Tegasorod. The selective 5HT4 receptor agonist, TD-5108, demonstrates robust *In vivo* activity in the guinea pig, rat and dog gastrointestinal tracts.\(^{34}\)

✓ **Wang Jian et al** reported the evaluation of gastric muco-adhesive properties of animated gelatin microspheres both *in vitro* and *in vivo*. The interactions of gelatin and microspheres with two kinds of commercial mucin were estimated in aqueous media. The various *in vitro* and *In vivo* results indicated that animated gelatin microspheres demonstrated higher gastric muco-adhesive ability than gelatin microspheres. The higher amino group content improved chain flexibility and favorable polymer conformation were suggested to be main factors that contributed to the stronger muco-adhesive properties of animated gelatin microspheres than that of gelatin microspheres.\(^{35}\)

✓ **Jain Sunil K. et al** prepared floating microspheres of calcium silicate as porous carrier; Orlistat, an oral anti obesity agent and Eudragit S as polymer, by solvent evaporation method and evaluated their gastro retentive and controlled release properties. Effect of various formulations and process variables on particle morphology, micromeritic properties, *in vitro* floating behavior, percentage drug entrapment and *in vitro* drug release was studied. The gamma scintigraphy of the optimized formulation was performed in albino rabbits to monitor the transit of floating microspheres in gastrointestinal tract. The Orlistat loaded optimized formulation was orally administered to albino rabbits and blood samples collected were used to determine pharmacokinetic parameters of orlistat from floating microspheres. The microspheres were found to be regular in shape and highly porous. Microspheres containing calcium silicate showed best floating ability in simulated gastric fluid compared to other formulations. Release patterns from all floating microspheres followed Higuchi matrix model and Peppas Korsmayer model.
Prolonged gastric residence time of over 6hrs. was achieved in all rabbits for calcium silicate based floating microspheres of orlistat

2.3 Category III: Research Articles Published on Drug Mosapride

✓ Hegazy Maha A. et al developed a simple; sensitive, selective, precise and stability indicating thin layer chromatography and high performance liquid chromatography methods for determination of Mosapride and Pantoprazole in pharmaceutical tablets with its validation. Aluminium TLC plates coated with silica Gel 60F254 as stationary phase and ethylacetate/methanol/toluene (4:1:2, v/v/v) as mobile phase to give compact spots for Mosapride ($R_f$ 0.73) and Pantaprazole ($R_f$ 0.45) separated from their degradation products and chromatogram scanned at 276nm. In HPLC C18 column and mobile phase of acetonitrile/methanol/20mH ammonium acetate (4:2:4, v/v/v) at a flow rate of 1.0ml min$^{-1}$ for separation of Mosapride ($t_R$ 11.4) and Pantoprazole ($t_R$ 4.4) from their degradation products, quantification being achieved with UV at 280nm. Same HPLC method was used successfully for analyzing human plasma samples. Mosapride and Pantaprazole were exposed to acid hydrolysis and then analysed and the techniques employed as stability indicating method to analyse pharmaceutical formulations without interference from excipients.

✓ Sakshita M. et al reported the pharmacokinetics and bioavailability of Mosapride citrate dihydrate, the gastro-kinetic agent studies being done in dogs and monkeys after I.V. and oral administration. After I.V. administration the mean plasma levels of Mosapride in male dogs and monkeys showed biphasic decrease with $t_{1/2}$ alpha of 0.3 and 0.6hrs. and $t_{1/2}$ beta of 2.4 & 2.4hrs. Mean concentration of mosapride increased and reached maximum 0.5-1hr. after oral administration to male dogs and monkeys, followed by quick decrease with $t_{1/2}$ of 1.5 & 0.9hrs. The Cmax was 207ng/ml in dogs and 862ng/ml in monkeys. Pharmacokinetic parameters of Mosapride in female dogs and monkeys were similar to those in males indicating no sex related differences in pharmacokinetics of Mosapride. Oral bioavailability was 8% of the dose in dogs and 14% in monkeys suggesting the extensive first pass metabolism of Mosapride.

✓ Hiroaki Kusunoki et al studied and clarified the effect of Mosapride citrate on proximal gastric accommodation and gastro-duodenal motility in healthy volunteers
using ultrasonography. 14 healthy volunteers were treated for 14 days with Mosapride citrate (15mg b.d.) or a placebo with double blind randomized fashion. Before and after drug treatment ultrasonographic assessment of gastro-duodenal motility was performed. The study showed that Mosapride citrate enhances the meal induced gastric accommodation reflex and promotes adequate gastro-duodenal coordination and motility in healthy volunteers\textsuperscript{39}.

\begin{itemize}
  \item Ueno N. et al investigated the potential role of Mosapride, a 5HT-4 receptor agonist in glycaemic control in Type II diabetic melitus patients without autonomic neuropathy. They interpreted that Mosapride could improve insulin action at muscle and glycaemic control in Type II diabetic patients\textsuperscript{40}.
  
  \item Hiroshi Iida et al studied the early effects of oral administration of lafutidine with Mosapride compared with lafutidine alone on intra-gastric pH values. They concluded that in H.Pylori negative, healthy male subjects, an oral dose of lafutidine 10mg with Mosapride 5mg more rapidly increased intragastric pH than lafutidine 10mg alone\textsuperscript{41}.
  
  \item Jorn Lotsch et al studied the pharmacodynamics and drug action of Mosapride. Experiments were carried out in rats and serotonin 4 receptor agonists (5HT-4) have been proposed as a novel therapeutic strategy for the selective treatment of respiratory depression caused by opioids while leaving analgesic effects unaffected. They concluded that with Mosapride, opioid induced respiratory depression cannot be prevented and because 5-HT4 agonists are not currently available for clinical use, a cure for opioid induced respiratory depression as promised by the previous successful experiments in laboratory animals is not yet available in clinical practice\textsuperscript{42}.
  
  \item Kenji Koshino et al studied whether Mosapride, a pro-kinetic agent stimulates esophageal functions and prevents acidic and non-acidic gastro esophageal reflux. The study was done using normal volunteers in whom salivary secretion, esophageal peristaltic contractions and resting lower esophageal sphincter pressure with and without Mosapride administration were recorded using a crossover protocol. Postprandial acidic and non-acidic reflux levels were also recorded. They found that Mosapride at a standard dose of 15mg/day did not stimulate salivary secretion or any esophageal motor function. It also failed to prevent acidic and non-acidic postprandial gastro esophageal reflux\textsuperscript{43}.
\end{itemize}
Bhan C.S. et al gave a short review on Mosapride, a pro-kinetic agent, a drug which enhances gastrointestinal motility by stimulating the frequency of peristalsis or contractions in the small intestine and reported that this rhythm is not disturbed at all. Abdominal discomfort, constipation, heartburn, nausea, vomiting, bloating and other gastrointestinal symptoms are relieved by these agents. Pro-kinetic agents also help in relieving motility disorders. The review included Introduction, Classification, Mechanism of action of pro-kinetic agents, brief description about other pro-kinetic agents, pharmacokinetic values of Mosapride, advantages and current status of Mosapride.

Seiji Futagami et al reported the pro-kinetic effect of Mosapride citrate combined with Omeprazole therapy which improved the clinical symptoms and gastric emptying in PPI resistant NERD patients (non erosive reflux disease) with delayed gastric emptying. It was found after study that administration of Mosapride citrate in addition to Omeprazole improved gastro esophageal reflux and gastric emptying in PPI resistant NERD patients with delayed gastric emptying.

Chen C.L. et al studied the effect of Mosapride on esophageal secondary peristalsis in humans. Secondary peristalsis is important for the clearance of refluxate or retained food bolus from the esophagus and Mosapride enhances sensitivity to distention induced secondary peristalsis and facilitates secondary peristaltic contractility. The data found provided an evidence for modulation of esophageal secondary peristalsis by the 5HT-4 agonist Mosapride, as well as support for its clinical utility.

Kazuhiro Narita et al assessed the effect of Mosapride on post operative ileus following colon surgery since Mosapride citrate is known to promote gastric emptying and large intestine motility. After doing the trials with patients, with and without Mosapride, they concluded that gastric emptying was improved by Mosapride. Their results suggested that the period of post operative ileus following hand assisted laparoscopic colectomy can be shortened by treatment with Mosapride and that no adverse effects were observed with Mosapride.
2. Literature Survey

2.4 References:


2. Literature Survey


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2. Literature Survey


