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Gastroprotective System

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CHAPTER 1
INTRODUCTION

Gastroprotective system for the supply of drugs is an approach to extend gastric residences and thereby aims to release locally or systemically specified drugs in the upper gastrointestinal tract (GIT). The gastric dosage formulations proceed for a longer time in the gastric area and thus extend the gastric preservation period for medicinal products considerably. (Nayak *et al.,* 2010).

For those that operate locally in the stomach, such as misoprostol, anti acids etc, the gastric drug delivery system is required. Medicines with a small window in GIT for example for medicinal products that are unbalanced in the colon or digestive organs, for example L-DOPA, para aminobenzoic acid, captopril, ranitidine HCl, metronidazole, furosemide, riboflavin, etc. (Nayak *et al.,* 2010).

It is beneficial for medications, such as antibiotics against Helicobacter pylori that disturb normal colonic microbes and drugs with low-level solubility at elevated pH values, e.g. diazepam, chlordiazepoxide, HCl verapamil.

GRDD systems extend the dosing intervals and thereby enhance conformity with patients Gastro retentive drug products are assisted by managed delivery inside the stomach for a longer time to reduce the repeated dose of the medication (Bhardwaj et al., 2011). While formulations or new types of dosage such as nanoparticle, microspheres, liposome etc. can still be used to regulate the release of gastro-retentive they are considered a much better way of enhancing stomach absorption. (Garg *et al.,* 2003).

1.1 GASTRIC EMPTYING TIME AND MOTILITY

During both fasting and fed states, gastric emptying happens. The time required to empty a gastric medication into the intestine is the right time. For drug absorption this is the rate preventive step as the intestine is the most critical site for absorption. Usually bioavailability of the drugs is increased by rapid gastric emptying. For drugs that degrade in gastric environment, faster onset is required (Mathur *et al.,* 2010). Moved gastric emptying promotes medications that are inadequately soluble at alkaline pH and are mainly absorbed by the intestines or proximal parts of its dissolution. In both states, though, the motility pattern is different. The interdigestive sequence of electrical events takes place every 2 to 3 hours during the fasting periods across the intestine and the stomach (Garg et al., 2008). This is defined as the myoelectric interdigestive cycle, or myoelectric migration (MMC), which also includes four phases summarized in figures 1.1 and Table 1.1.

Table 1.1 Different phases involved in interdigestive myoelectric cycle

Phase-1(Basal phase)	It lasts for 50-70 min by reductions which are rare.
Phase-2(Preburst phase)	With occasional action and contractions, it takes 40-60 minutes. Power and frequency progressively evolve as the phase continues.
Phase-3(Burst phase)	It lasts 4-6 minutes and requires intensive, frequent, short-term contractions, which is why all non-grown material has been absorbed by the stomach behind to the small intestine. It is also regarded as a surge of housekeepers.
Phase-4	The phase-3 and phase-1 transition times are 0 to 5 minutes.

Source: Talukder *et al* (2004)

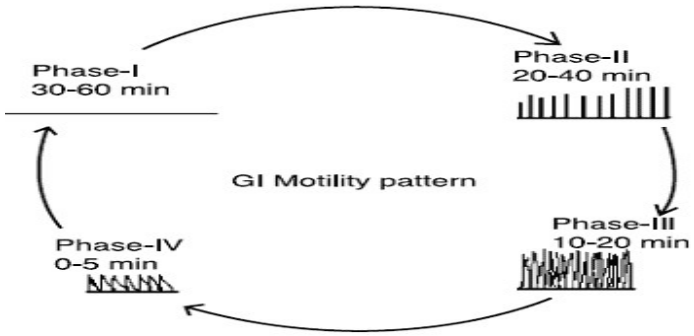

Figure 1.1 The schematic representation of the GI motility pattern

1.2 FACTORS INFLUENCING GASTRIC RETENTION OF DOSAGE FORMS

The symphony and structure of the stomach provide guidelines for the production of gastro-retentive modes of exposure.

Relevant criteria for gastric retention management include:

A. Density of dosage forms

The dosage form density controls the gastric emptying rate and specifies the system's position in the stomach. Dosing types that have a density smaller than the gastronomical material are capable of rising to the outside when high thickness processes fall down to the lower stomach (Nayak et al., 2010). Streubel et al (2003) produced single-unit floating tablets made of polypropylene and polymer matrix and inserted high porous foam powder into the matrix tablets resulting in very low density compared with discharge. In-vitro release of 17% wt/wt foam powder was demonstrated for at least eight hours (based on tablet mass). The disparity in polymers and foam powder matrix-forming ratios could thus affect the drug release patterns. The mixed matrices from Chitosan-Carbopol 940 used to adjust the release rates in matrix tablets organized by direct density and integration to the matrix tablets of the high-

porous low-density copolymer polymer (Styrene-divinyl benzene) Copolymers [PSDVB] have densities that were below the release medium density, and 17 percent w/w below the densities of the release medium. Raval et al (2011)

B. Shape and size of the dosage form

The type and size of the dosage forms are essential for the production of indigestible solid dosage forms (Pandey et al., 2012). The larger the dosage form, in most cases, the longer the gastric preservation period (GRT). The bigger dosage form makes that the pyloric antrum will not migrate easily through the intestine (El-Kamel et al. 2001). Tetrahedron and ring forming devices were stated by Garg and Sharma et al (2003) in comparison with other types, as a better gastric residential period. A significant formulation parameter is also the diameter of the dosage unit. Dosage forms of over 7.5 mm diameter indicate a greater gastric length relative to a 9.9 mm diameter.

C. Single or multiple unit formulation

More stable release profiles occur in multiple unit formulations. The slight decrease in unit efficiency requires units that contain multiple release profiles or incompatible compounds to be co-administered and thereby provides an improved degree of protection for a dosage type failure as opposed to unit-dosage forms (Pandey et al., 2012). The multi unit floating system was developed by Sungthongjeen et al. (2006), which was prepared by spheronisation of extrusion and composed of medicinal purposes filled core pellets, accompanied by double layers of an internal gas forming layer (sodium bicarbonate) and an external membrane with a gas-entrapped aqueous phase dispersed membrane. This method then received instantaneous resulted in an increase and booming for 24 hours with the continuous release of medications. It was also covered in protective coating of HPMC, a sodium-bicarbonate gas layer and polymer (Eudragith RL30D), respectively. The polymeric film was highly flexible (Eudragit RL30D) and was capable of absorbing CO2 and had the possibility to move on. Sungthongjeen et al. (2008) organized the floating multi-layer-covered tablets in which theophylline was within the tablet core. Ichikawa et al (1991) has developed a floating device of tartaric acid, sodium bicarbonate and plastics composed of polyvinyl acetate and shellac in the continuing release granules.

D. Food intake and its nature

The considerations which are deeply important to the gastric retention of dosage types include absorption of food, viscosity and food volumes, caloric content and feeding duration. Food involvement or lack effects the stomach retention time (stomach retention time). Usually, the existence of food in the GTT enhances stomach preservation by causing it to linger for a long period of time at the absorption site. Increased calorie content and acidity reduces gastric emptying (GET) again, thus increasing gastric accumulation of dose forms (Garg et al., 2008). The effect of food consumption on gastroretentive and mucoadhesive submicron sized Chitosan coated liposomes was studied by Sugihara et al (2012). In this study, fasted or feeding rats were treated orally with chitosan coated liposomes and uncoated liposomes containing fluorescent dye. The stomach and small intestine of rats were removed

after certain duration of time. By calculating the amount of dye in each component, the dye retention properties were quantitatively verified.

1.3 FORMULATION TECHNIQUES

Due to physiological variation in the gastric environment, the aim to achieve retention of drug in the stomach could be fulfilled by modifying drug delivery systems. Thus dissimilar approaches have been utilized to maintain drug in the gastric environment for longer duration of time.

1.4 CINNARIZINE

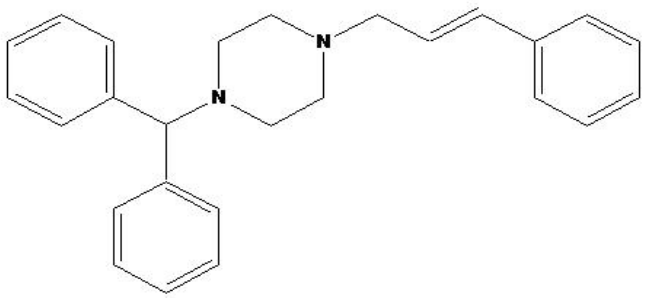

Figure 1.3 Chemical structure of Cinnarizine

Cinnarizine chemical name is (E)-1-(diphenyl methyl)-4-(3-phenylprop-2-enyl) piperazine (Figure 1.3). Cinnarizine shows antihistaminic properties blocking the histamine H1 receptors. It also has weak antimuscarinic and local anaesthetic activity. Cinnarizine is Sedative calcium antagonist and acts by inhibiting influx of calcium intracellularly. Cinnarizine by blocking calcium channels restrains contractions of vascular smooth muscle cells (Tarkase *et al.,* 2012)

1.4.1 Pharmacokinetics

Cinnarizine is consumed very easily after absorption and achieves a plasma peak in 1–3 hours (Spagnoli et al., 1983). The median drug level in a research area was Cmax (typically blood plasma) of 275 +/- 36 ng/mL, while the maximum blood time was AUC (area under curve extrapolated to Infinity) with an average bioavailability of 4437 +/- 948 (ng.h/mL). The maximum blood concentration was 275 +/- 36 ng/mL. The mean half-life removal was determined to be 23,6 +/- 3,2 hours for young volunteers who were given 75 mg of cinnarizine (Hernández *et al*., 1993).

Since administered 75 mg cinnarizine doses to healthy volunteers twice a day for twelve days, the body revealed that cinnarizine had improved with a factor of 2.79 +/- 0.23 static accumulation. Depending on age, half-life disposal ranged from 3.4 to 6.0 hours (Krukowska et al., 2007). However, with 12 days sustained and this was estimated on the single dose administration, the AUCT was not substantially different from AUC Tim. Due to its poor and lipophilic nature, cinnarizine can cross the blood brain barrier by easy diffusion (Kornhuber et al., 2010; Kalava et al., 2005). Due to this feature of cinnarizine, it can affect brain blood flow in the brain (Emanuel et al., 1979)

Bioavailability is normally low and variable due to the high rate of degradation in orally administered cinnarizine (Kalava et al., 2005). It has been concluded, however, that improved pharmacokinetics and tissue distribution were shown when administered intravenously through lipid emulsion (Shi et al., 2010). The administration of this lipid emulsion was higher AUC and less clear than the solution, resulting in an improved bioavailability of cinnarizine, thereby improving the therapeutic effect. Cinnarizine plasma pharmacokinetics is intravenously administered using the three-part model, during which the initial step of distribution was fast, followed by a slower phase of distribution and finished by very slow removal. In contrast to solution-administered cinnarizin (14,018 +/- 5,598 l/kg), V (standing state apparent amount of distribution) was 2x smaller (6,871+/- 1,432 l/kg) and thus it was concluded that considerably less cinnarizine was absorbed in lipid-emulsion condition into the lung and brain. This is necessary because adverse side effects in the central nervous system can be minimized.

1.5 DOMPERI DONE

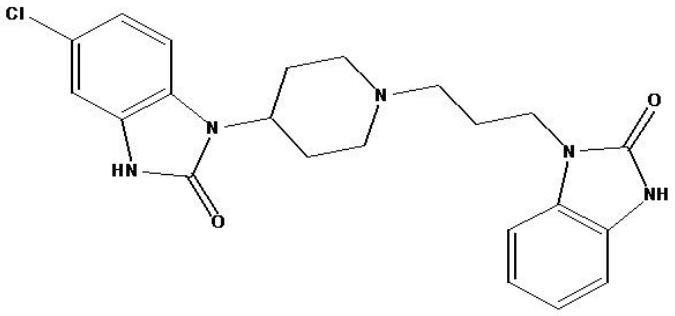

Figure 1.4 Chemical structure of Domperidone

Domperidone is an antidopaminergic drug typically used to treat movement disorder. Chemically, Domperidone is called 5-Chloro-1-(1-[4-yl)-1H-benzo(d]imidazol-1-yl)Piperidine-4-yl)-1H benzo[d]imidazol-2(3H)-one[d]imidezol-2(3H)-one (Figure 1.4). Domperidone facilitates gastric emptying and reduces the transient time of bowels by increasing gastric and esophageal peristalsis. Following oral administration, successful transport easily consumes the stomach and top of GIT (Arora *et al.,* 2011).

1.5.1 Pharmacodynamic Studies

Domperidone is a dopamine antagonist that has a strong affinity with antiemetic effects comparable to metoclopramide and some neuroleptic drugs for D2 and D3 receptors. Domperidone does not quickly cross blood-brain barrier as other neuroleptic drugs and never induces adverse effects extrapyramidal (Brogden *et al.,* 1982).

Intravenous and oral domperidone studies in humans have shown that low esophageal sphincter pressure is raised in antral and duodenally, that liquids and semi-solids such as barium meal are emptied more gastric and that solids in stable individuals as well as patients with delayed stationary phases are reduced (Agid *et al*., 1979).

Whether orally or intravenously, domperidone has a powerful reinforcing effect in both men and women on prolactin release, even though peak prolactin levels in females are time after

time higher than in males. This is done through an X-ray or Gamma sensor which enables the dosage form to be located within the GIT and with which the gastric emptying time and dosage transit in the GIT can be estimated and associated. The growth hormone plasma or domperidone aldosterone levels have no effect (Hiland *et al.,* 1981).

1.5.2 Pharmacokinetics

Domperidone peak plasma attentiveness are reached 20-40 minutes following oral in-museum and 1-2 hours after rectal prescriptions. Intramuscular domperidone is nearly 90% systemic, while oral domperidone is between 13 and 17%. The initial liver and intestinal metabolism is likely to result in poor systemic bioavailability. Oral bioavailability is improved after 90 minutes of administration; However, cimetidine or sodium bicarbonate has been decreased before food. (Heykants *et al*., 1981).

Distribution results in human beings are lacking, but experiments of radiolabelled drugs in rats indicate that body tissue is abundant, in very low doses, in the central nervous system. The placental membrane moves through only small levels of radioactivity.

Following intravenous administration, the apparent amount of human delivery is 450L or 6.8 L/kg. The tritiated domperidone human plasma protein bonding is around 93%.

Through various pathways hydroxylation and Oxidative N-dealkylation, Domperidone undergoes fast and thorough biotransformation. The percentage of the unchanged drug is just 1.5% of the overall urinary radioactivity and 20% of faecal radioactivity. With 40 mg l4C-domperidone oral administration in healthy volunteers (healthy volunteers), 31% of the urine and 60% of the faeces can be excreted within 4 days. In the first 24 hours, nearly all urinary radiation is recovered and only 1.4% (0.43 percent dose) remains unchanged. The largest component of the urinary dosage is the oxidative glucuronide glucuronide conjugate N-dealkylation of the metabolite. Domperidone half-life for healthy individuals is 7.5 hours and in severe renal disease cases extends to 20.8 hours. However, provided that renal clearance is limited relative to total plasma clearance (700 ml/min), deposition of renal dysfunction should not therefore occur (Brogden et al., 1982).

1.6 CORN FIBRE GUM

(CFG) the corn alkaline extract "fibre," the primary by-product of low-value food consumed in wet and/or dry milling. Corn fibre consists mainly of non-starch polysaccharides from cell walls extracted from pericarp kernel corn and tissues of endosperm. CFG has unusual features such as high solubility and low viscosity and is an arabinoxylan (hemicelluloses B). Mixture of coarse and fine fibres is corn fibre generally known as "white fibre' obtained from the wet-milling industry. The fine fibre is the inner cell fibre made from seed endosperm which comes from the kernels of the pericarp or hull (Singh, Doner, Johnston, Hicks, & Eckhoff, 2000). The corn bran derived from the exchange method of corn-dry milling is a byproduct and can also be referred to as the corn pericarp fibre because only the portion of this kernel comes from. In this class, sugar was described as being compatible primarily with the sugar classes: Dxylosis (48–54%), Larabinosis (33–35%), Galactose (7–60%), and Glucuronic Acid (3–6%), etc. (Whistler & BeMiller, 1956) (Whistler and BeMiller, 1956; Montgomery and Smith, 1957) Saulnier, Marot, Chanliaud, & Thibault, 1995a; Whistler &

BeMiller, 1956). The gum is closely related to a b-(1–4), xylopyranose and l-arabinofUranose column in both primary and secondary hydroxyl groups as side chains (Saulnier et al., 1995a). The majority of the D- glucuronic acid corneal fibre remaining are attached to the O-2-position xylose backbone. (Montgomery & Smith, 1957). The arabinofuranosyl branches are fastened by galactose and some xylose residues in corn gum (Whistler & Corbett, 1955).

Like other hemicelluloses, CFG cannot be isolated with water, but can instead be separated from plant cell walls using alkaline which alkaline H2O2, and is thought to be cross-connected to other cell walls. The cell wall components of Carpita and Gibeaut include covalent, ionic and hydrogen joints (1993). Doner and Hicks (1997) examine in detail the potential connections between hemicellulose and the cell walls and describe the very important role of ferric, differential and pcoumaric acids in connecting these with one another (Saulnier, Vigouroux, & Thibault, 1995b). Lignin as well as polyphenolics is indicated to form alkali-resistant contacts (other linkages) with hemicelluloses that can be broken up by the application of alkaline hydrogen peroxide. The cell wall has a stable relationship among hemicellulose and protein in corn bran (Saulnier et al 1995a) and rye bran was found to be closely bound to arabinoxylan and to the protein. (Ebringerova, Hromadkova, & Berth, 1994).

The emulsifying features of CFG samples are usually greater or equivalent to the acacia gums in this test procedure. It has been found. CFG is promising for drinks emulsion due to its high water solubility, low volume viscosity and consistency of the temperature (Whistler, 1993; Doner et al., 1998).

Strengthening. There are different extraction procedures for the CFX from maize fibre but the preparation of 2K-BC tends to be the most appropriate (e.g. 3% potassium hydroxide, 70°C, dry calcium hydroxide treatments). The xylan produced is highly pure chemically and provides clear solutions.

CFX may be used as a thickener or supplement for other existing gums in the manufacture of biofilms and food uses (1993).

The various forms of natural and synthetic polysaccharides are employed by FDDS to manage the liberate rate of drugs (Guo et al., 1998; Varshosaz et al., 2006). Natural polymers are typically prefered for pharmaceutical applications as they are low-priced, voluntarily available, not harmful, able of chemical changes, potentially biodegradable and are often biocompatible with few exceptions (Satturwar et al., 2003; Chaurasia et al., 2006; Malafaya et al., 2007). The different types of polymers that are widely used for floating drug delivery system includes alginic acid, carbopol, guar gum, polyethylene oxide, chitosan, hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (CMC), hydroxyl ethyl cellulose (HEC), hydroxy propyl cellulose (HPC), gellan gum, xanthan gum etc (Prajapati *et al.,* 2013; Nirmal *et al.,* 2010; Tiwari *et al.,*2009; Thumma *et al.,* 2008; Garg *et al.,* 2007; Perioli *et al.,* 2004; Nafee *et al.,* 2003; Repka *et al.,* 2001; Shah *et al.,* 2010; Peppas *et al.,* 1996). Rao *et al* (2013) formulated cefuroxime axetil cefuroxime axetil floating tablets using different grades of HPMC and the formulation gave lag time of 2 min and total floating duration of 12 hrs. Gaikwad *et al* (2012) formulated floating tablets of diltiazem using HPMC, Sodium CMC and carbopol and the formulations gave lag time of 1-3 min and

floating duration of 17 hrs. Kumar *et al* (2012) formulated floating tablets of clarithromycin and esomeprazole using guar gum, xanthan gum, HPMC, polypropylene and aerosol and these formulations gave different lag times. Verma *et al* (2012) formulated furosemide tablets using HPMC, chitosan and these formulations gave the lag time of less than 1 min and floating duration of 8 hrs. The MFD 5-fluorouracil(5-FU) has been prepared by Shishu et al(2007) for prolonging the duration of gastric residence, targeting stomach cancer and enhancing medication bioavailability. Shishu et al. (2007) 4-amino-3-nitroquinoline 1-oxide was combined with calcium carbonate, sodium alginate and hydroxypropyl methylcellulose and then dissolved into acidified solutions of calcium chloride. Thus, ionotropic ionotropic calcium alginate beads.

Polymethacrylates are also used in floating drug dosage forms. These are polymers consisting of eudragit that are made by free-radical polymerization. The dimethylaminoethyl methacrylates, methacrylic acid and methacrylic acid esters are synthetic cationic or anionic or acidic. They have got different percentages. During commercial processing of dry powder, water dispersion or organic solution, their different forms are available (Chang et al., 2009). These polymers serve as film formers for realistic pharmaceutical coating to track drug releases (Chang and Hsiao et al., 1989; Chang et al., 1989; Pearnchob et al., 2003). In addition, they are used in granulation and direct compression as matrix formers (Evonik et al., 2009; Pereira de Souza et al., 2007).These polymers are harmless and inert in nature (Eudragit acrylic resins). They are not taken up in the GIT and body fluids immune. They exist inside the GIT for a limited period, are unchanged and do not contain deteriorating items (Evonik et al., 2009). Floating bioadhesive tablets with the application of sodium carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), poliacrylic acid (AA), polymetacrylic acid (MAA), citric acid and sodium bicarbonate is prepared by Varshosaz et al (2006). The type of polymer used did not influence the floating lag time greatly. All the tablets were floated 24 hours above the medium.

The reason of the present research was to devise gastroretentive floating tablet using corn fibre gum and its derivatized form with cinnarizine/domperidone as model drugs. Further, the organized floating tablets were appraised for their *in-vitro* as well as *in-vivo*/*ex vivo* performance.

1.7 RESEARCH ENVISAGED

1. Cinnarizine (CNZ) is the essential medicine with low aqueous and pH-dependent solubility (0,29 mg/ml, 0,01 N HCl, pH 2.0) but is widely absorbed from the stomach. pH 6,5 phosphates are 0,002 mg/ml (Nagarwal et al., 2010).Thus, gastroretentive drug delivery system will be formulated using cinnarizine for improving patient compliance.
2. Domperidone (DOM) has very less solubility in alkaline pH but has good solubility in acidic pH (Prabakaran *et al.,* 2006). Thus domperidone is an effective candidate for a gastric retention system, because of its low bioavailability and strong solubility for an acidic pH (Saritha et al., 2012).

3. The acrylamide grafting of gum was selected as the mucoadhesive strength generally increases with acrylamide grafting so this polymer could provide an excellent sustain release properties and was so selected for the formulation of bioadhesive floating gastroretentive tablet.
4. This type of study has not been performed earlier using this gum so that is why it was selected for bioadhesive floating tablets.

1.8 OBJECTIVES

1. To extract corn fibre gum from the corn kernel pericarp.
2. To derivatize the corn fibre gum by acrylamide grafting using microwave assisted method
3. To formulate floating bioadheshive tablet of cinnarizine and domperidone using corn fibre and derivatized gum
4. To compare the formulated floating tablets with standard HPMC polymer.
5. To perform in-vitro, ex-vivo and in-vivo studies of the formulation using suitable animal model.

CHAPTER 2

REVIEW OF LITERATURE

2.1 REVIEW OF LITERATURE

Sethi et al., 2018 Immediate and protracted buoyant conceived and established polyacryl amide-g-corn rubber tablet cinnarizine. For processing buoyant tablets, a QBD technique has been used. Gum grafted polyacryl amide corn fibre has been produced and compared with HPMC K4M polymer, already in use. Optimized conc. With optimised conc. P-CFG (X1), NaHCO3 (X2) or vibrant agent have selected the central composite architecture with 2 quantitative and one categorical factor (X3). The formula used for this selection was 2.4x stronger than the tablet-bearing HPMC K4M, the mixture selected included P-CFG (65.4%), sodium bicarbonate (13.8%) and citric acid (3%). The outcome was in vivo animal pharmacokinetic findings and lower removal rate relative to the CNZ suspension. The optimized formulation demonstrated 3 times increased absorption than with a CNZ suspension, while improving the oral bioavailability of CNZ showed a sustained gastric residency.

Talwar et al., 2015 Ciprofloxacin floating matrix tablets developed for oral administration. The formulated ciprofloxacin shaped by 69.9 per cent ciprofloxacin base, 0.35 per cent sodium alginate, 2.04 per cent xanthan gum, 14.8 per cent sodium bicarbonate and 12.1 per cent bridge cross connected polyvinyl pyrrolidone. The creation of the hydrated gel matrix provided a torturing pathway to the release of the drug.

Rao et al.,2013 demonstrated floating drug delivery system of drug cefuroxime axetil by using polymer HPMCK4M, HPMC 15 M, HPMC100M, sodium bi carbonate as gas generating agent showed *in-vitro* release for 12 hr and in vivo radiographic studies indicated that drug in stomach for about 6 hrs. Thus by selecting suitable composition desired floating duration of more than 12 hrs was achieved.

Kumari et al., 2013 have demonstrated the sodium bicarbonate in-vitro buoyancy can be accomplished using gel forming polymer HPMC K100 and gas producing agents .The floating drug delivery system of metformin Hcl and gliben climade were formulated using this composition and in vitro release for more than 8 hrs was achieved.

Mandeep Sharma. et al., 2013 Prepared famotidine floating effervescent tablet. Tablets were developed using direct density methods using polymers including HPMC K4M and HPMC K100M. Weight uniformity, favorability, medication content, invitro bouncy and dissolution tests were tested. For 6 to 10 hours all the formulations were well in-vitro. The tablets made with the HPMC K100M have been shown to be floating for a longer period of time relative to the HPMC K4M tablets. Stability tests have shown that room temperature tablets can be stored [8].

Daisy chella kumara S. et al., 2012 have prepared and appraised the gastric floating drug delivery system (GFDDS), which uses different proportions of polymers like HPMCK4M which Ethylcellulose, and includes hydrochloride as model drug. The formulation was

optimised through the analysis of the power of drug to polymer ratio on drug release, which increased bioavailability and therapeutic performance. FT-IR experiments have demonstrated no association of polymer (HPMC K4M, Ethyl Cellulose) and excipients of Ondansetron Hydrochloride. The formulation F6 had strong floating property and had a total period of 8 to 12 hrs, prepared six formulations. The tablets have also been tested for their longevity, friability and in-vitro testing. The findings revealed that hydrophilic and hydrophobic polymers are ideal for an integrated continuous drug supply system. [9].

Dhiman S. et al., 2012 formulated gastro retentive floating tablet of famotidine HPMC K15M as a polymer. Variable concentrations of HPMC K15M and sodium bicarbonate were utilized to produce the controlled release formulations. The matrix tablets have been engineered for carbon dioxides, which are trapped into the jellified hydrocolloids in the gastric fluid, by using sodium bicarbonate (NaHCO3) and citric acid as gas forming agents, which cause the dosage shape to move upwards to maintain its lift. Polymer amount-HPMC K15M (X1) and gas forming agent quantity-Sodium bicarbonate are the independent variables optimised in the formulation (X2). As dependent/response variables, time needed for 50 percent drug release and floating lag time were taken. HPMC K15M (30mg) and sodium bicarbonate found in the optimized formulation (20mg). The findings found that famotidine floating matrix tablets for the action of gastric ulcers would solve the issue of limited residence period experienced by an oral forbidden release formulation.[10]

Gaikwad et al., 2012 described the formulation, dissolution, buoyancy and *in vivo* release tests of a floating drug delivery system diltiazem HCL containing polymer HPMC K4M,NA CMC,Carbopol 934 which showed floating duration of 17 hrs and gave 100% drug release in 12 hr

Rangapriya et al., 2012 formulated floating formulations of pioglitazone hcl using HPMC5LV, HPMC 15 LV, HPMC50LV, ethyl cellulose, NaHCO3 as gas generating agent Lag time 60-80 Sec which gave floating duration 18 -20 hrs and gave *in-vitro*drug release for more than 24 hrs was achieved .

Vinoth Kumar M. et al., 2011 formulated Domperidone floating bilayer tablet. The objective of the research was to build a two-layer floating tablet to test domperidone maleate by using liquid granulation technology. As a gas formation agent that formed the floating layer, they used HPMC,K Grade and sodium bi carbonate. Invitro dissolution experiments and floating actions were analysed in simulated gastric fluid using USP paddle apparatus 2. Statistically meaningful differences were found in the drug release profile between various formulations. This improved formula was based on the higuchi release model and demonstrated that after 3 months of storage at 45°C/75 percent HR there were no apparent improvements in the physical appearance, drug quality, fluidity and pattern of in vitro concentration.

Denish Kalaria et al., 2011 Established Gastric retention floating tablets for oral administration of acyclovir to develop the bioavailability of the drug and to prolong gastric residence period. By adding the gas producing agent along with the polymer HPMC, the tablets were prepared using wet granulation processes. A floating lag time of below 30 s and a cumulative floating time of in excess of 12 h were seen in the distilled formulation. For

about 11 hours, the drug release was properly maintained and a non-fickian dissemination method followed zero order models.

Gangadharappa H.V et al., 2011 developed **gastro** retentive floating tablets of atenolol using direct compression technique. Karaya gum, HPMC and Sodium bi carbonate as gas generating agent were incorporated for preparing the tablets. Shorter floating lag time, good floating capability and continuous drug release for 12 h were seen in the optimised formulation. Various styles such as Korsmeyer, Peppas, and Huguchi accompanied the drug release. Fickian and anomalous transport suggested diffusion exponent values (0.3771 to 0.6997).

Laxmi Goswami et al., 2011 Metformin and pioglitazone bilayer floating tablets have been developed for use as an oral hypoglycaemic agent for diabetes management. Through the use of the direct compression process, floating bilayer tablets were developed to facilitate immediate release of pioglitazone and secure the release of metformin through the addition of polymers such as HPMC, carbopol, and PVP. Different parameters were tested for the capsules, such as drug content, in vitro dissolution tests etc. The tablets developed were booming for 12-20 hours and were more than 80 percent drug released.

Chandira et al., 2010 developed Itopride hydrochloride floating tablets, a new prokinetic medication to extend gastric residence time and improve bioavailability of medications. The tablets were formed using the method of direct compression, and sodium bicarbonate and citric acid producing gases, along with HPMC K100M, HPMC K15M and carbopol 934 P polymers were applied. The findings concluded that tablets containing 125 mg HPMCK100M, 40 mg HPMC K15M and 40 mg carbopol give a better alternative and increased bioavailability for 24-hour release action.

Danki et al., 2010 Studied Creation of Alfuzosin Hcl's hydrodynamically balanced mechanism as an anti-hypertensive drug intended to maximize gastric residence instance, thereby prolonging the release of the drug. Different parameters for example the drug polymer ratio, HPMC viscosity grades, gas producing agents, enhanced drug release and floating property of prepared HBS were prepared for HPMC HPMC of various viscosity grades by direct compression technique. All the HBS-containing formulations showed strong floating properties in vitro. It was concluded that three HPMC (K4M, K15M, K100M) viscosity grades along with lactose as diluents were found to be helpful in improving the rate of drug release and floating property.

Kannan C et al., 2010 formulated Gastroretentive floating rosiglitazone maleaste tablets using the method of melt granulation. Materials such as hydroxy propyl methyl cellulose (HPMC) K4, K15, K100, sodium bi carbonate act as an effervescent agent and as bees wax as a hydrophobic meltable material. Sustained release profile and release up to 12 h were shown by the optimised formulation F7 containing HPMC K15M and K100M and showed reasonable buoyancy and total floating time. The optimised floating tablets have provided essential advantages such as site specificity and increased absorption and effectiveness to sustain release characteristics.

Shinde et al., 2010 The oral bloating tablet of cepalexin was developed and formulated with a sodium bicarbonate gas producing agent and citric acid hydrophilic polymers 2 hydroxy propyl methyl cellulose(HPMC). A 32 factory concept was selected and introduced systematically. The cumulative amount of citric acid (X1) in HPMC K100M (X2), 50% drug release time (t), 12% drug release time (T), and 50% drug release time at 6 hours (Q) was used as dependent variables as segregated variables. The findings concluded that elevated levels of HPMC K100M and citric acid facilitate the preparation of cephalexin floating continuous release tablets. For the processing and examination of granules, a wet granulation technique was used. Variously studied in vitro boosters study, swelling properties, scanning electron microscopy, and kinetic release data for comprises, including diameter, width, average weight, hardening, cold, medicines, drug content. At the end of 12 hours, the tailored tablets showed a drug release of 72.28 to 99.461 percent. Korsmeyer and Peppas also disclosed the medication release process for the improved formulation of cephalexin tablets.

Rao et al.,2009 The cephalexin floating drug delivery system was formulated and analysed. Tablets were prepared as a gas producing agent using HPMCK4M, xanthan gum, guar gum, sodium bi carbonate and tartaric acid as a direct compression technique. The substance followed the model of Korsemeyer peppas dissolution and the exponent of diffusion diffusion was establish to be 0.755, which greatly suggested the drug release process.

Bomma et al., 2009 Norfloxcin's floating matrix tablets are designed for growing gastric residence times and bioavailability of medicines that use polymers such as HPMC K4M, HPMC K100M and Xanthan using a wet-granulation technique. The tablets displayed a controlled and maintained drug release profile and confirmed floating properties on the medium dissolution via the process of drug release.

Rao et al., 2009 The formulations for salbutamol sulphate with an effervescent floating matrix were developed and tested with complete factorial architecture. A 3-2 full factorial configuration was used to optimise the formulation in which HPMC (X1) and sodium bicarbonate (X2), percentage of drug released by independent variables were selected after six (Y1), T50 percent (Y2) and booing lag (BLT) (Y3). Two grades of HPMC viscosity were used as matrix materials in the formulation of salbutamol tablets by the wet granulation process. The in vitro release findings showed anomalous transport. There was a decrease in the rate of releases due to increased concentration in the polymer and viscosity, but a higher HPMC levels and viscosity did not affect the release of the compound significantly. It was concluded that HPMC's viscosity grade did not significantly affect the dosage form's flobility and thus a mixture of HPMC, stearic acid, sodiumbi carbonate

N. Damodharan et al., 2009 developed bilayer Theophilline floating tablets, using the method of wet granulation. The tablets were formulated with theophilline with lactose as diluents and maintain release layer instantly releasing layer and were formulated with theophilline and in combination with various polymer ratios. The combination of HPMC and MC was tailored and considered appropriate for the maintenance portion of bilayered floati, which produced gradual release of theophilline over duration of 9 h. Theophylline release from these tablets, was regulated by diffusion and followed the kinetics of the first order.

Vishnu M Patel et al., 2009 Optimized verapamil hydrochloride gastroretentive floating tablets by direct compression. Polymers used for formulation were carbopolis (CP 934P; CP 940P), methylcellulose hydroxypropylcellulose (HPMC K4M; HPMC K15M; HPMC E15), and xanthane gum. Both formulations demonstrated high in vitro boostability and retained release properties. In a 24 h in-vitro dissolution analysis, the xanthan gum-containing formula was selected and demonstrated 97.89 percent drug release, while the buoyancy lag period was 24.6 ± 3.2 sec and the tablet stayed buoyant for > 24 h. The optimised tablets followed the Zero order and non-Fickian release transport model.

Ganesh Rajput et al .,2009 prepared gastroretentive floating tablets of Metformin Hcl by direct solidity method . HPMC K100M and HPMC K4M were used for preparation of tablets. It was noted that the factor that influenced drug release from hydrophilic matrix tablet was polymer viscosity,as the viscosity increased the resemblance factor f2 was enlarged . It was also completed that the resemblance factor f2 was impaired by polymer viscosity. To obtain an apparent viscosity of 66633 cps, various combinations of HPMCK4M and HPMC K100M were tested. The highest f2 value of the optimised batch were (82).

Shalesh T. Prajapati et al., 2008 Prepared the Domperidone-containing Model Drug Floating Gastric System. They used HPMCK4M,Carbopol 934 P and sodium alginate sodium bi carbonate as a gas forming agent which formed the floating layer. As independent variables for planning the GFDDS for the K4M (X1), Carbopol 934P (X2) and Sodium alginate HPMC tree polymers, the Box-Behnken setup was used (X3). Floating time lag (FLT), time to release 50% of medications (t1/2) and diffusion exponent (n) have been chosen as dependent variables. Total floating time (TFT) for floating properties, HPMC loading was found to be substantial. Carbon loading has an effect on floating properties; moreover, the regulation of the release rate for the compound has been shown to be positive. Sodium alginate had no main impact on floating characteristics, but for gel production it was significant.

Thakkar et al., 2008 Levofloxacin Floating Tablets are formulated and tested using gelucire 43/01 and HPMC polymers in dissimilar ratios through the direct compression process. Invitro release studies have shown that the cost of release has deteriorated with the enlarge from 5% to 40% of gelucire 43/01 comprises of 25% HPMC K4M and 15% gelucire 43/01.

Jaimini et al., 2007 Famotidine floating tablets have been developed and assessed using a effervescent combination of Methocel K100 and Methocel K15 M. Sodium carbonate (130 mg) and citric acid (10 mg) were found to be sufficiently booming in vitro. The tablets produced by K100 were found to float longer than those containing Methocel K15MThe K100 tablets have been observed to float longer than the Methocel K15M formulations.

Ali et al., 2007 As a single floating capsule, the hydrodynamic stabilised metformin system was prepared. The formulation has been modified to the in vitro raise and release in the simulated gastric fluid fed by the State. To ensure long-term medicines transmission from HBS capsules, findings of various release modifiers have been evaluated. The highest percentage of in vitro release in HBS capsules developed with K4M and ethyl cellulose were classified as drug solution

Narendra et al.,2006 The manufactured floating bi-layer tablet with metoprolol tartrate is a model medication for gastric retention.23 The GFDDS are designed as an independent variable in the total polymer content of drugs (X1), the polymer to polymer ratio (X2) and the various grades of viscosity of HPMCs. Factorial designs (X3).The findings showed that the floating time and release properties were influenced by XI and X2, but the influence of various HPMC grades (K4M and K100M) was not important.

X. Xiaoqiang et al.,2006 optimized three floating matrix formulations of phenoporlamine for prolonging release of the drug. To devise the hydrogel drug delivery method, hydroxypropyl methylcellulose K4M and Carbopol971P NF were integrated. As a gas producing agent, sodium bi carbonate was used. Both of the tablet batches demonstrated non-Fickian diffusion in simulated gastric fluid. Six stable human male volunteers were tested in vivo for these formulations to equate the long release tablets with immediate release.

Srivastava et al.,2005 Floating atenolol matrix tablets for extended residence and increased biological supply of drug Tablets have been prepared on their own or by direct density using polymers like HPMC K4M, HPMC 15M, guar gum, sodium carboxymethyl cellulose in combination with other excipients (SCMC). Different physical parameters, including stiffness, were evaluated for the prepared comprises sw Linear regression testing of the in vitro release process. GG and SCMC matrix tablets shown a significantly higher swelling index relative to other batches. When floating over the dissolution medium, the tablets displayed controlled and extended drug release profiles.

B.S.Dave, et al., 2004 A gastro retention system, comprising guar gum, xanthan gum and HPMC as gel-forming polymers, was designed to prolong the release of ranitidine. As a gas-generating agent, sodium bicarbonate was used. Drug release and floating properties have been studied in citric acid and stearic acid. The factory design successfully shows that the release of ranitidine hydrochloride is supported with high concentrations of citric acid and stearic acid. Using pharmacokinetic parameters of ranitidine chloride, theoretical dissolution profile was determined. The theoretical dissolution profile did not vary statistically, as the similitude factor revealed, from factorial nature batches. The findings were that the best combination of an enhancer and a hindering release rate produces a substance dissolution profile close to a theoretical profile of dissolution.

Dave et al., 2004 Prepared a gastroretentive drug delivery method for ranitidine hydrochloride which uses Guar gum, xanthan gum, propylhydrochloride hydroxide as a ga sgenerating agent, and gum sodium bicarbonates. The effect on profile and floating properties of drug release of citric acid and stearic acid has been investigated. They concluded that a substance dissolution profile comparable to the theoretical dissolution profile could be created by a compromise between release rate retardant and release rate enhancer

Amin et al., 2004 description a ranitidine hydrochloride gastroretentive drug delivery device that uses guar gum, xanthan gum and HPMC as a gas-generating agent, and sodium bicarbonate. Citric acid and stearic acid have been investigated for their profile and floating properties. They concluded that due to its hydrophobic nature, styearic acid decreased drug dissolution. Optimization was performed using 3^2 factories and Results revealed that a low

citric acid level and high stearic acid value favoured a continuous release of Hcl ranitidines from a gastroretentive formula.

Baumgartner et al., 2001 formulated floating tablets of ciprofloxacin Hydrochloride which offered a new opportunity of treating stomach impure with *Helicobacter pylori*. The purpose behind this study was to choose appropriate materials such as polymers hydroxyl ethyl cellulose (HEC), hydroxyl-propylcellulose (HPC), HPMCK4M and to obtain controlled drug release for more than 8hr. These polymers played a significant role in expanding the tablets' gastric residence period.

Baumgartner. S et al., 2000 Formulated Hydroxyl propyl methyl cellulose-containing floating matrix tablets for oral administration to extend gastric residence time and reduce the side effects of annoying medications. The formulated tablets were tested for various metrics, for example floating lag time and floating duration. The characterization revealed that the structure of the tablet and mechanical strength had a significant effect on the tablet's floating and drug release properties. The formulated tablets adopted a non-fickian model for the drug release transport mechanism.

Nur and Zhang et al., 2000 HPMC (4000 AND 1500 cps) and carbopol 934 P are used for optimized floating tablets of the Captopril. The in vitro buoyancy tests found that 2kg/cm2 hardness tablets floated instantly and 4kg/cm2 tablets had a floating lag time of 4-5 min and then came to the surface and both tablets stayed for 24 hours in the buoyant state and 8kg/cm2 tablets showed no floating ability.Thus prolonged release tablets were formulated as compared to conventional release tablets.

Timmermans J et al., 1990 Described that floating curves demonstrated that the mass density of the form of dosage was not the most fitting parameter for characterizing its buoyancy capacity. These capabilities were represented and monitored by resulting measurements of weight. Their observations revealed that as a function of time, the magnitude of floating pressure will differ and typically reduces following fascination of the dosage type into the fluid and ultimately to the evolution of its hydrodynamic equilibrium.

CHAPTER 3

MATERIAL AND METHODS

3.1 PRELIMINARY INVESTIGATIONS

3.1.1 Identification of Cinnarizine and Domperidone

1) FTIR-ATR Analysis

Cinnarizine or domperidone using the FTIR-ATR spectrometer (Bruker, alpha E, Germany) were detected in the 500-4000 cm-1 spectral region. The spectrum of each drug was compared with standard spectra (Patnaik *et al.,* 2012; Palem *et al.,*2011).

2) Thermal analysis

An correctly weighted sample (approximately 10-15 mg) of cinnarizine or domperidone was placed under the flow of nitrogen in sealed aluminium pans. A sample was heated from room temperature to 400 °C at a heating rate of 10 °C/min. For comparison, an empty aluminium pan was used. From the DSC thermogram (SETARAM), peak transition and fusion enthalpy were calculated and compared with the normal thermogram available in the literature (Nagarsenker et al., 2000; Kalava et al., 2005).

3) Chemical tests

a. Cinnarizine

In a water bath at 80 °C, dissolve 0.3 g of anhydrous citric acid in 10 ml of acetic anhydride and hold the temperature at 80 °C for 10 minutes during the water bath. The addition of 20 mg of cinnarizine produces a purple colour. Cinnarizine confirms this (IP).

b. Domperidone

A solution of DOM in 0.01M HCl was scanned spectrofluorimetrically from 200 nm to 700 nm using Spectrofluorimeter (SL-174, Elisco Ltd, India). Fluorescence measurements were made using 10 nm excitation and emission windows at a sensitivity of 650 nm. The fluorescence spectra were recorded at a rate of 600 nm/min.

4. Solubility of CNZ/DOM

The solubility was measured by applying 0.1 g of CNZ/DOM to a 10 ml graduated cylinder with a glass stopper. The rising volumes of different solvents such as water, ethanol, methanol, dichloromethane or acetone for determining the solubility of CNZ. The solubility of DOM was estimated on similar lines in water, ethanol, ethanol or DMF. All the solubility studies were conducted at room temperature. The criteria for analyzing the solubility of drugs is summarized in Table 4.1

Table 3.1 Solubility criteria for different solvents

0.1gm soluble in v ml of solvent	0.1	0.5-1	2	10	100	>100
Apparent solubility (grams per litre)	>1000	1000 to 200	100 to 50	50 to 10	10 to1	<1
Solubility (USP)	Very soluble	Freely solubl e	Soluble	Sparingly soluble	Slightly solubl e	Practically insoluble

The mixture was vigorously shaken for 10 minutes after each addition of the specified quantity of solvent and visually tested for any undissolved sections of the sample. If the sample or portions of it appear undissolved despite the addition of 10 ml of water, the experiment needs to be performed in a 100 ml measuring cylinder with greater solvent volumes.

3.1.2 Drug-Excipient Interaction Studies

FTIR/ATR

AG's FTIR-ATR spectra or their physical mixture with CNZ and DOM and other excipients were registered with the spectrophotometer FTIR/ATR (bruker, alpha E, Germany). The absorption samples were scanned for 500-4000 cm-1.Due to drug-excipient interaction, the disparity in spectral peaks was studied.

3.2 STABILITY OF CINNARIZINE /DOMPERIDONE IN DISSOLUTION MEDIA

The stock solutions of cinnarizine /domperidone (10µg/ml, 15µg/ml and 20µg/ml) were prepared in 0.1N HCl and stored at 37°C for 8 hrs. Aliquots of 5 ml sample was withdrawn after every 2 hrs and analyzed at 253 nm or 282 nm, respectively for CNZ/DOM using UV-Visible spectrophotometer. The initial concentration to concentration obtained at time t was compared and evaluated for any difference.

3.3 SYNTHESIS OF DERIVATIZED CORN FIBRE GUM

The Kamboj and Rana process has been used to remove maize fibre gum (2014). This extracted gum was then grafted by the technique reported by Singh et al. 2017 using acrylamide. Briefly, the formula was made in water with 2.5 percent (w/v) gum. Separate amounts are arranged in purified water with 1-5 gm batch of acrylamide solution (monomer). The monomer solution was used with a continuous stirring for 2 hours and the varying amounts of ammonium persulfate (0.2-0.4 gm) were then added (initiator). This explanation

had been microwaved at 500 MW for 20 seconds prior to the beginning of heating. This hot solution easily kept in the fridge in ice-cold water. This method was frequent for 19 cycles prior to gel stabilisation. This solution was put in a refrigerator overnight for 24 hours. A transformed gum precipitated the addition of acetone. To clear some homopolymers with methanol: vapour, the purified precipitation cleaned (70:30). The precipitated gum was lyophilized for the extraction of the dry product.

3.4 PREPARATION OF FLOATING TABLETS OF CINNARIZINE AND DOMPERIDONE

Cinnarizine/domperidone floating tablets is prepared by means of a direct compression technique. AG (45-60 percent w/w) was used as a floating polymer in contrast to HPMC E4M (45-60 percent w/w) and Pure Corn Gum (60 percent w/w) for this reason.

The tablet used mild effervescent generators (glycine (2-15 percent W/W) or high vibrant generators (citric acid (1-2 percent W/W) or alone (8-10 percent W/W) with sodium bicarbonate. The tablet was floated using mild effervescent generators. Thus the geometrical procedure combined the various formulations shown on the table to achieve a standardised mixing of the tablets. 5-minute magnesium stearate lubrication was then made to the powder mix and directly packed with one tablet station into 250 mg and 8 mm tablets. The tablet's hardness has been retained in the range of 8-10 kg/cm2.

3.5 SWELLING AND WATER UPTAKE STUDIES

The weight control of the tablet was used for swelling experiments. The polymer absorption rate was estimated using a weight gaining process close to that of Efentakis and Vlachou (2000). The tablets were weighted accurately and stored in the sponge of 0.1N HCl at 37 ± 0.5°C in a filter paper. The pre-waved matrix tablet was partly blown with tissue paper to remove excess test fluid and repound in a certain interval (2, 4, 6, 8 h) from the medium. The swelling activity of the tablet was calculated by the following equation:

$$Ps = (Ws-Wi)/WP\times100$$

Where

Wi = initial weight of the matrix

Wp = weight of polymer in the matrix

Ps = percent swelling

Ws = weight of the swollen matrix at time‘t’

3.6 MATRIX EROSION STUDIES

The Ranga Rao et al (1988), Dhopeshwarkar et Zatz (1993) and Ebube et al(1994) Matrix Erosion Experiments were performed using a method (1997).The polymer containing tablets were carefully weighted on the filter paper mounted on a sponge dipped into 0.1N HCl and held at 37 ± 0.5 °C. The tablets have been carefully extracted periodically from the dissolution vessels (2, 4, 6, and 8 h) and dried in a hot air oven to a steady weight at 50 °C. The erosion percentage was not determined by the next equation at the time:

Pe= (Wi-Wt)/Wi×100

Where

Wi = initial starting weight of the matrix tablet

Wt = weight of matrix tablet subjected to erosion for time‘t’

Pe = Percent erosion

3.7 PHARMACOKINETIC STUDIES

The experiments were conducted according to the protocol..... For a 15 days comparative in vivo pharmacokinetic study and for 12 hours prior to dosage administration, In wildlife room with free access to drinking water, stable rabbits (New Zealand albino) of 2.5–3.0 kG were administered. The batch formulation contrast with the 2% sodium carboxymethyl cellulose (CMC; reference) of the CNZ suspension sample:

Single dose, 2 treatments, 2 periods, randomised setup and complete crossover under fast conditions. For contrast, 2 per cent sodium CMC were used for CNZ (5 ml of 10 mg/ml) suspension. Floating tablet formulations of 50 mg CNZ have been used for testing. Between consecutive runs, 1 week or seven half of life was washout time was allowed.

3.8 X-RAY STUDIES

As per the protocol reported by Kumar et al, the X-ray studies were conducted (2012). Barium sulphate (BaSO4) was used as an opaque X-Ray agent in the study. CNZ or DOM was therefore substitute with 25 mg of BaSO4 per tablet. The 250 mg tablet ratio was substitute to a 6 mm ratio of 125 mg. These X-ray imaging studies have been used to monitor tablets' gastro-retentive behaviour. There was taken in New Zealand for research a number of rabbits (2.5 kg) of both genders. It investigated two rabbits. Any animal was consumed orally with barium sulphate tablets after overnight fasting. At a set amount of time (0, 2, 4, 6, 8 h), abdominal x-rays were taken and x-rays of the tablets revealed whether or not 8 h were left in the stomach. A automated ray machine supported each animal approximately 0.1 metres of radiation (Alliger, Chandigarh).

3.9 RESULTS AND DISCUSSION

In our prior investigation we had prepared and optimized derivatized CFG based DOM loaded floating tablets. The optimised polymeric buoyant formulation (F_{14}) exhibited minimal or no floating lag with the total floating time >8h.

3.9.1Pharmacokinetic Studies

The plasma concentration time profile of CFG based floating tablets of DOM (F_{14}) and marketed preparation (Domperon ®) following their oral administration is shown in Figure 1 and pharmacokinetic parameters attained are summarized in Table 1.

The study was conducted to analyse the release behaviour of drug from the floating tablet when administered orally over the period of 24h. For this optimised floating tablet batch (F_{14}), selected on the basis of its *in-vitro* performance and lag profile, was evaluated 24h post administration and compared with that of Domperon®.Plasma concentration *vs* time graph

revealed the mean T_{max} values of F_{14} and Domperon® of 4h and 1.33h, respectively. This exhibited the quick absorptive nature of marketed preparation while floating tablet displayed a slow and prolonged absorption pattern, thereby indicating the potential of derivatized CFG in effectively delaying the peak plasma concentration and achieving the controlled drug release from the formulation. Further mean peak plasma concentration (C_{max}) values of floating tablet (819.2±25.1 ng/ml) and Domperon® (912.2±37.5 ng/ml) at the same dose level revealed the former preparation to effectively control the drug release from the disintegrating matrix. The mean biological half-life ($t_{1/2}$) of DOM tablets was found to be 3.9 times higher than that of Domperon.

CHAPTER 4

ANALYSIS AND DISCUSSION

The floating drug systems (FDDS) or technique is utilized water systems are low density systems that, because of their sufficient to float in the bowels for a long time without impacting GER, float over gastric material (Pande et al., 2013). CNZ is a basic low solubility substance in aqueous and pH-dependent conditions, but is widely consumed in a stomach (0.29 mg/ml, 0.01 N HCl(pH 20) (Nagarwal et al., 2010).Thus, gastroretentive drug delivery system can be formulated using cinnarizine for improving patient compliance. Domperidone has very less solubility in alkaline pH but has good solubility in acidic pH (Prabakaran *et al.,* 2006). Thus, the low bioavailability and strong solubility in acidic pH allows domperidone a perfect candidate for the delivery mechanism of gastro retentive drugs (Saritha et al., 2012). Therefore, an effort was complete to prepare a gastroretentive drug delivery system using grafted corn fibre gum in the form of floating CNZ tablets of DOM.

4.1 PRELIMINARY STUDIES

The samples of both CNZ and DOM were gifted by Helios Pharmaceutical, Baddi and Nayan Pharmaceutical, Patiala respectively. A quality control report obtained with these samples showed 99.9% purity. However, a need was felt to further identify and check the purity of these samples.

The peaks observed in FTIR/ATR spectra of DOM as shown in Figure 4.3 are 2918 cm^{-1} (N-H stretching), 2810 cm^{-1} (asymmetric C-H stretching), 1689 cm^{-1} (C=O stretching), 1484 cm^{-1} (N=C stretch peak) and some other characteristic peaks observed at 1067 cm^{-1}, 1147 cm^{-1} found to be similar as that observed in the FTIR/ATR spectra (Figure4.4) of standard DOM sample (Palem *et al.,* 2011).

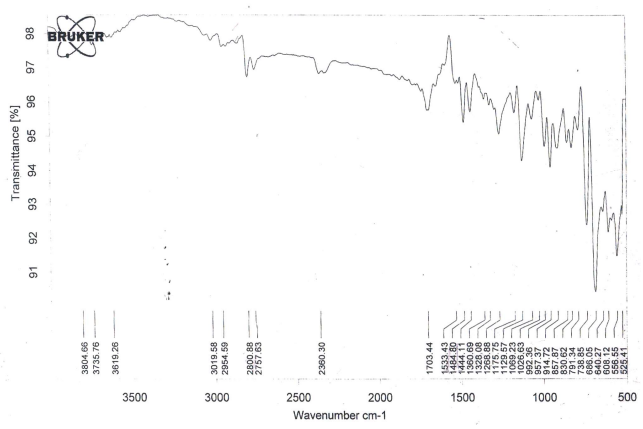

Figure 4.1 FTIR/ATR spectra of Cinnarizine (observed)

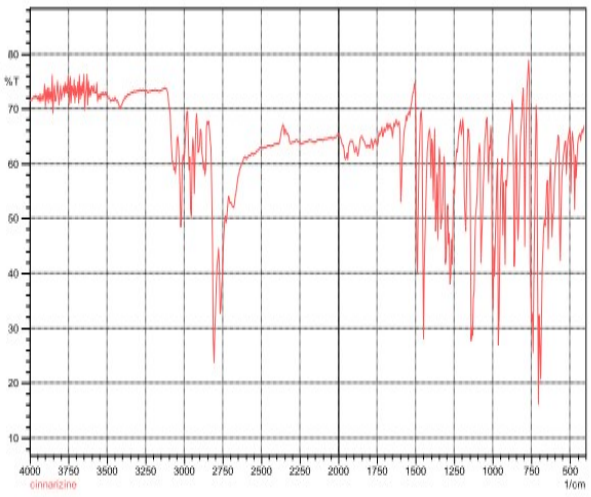

Figure 4.2 FTIR/ATR Spectra of Cinnarizine (Std) (Source:Patnaik *et al* (2012))

4.2 VALIDATION OF ANALYTICAL METHOD

4.2.1 Caliberation curve of CNZ

The calibration curve of CNZ in 0.1N HCl was prepared and provides 253 nm lambda max (Figure 4.15). It was observed that CNZ observed Beer's Lambert law in the attentiveness range of 2.5µg/ml to 15µg/ml (Table 4.2).The equation of linearity is Y=0.0601x+0.0003.

Table 4.2 Results obtained after validating the analytical method of Cinnarizine employing UV –Visible Spectrophotometer.

SNo	Parameter	Results	Reported (Tarkase *et al.*, 2012)
1	Absorption maximum	253nm	254nm
2	Linearity	2.5-15µg/ml	5-20 µg/ml
3	Limit of detection	0.05µg/ml	0.015 µg/ml
4	Limit of quantification	0.16µg/ml	0.070 µg/ml

4.3 CHEMICAL CHARACTERIZATION

FTIR –ATR Analysis

There was a compelling rubber match between 1643 cm-1, 1516 cm-1 and 1018 cm-1 in the FTIR-ATR spectrum. The FTIR-ATR(G) pure gum. A syringle, a guaiacyl loop of c=O,

stretching C-H with aromatic fragrance in plane deformation and a C-H with aromatic C-H in G, bent smoothly and indicating small bands with 1334 cm-1, 1242 cm-1 and 855 cm-1, indicate a minor lignin samples. The pure gum obtained was transparent from residual lignin with no matches of 1,410 cm-1, 1220cm-1 and 1,155 cm-1. The existence of sharp 890cm-1 belt, which is a β-glycosidic relation between sugar units, characteristic of its peak. This suggested that the residue of xylose in the backbone of macromolecules is connected by β-shaped connections. FTIR was shown to be similar to the obtained spectrum (Gupta et al., 1987). Certain additional peaks in the case of AG have been found. The peak at 1606 cm-1 (N-H bend), 1424 cm-1 (CN stretching) and 3172 cm-1 in conjunction with the symmetrical NH stretching of the NH group (Figure-4.21). These extra peaks were found to be strong grafted in derivatized polysaccharides.

4.4 PREPARATION OF FLOATING TABLETS

To discover the usefulness of AG, dissimilar batches of floating tablets were prepared. This may be used for the production of directly compressible tablets because AG is a free flowable powder. Therefore, various tablet batches containing varying proportions of AG/HPMC E4M, citric acid, glycine and sodium bi carbonate have been prepared. The results of lag time matrix integrity is depicted..

A mixture of glycine and sodium bi carbonate releases 1 moles of CO_2 / gm when reacted with acids (Delcour *et al*., 1991). However, reaction between citric acid and sodium bi carbonate releases 3 moles of CO_2 of water (Hans *et al., 2*010). Therefore, for the floating tablets we classify effervescent agents depending upon their CO_2 releasing capacity in to two categories –mild and strong CO_2 producing agents.

4.5 EVALUATION OF POWDER BLENDS

Direct compression technique was organised for CNZ and DOM tablets. Different parameters were determined while characterizing the powder mixture of CNZ and DOM.

Angle of slow down is the measure of the frictional forces among the atoms which provides an insight into flow properties of powder and granules, electrostatic properties and their tendency to bridge in a cone shaped hopper. The resting angle of values up to 40 suggests a reasonable flow potential, and those above 50 suggest that the substance only flows with considerable difficulties (Wells and Aulton, 1988). For physical properties, i.e. bulk density, tapped density, angle of repose and Hausner's ratio, powder mixture are measured. The resting angle findings (<30) demonstrate strong flow characteristics of the tablet powder mixture. Hausner's ratio is attributed to interparticle friction and may be used as such to predict the properties of powder streaming. In general, a value lower than 1.25 implies strong flow properties. Thus, the results supported that the tablet blend is flowable and suitable for direct compression.

4.6 EVALUATION OF NON PHARMACOPOEIAL AND PHARMACOPOEIAL TESTS OF TABLETS

The test of the weight variation tablets revealed that these lots were USP compliant. The hardness was calculated by means of a texture analyser that shows tablets tougher and can endure stress throughout packaging or transport. The tablet thickness was less than 1gm/cm3,

showing the floating existence of the tablets (Rangariya et al., 2012). Furthermore, the findings showed that there was no major impact on the multiple assessment studies, regardless of the type of drug (CNZ or DOM) used.

4.7 BIOADHESIVE STRENGTH OF FLOATING TABLETS

When inserted into floating tablets, the bioadhesive property of AG was calculated in contrast to HPMC E4M. Compared to tablets containing HPMC E4M, the bioadhesion of tablets containing AG demonstrated a 2.7 fold improvement compared to tablets containing HPMC E4M. As a result, the finding indicated that AG was superior to bioadhesive and floating tablets.

CHAPTER 6

CONCLUSION AND FUTURE SCOPE

6.1 CONCLUSION

Since it is a simple substance of low aqueous and pH-dependent solubility, CNZ is widely absorbed from the stomach (Nagarwal et al., 2010). Depending on age, half-life removal ranged from 3.4 to 6.0 hours (Krukowska et al., 2007). Because of its high rate of degradation, the bioavailability of orally administered cinnarizine is usually limited and variable. (Kalava *et al*., 2005). Thus gastroretentive drug delivery system was formulated using cinnarizine for improving patient compliance.

Domperidone has very less solubility in alkaline pH and has good solubility in acidic pH (Prabakaran *et al.,* 2006). Hence, the good solubility in acidic pH and its low bioavailability makes domperidone a appropriate applicant for gastro retentive drug delivery system (Saritha *et al.,* 2012).

Thus, the present investigation is aimed at development of floating tablets prepared using acrylamide grafted corn fibre gum polysaccharide and its comparison with natural corn fibre gum and standard HPMC E4M polymer. For this purpose, corn fibre gum was grafted chemically to synthesize acrylamide grafted corn fibre gum polysaccharide (AG). The synthesis of AG was optimized by 3^2 full factorial design. The FTIR-ATR spectra and the DSC studies proved that the AG was successfully grafted.

The X-RD spectra of pure gum and AG suggested amorphous nature of both AG and pure gum. The SEM images further ensure that pure gum and AG were amorphous in nature. However, attaching of monomer onto pure gum gets regarding change the particle shape and size of pure gum .

The AG was then utilized for preparing bioadhesive floating tablets of cinnarizine or domperidone which were compared with pure gum or HPMC E4M. Various floating tablet batches were prepared with different effervescent agent i.e. mild (sodium bi carbonate) or (sodium bi carbonate with glycine) or strong (sodium bi carbonate with citric acid). This classification was on the basis of carbon dioxide releasing capacity. Further, the prepared tablets were calculated for their lag time behaviour. The lag time was found to follow the order $NaHCO_3$> $NaHCO_3$-glycine> $NaHCO_3$-citric acid. However, no important dissimilarity in floating time was experiential. Further, the findings indicated formulation prepared with a blend of glycine/ $NaHCO_3$ or citric acid/ $NaHCO_3$ and AG were found suitable in floating tablets that floated for 8hrs. Therefore formulation F7, F8, F13, F14, F21, F22, F23, F24, F25, F26 was chosen for further studies.

6.2 FUTURE SCOPE OF THE WORK

1. Floating drug delivery system is a system that can provide sufficient gastric retention which may help to provide sustained release dosage form by enhancing absorption and minimizing fluctuation.

2. The Drug absorption in the stomach is a variable process and depends on various factors such as gastric emptying, physiological factors etc. Different approaches for gastro retention are studied each having their own merits and demerits. Due to unpredictability of human GIT therefore development of efficient GRRD is a real challenge to pharmaceutical technological sector as the drug delivery.
3. Cinnarizine is a basic drug with poor aqueous and pH dependent solubility (0.29 mg/ml, in 0.01 N HCl (pH 2.0), 0.002 mg/ml in pH 6.5 phosphate buffer) but it is extensively absorbed from stomach (Nagarwal *et al*., 2010). Thus, gastroretentive drug delivery system can be formulated using cinnarizine for improving bioavailabity and hence patient compliance.
4. Domperidone has very less solubility in alkaline pH but has good solubility in acidic pH (Prabakaran *et al.,* 2006). Hence, the low bioavailability and good solubility in acidic pH makes domperidone a suitable candidate for gastro retentive drug delivery system (Saritha *et al*., 2012).
5. Since a single excipient that could float as well as adhere to the walls of stomach for prolonged release gastroretentive drug delivery systems was the need of the hour. Therefore, acrylamide grafting of natural corn fibre gum was done that bears both mucoadhesive as well as floating behaviour.
6. The development of floating bioadhesive system of cinnarizine and domperidone using natural polymer will help in effectively delivering drug to systemic/ local circulation with improving efficiency of various type of pharmacotherapy's.

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