Development of gastroretentive sustained release drug delivery system for certain antibiotic and its *in-vitro* and *in-vivo* evaluation

A Thesis Presented By

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"**Pharmaceutics**"

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Chapter 1:

Development and evaluation of ofloxacin floating drug delivery system.

This chapter aims to preparation and *in-vitro* evaluation of ofloxacin floating tablets using different hydrophilic swelling polymers to localize the dosage form in the stomach in order to achieve gastric retention, and hence increase drug stability, sustainment and patient compliance leading to better treatment outcomes.

Full factorial design using Design Expert® software was used to prepare different formulations where evaluation of significant factors was done by Analysis of variance (ANOVA).

A 2^3 full factorial model was developed to study the main effects of three factors namely: the type of polymer (X1), the concentration of polymer (X2), and the concentration of sodium bicarbonate (X3). The floating lag time, floating duration, percentage release after 8 hr, percentage released after 24 hr, and absorption half-life were chosen as dependent variables.

Eight formulae of ofloxacin floating tablets were prepared. Characterization of ofloxacin floating tablet was investigated:

- Compatibility of ofloxacin with different pharmaceutical excipients was investigated using visual examination, differential scanning calorimetry (DSC) and Fourir transform infrared (FT-IR) spectrophotometery confirm the absence of any chemical interaction.
- Angle of repose, Carr's index and Hausner's ratio used to investigate blend characterization that showed acceptable blend flow properties.
- The prepared formulae showed that all tablet formulae had acceptable weight values between 689 and 709 mg.
- Hardness study showed that all tablet formulae had acceptable hardness values between 9.
- Friability study showed that all tablet formulae had acceptable friability values by having percent friabilityless than 1%.
- All formulae were found to confirm to pharmacopoeial limits (85 to 115 % w/w) with respect to the mean values of ofloxacin content.
- According to ANOVA test results the only factor having significant effect on the floating duration was the polymer type (X2) where the formulae

containing HPMC K100M had significantly higher floating lag time than that of the formulae containing HPMC K15M ($p = 0.0002$).

- According to the factorial ANOVA test results, the only factor had a significant effect on Q8, Q24 was the polymer type (X2) where the formulae containing HPMC K100M had significantly slower release profile than that formulae containing HPMC K15M ($p = 0.0005$, $p = 0.0030$) respectively.

- The formulae containing HPMC K100M had significantly higher $t_{50\%}$ than that of the formulae containing HPMC K15M ($p < 0.0001$).

Numerical optimization was performed using Design Expert® software to minimize FLT and maximize FD, Q8, Q24 and $t_{50\%}$.

- The formula B6 that was prepared using Lower concentration of HPMC K100M and higher concentration of sodium bicarbonate giving the highest desirability with a value of 0.489.

- B6 was selected for the comparative pharmacokinetic study.

<u>Chapter 2:</u>Development and evaluation of ofloxacin size increasing drug delivery system.

This chapter aims to prepare directly compressed size increasing tablet of ofloxacin by using different polymers,in order to obtain a first configuration enables oral intake and a second configuration after intake which permit gastro-retention of the dosage form and hinder its passage from the pyloric sphincter to a certain time, then evaluation of the matrices for *in-vitro* drug release properties. Full factorial design using Design Expert® software was used to prepare different formulations where evaluation of significant factors was done by ANOVA.

A 2^3 full factorial model was developed to study the main effects of three factors namely: the type of polymer (X1), the concentration of polymer (X2), and the concentration of PVP K30 (X3). The increase in tablet size at 0.5 hr (Q0.5) (Y1), The increase in tablet size at 8 hr (Q8) (Y2), percentage release after 8 hr (Q8) (Y3), percentage released after 24 hr (Q24) (Y4), and absorption half-life ($t_{50\%}$) (Y5) were chosen as dependent variables.

Eight formulae of ofloxacin size increasing tablets were prepared. Characterization of ofloxacin floating tablet was investigated:

- Compatibility of ofloxacin with different pharmaceutical excipients was investigated using visual examination, DSC and FT-IR that confirm the absence of any chemical intereaction.

- Angle of repose, Carr's index and Hausner's ratio used to investigate blend characterization that showed acceptable blend flow properties.
- The prepared formulae showed that all tablet formulae had acceptable weight values between790 and 850 mg.
- Hardness study showed that all tablet formulae had acceptable hardness values between 6.5 and 9 kg.
- Friability study showed that all tablet formulae had acceptable friability values by having percent friability less than 1%.
- All formulae were found to confirm to pharmacopoeial limits (85 to 115 % w/w) with respect to the mean values of ofloxacin content.
- According to the ANOVA test results the only factor having significant effect on SI Q0.5 was the polymer type (X1) where the formula containing PEO wsr303 had significantly higher SI Q0.5 than that of the formulae containing HPMC K100M ($p = 0.0083$).
- While both polymer type (X1) and polymer concentration (X2) had a significant effect on SI Q8, where the formula contains higher concentration of PEO wsr303 had significantly higher SI Q8 than other formulae ($p = 0.0008$ and $p = 0.0005$) respectively.
- According to the ANOVA test results there is no factor having significant effect on Q8, while the only factor had significant effect on Q24 was the polymer type (X1), where the formulae containing PEO wsr303 had significantly slower release profile than formulae containing HPMC K100M ($p = 0.0182$).
- According to the ANOVA test results there is no factor having significant effect on $t_{50\%}$.

Numerical optimization was performed using Design Expert® software to maximize SI Q0.5, SI Q8, Q8, Q24 and $t_{50\%}$.

- The formula B5 that was prepared using lower concentration of PEO wsr303 and low concentration of PVP K30 giving the highest numerical desirability with a value of 0.423.
- B5 was selected for the comparative pharmacokinetic study.

Chapter 3: *In-vivo* comparative study of selected ofloxacin formulations and conventional tablet.

Pharmacokinetic study was done to compare the absorption and disposition kinetics of three tablets products containing ofloxacin equivalent to 400 mg ofloxacin/tablet in six healthy male volunteers. These three products are two **Test products**; floating gastroretentive tablet and size increasing gastroretentive tablet, and a **Reference product**; Tarivid® tablet (2x200) mg/tablet manufactured by Aventis Pharma Deutschland GmbH, Germany.

The bioavailability of a single oral dose of 400 mg was assessed for ofloxacin included in the test and reference products by comparing the pharmacokinetic parameters derived from the plasma concentration-time profiles.

The study outcome will provide scientific value for the two developed formulations and may help commercial development, it will ensure safe and clinically reliable management of bacterial infections using interchangeable generic product therefore benefiting society by lowering treatment costs and increase patient compliance.

Key words

Ofloxacin, gastroretentive, invitro and invivo evaluation, floating tablets, size increasing tabelts

esults were expressed as mean values ± SD One way analysis of variance (ANOVA) was performed using Statistical Analysis System SAS® Univeristy Edition Software (Online).Development of Gastro-Retentive Sustained Release Drug Delivery System for Certain Antibiotic and Its *in-vitro* and *in-vivo* Evaluation

INTRODUCTION

Oral administration is the most convenient and preferred means of drug delivery to the systemic circulation and it can achieve improved therapeutic advantages (1). Unlike the majority of parenteral dosage forms, it allows ease of administration by the patient, patient compliance and flexibility in formulation.

Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects.

Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolic excretion.Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects (2, 3).

Among types of oral modified release delivery systems are 1) delayed release (e.g., by using an enteric coating); 2) extended release (ER) (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention).

Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics (4). Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as mini-tablets, pellets, beads or granules, either as coated (reservoir) or matrix devices (5).

Extended release DDS offer several advantages compared to conventional DDS including (6):

A. Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub-therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects.

B. Reducing the administered dose while achieving comparable effects.

C. Reduced frequency of administration leading to improved patient's compliance and subsequently improved efficacy of the therapy and cost effectiveness.

D. Targeting or timing of the drug action. Hence, it is highly desirable to develop sustained DDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

On the other hand, they may have some disadvantages including:

A. Longer time to achieve therapeutic blood levels.

B. Variation in bioavailability and liability to dose dumping

C. These systems are usually more expensive compared to conventional systems.

D. Individual differences in higher and lower steady state drug level in different individuals.

Drugs administered as sustained or extended release oral dosage form should comply with the following parameters:

(A) Maintain a constant plasma level over prolonged time periods.

Have a broad therapeutic window to avoid health hazard to the patient in case of undesirable burst release of the nominal dose (7).

The maximum achievable sustained drug release is subject to inter individual variations, with an average gastrointestinal transit time of around 24 hr in humans (8). The transit time is affected by age, gender, body mass index and the state of health of the individual as well as his emotional state and composition of meals. In addition, drugs affecting gastric motility, such as opioid analgesics or metoclopramide, have to be taken into account.

Numerous oral sustained drug delivery systems have been developed to prolong drug release. The key point in this respect is that the API has to be absorbed well throughout the whole gastrointestinal tract (GIT). Generally, the absorption of APIs from oral DDS is precluded by several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired regions of the GIT and the high variable nature of gastric emptying process (9).

The gastric emptying process can vary from a few minutes to 12 hr, depending upon the physiological state of the subject and the design of pharmaceutical formulation. This variation, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine (9).

In addition, the relatively brief gastric emptying time in humans, through the stomach or upper part of the intestine (major absorption zone), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose.

Gastro-retentive drug delivery systems

Gastric retention is designed to prolong gastric residence time of oral controlled release dosage forms (10). The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance (11).

Gastroretentive dosage forms help in sustaining drug delivery mainly for drugs that show site specific absorption from the upper intestine or from the stomach. This encompasses drugs which have local action in the stomach such as antacids and drugs acting locally on the ulcers. Also, drugs which have narrow absorption window from the upper intestine such as actively transported drug.

Physiological factors affecting gastric retention

I. The gastric emptying process

The stomach is anatomically divided into three parts: fundus, body and pylorus (pyloric antrum and pyloric sphincter). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region, pylorus, is the major site for mixing motions, acting as pump to accomplish gastric emptying (12).

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility have been identified, feeding results in a lag time prior to the onset of gastric emptying (11).

Factors affecting the gastric emptying and hence the gastric retention time of an oral dosage form include (13):

A. Size, shape and density of the dosage form

The effect of size of floating and non-floating dosage forms on the gastric emptying was studied and it was concluded that the floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the non-floating units, which lie in the antrum region and are propelled by the peristaltic waves (14).

Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multi-particulate formulations as compared with single unit formulations, which suffer from "all or none concept". As the units of multi-particulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulation (15).

It was reported that tetrahedron and ring-shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is equally important as a formulation parameter (16).

B. Concomitant ingestion of food, its nature, caloric content and frequency of intake

Generally, the residence time of food in the stomach depends upon its nutritive and physical properties: emptying of liquid nutrients has a rate of 200 kcal / hr, regardless of whether those calories are in the form of fats, proteins or carbohydrates. Non-nutrient liquids empty rapidly, with a time to 50% emptying of 8-18 min. Solids empty much more slowly than liquids.

Solid or semisolid fats, after being consumed and warmed to body temperature in the stomach, are converted into a liquid. Due to a nervous mechanism inhibiting gastric peristalsis and floating over gastric liquids, liquid fats empty much more slowly than aqueous liquids (17).

A comparison was made to study the effect of fed and non-fed stages on gastric emptying. For this study, all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase has not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

It was reported that the mean GRT of a bilayer floating capsule of misoprostol was 199 ± 69 min after a single light meal (breakfast). However, after a succession of meals, the data showed a remarkable prolongation of the mean GRT, to 618 ± 208 min. Obviously, when the gastroretentive properties of a floating dosage form is independent of meal size, it can be suggested that the dosage form will be suitable for patients with a wide range of eating habits(18).

Interestingly, most of the studies related to effects of food on GRT of floating systems share a common viewpoint that food intake is the main determinant of gastric emptying, while the specific gravity has only a minor effect on the emptying process (19-22). Stated otherwise, the presence of food, rather than buoyancy, is the most important factor affecting GRT and floating doesn't invariably increase GRT. In fact, studies have shown that the gastric emptying time (GET) for both floating and non-floating single units are shorter in fasted subjects (less than 2 hr), but are significantly prolonged after a meal (around 4 hr) (20, 22).

In another study, it was found in the fed state, floating tablets prolonged the GET by an average of 6 hr over that of uncoated, non-disintegrating tablets; however in the fasted state, the floating tablets didn't significantly prolong GET and both tablets had much shorter emptying times compared to the fed state (23).

Drugs such as anticholinergic agents (e.g. atropine, propantheline); opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride) (24).

C. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease.

The effects of gender, posture and age on the GRT of an indigestible solid was investigated, the authors found that the mean ambulatory GRT in males was significantly faster than in their age (±3 years) and race-matched female counterparts. Further, the data indicated that women emptied their stomach slower than men, regardless of weight, height, body surface area and even when the hormonal changes due to menstrual cycle were normalized(25).

The mean GRT for volunteers in the supine state was not statistically significant from that in the upright, ambulatory state. In the case of elderly, the GRT was prolonged, especially in subjects > 70 years old. Stress increase gastric emptying rates while depression slows it down (24).

The resting volume of the stomach is 25 to 50 mL, Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves (26).

Recently, a triple radionuclide scintigraphic technique has been described for intragastric monitoring that allowed the measurement of the effects on GRT of galenic parameters (size, density of matrices), as well as of physiological parameters such as subject posture (27). Studies were conducted in non-fasting human volunteers either in upright or in supine posture, who concurrently were given one optimized floating and one non-floating hydrophilic matrix capsules of the same size, and three different sizes.

In the upright subjects, all of the floating forms stayed continuously above the gastric contents irrespective of their size, whereas the non-floating units sank rapidly after ingestion and never rose back to the surface thereafter. Thus, in upright subjects, all the floating forms were protected against postprandial emptying. Consequently, the floating forms showed prolonged and more reproducible GRTs compared to the non-floating forms.

However, there was no significant difference between the mean GRTs of the small, medium, and large floating units. These findings indirectly confirm that the intra-gastric buoyancy of the floating forms is the main factor determining their prolonged GRTs and protecting them from random gastric emptying related to antral peristaltism (28). The mean GRTs of the non-floating forms were much more variable and highly dependent on their size, which were in the order of small < medium < large units.

Moreover, in supine subjects, a size effect influenced the GRT of both the floating and non-floating forms. The floating forms were more often emptied before the non-floating forms, but size for size, the mean GRT did not differ in the aggregate.

Bennett et al have also demonstrated the role of posture in gastric emptying. They observed that an alginate raft emptied faster than food in subjects lying on their left side or on their backs and slower in subjects lying on their right side with raft positioned in the greater curvature of the stomach (29). This is because when the subjects lay on their left side, the raft was presented to the pylorus ahead of the meal and so emptied faster (30).

II. The gastric pH

It is influenced by many factors like diet, disease, presence of gases or fatty acids, and other fermentation products, age, pathological conditions, as well as intra- and inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs (1, 13).

It has been reported that the mean value of gastric pH in fasted healthy males is 1.7 ± 0.3 while that of females was reported to be slightly lower (31), In fed state, the mean gastric pH in healthy males has been reported to be between 4.3 – 5.4 (32).

About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5. Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH. In addition, drugs like H_2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion (33).

Drug candidates for gastric retention

Gastroretentive DDSs exhibiting controlled drug release are significantly important for drugs which are (34):

i. Acting locally in the stomach (e.g. antibiotics against Helicobacter Pylori, antacids and misoprostol).

ii. Absorbed incompletely due to a relatively narrow window of absorption in the GIT, such as cyclosporin, ciprofloxacin, furosemide, L-DOPA, p-aminobenzoic acid and riboflavin.

iii. Drugs that are absorbed in the proximal part of the gastrointestinal track and are less soluble in or degraded by the alkaline pH such as captopril, verapamil HCl, diazepam and chlordiazepoxide.

Gastroretentive DDS, on the other hand, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents and drug substances that are unstable in the strong acidic environment of the stomach. In addition, gastroretentive systems do not offer significant advantages over conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract (13).

Approaches to gastric retention

Among most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include a) Bioadhesive systems, b) size increasing systems, which are either due to expansion or shape modification or swelling, c) density controlled systems which are either, high density systems or effervescent systems, and d) magnetic system.

A. Bioadhesive systems

This approach exploit the interaction between the mucosa and bioadhesive polymers where a delivery device localize within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner(12).

It involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GIT. These are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate. It was concluded that anionic polymers have better binding capacity than neutral or cationic polymers (35).

The proposed mechanism of bioadhesion is the formation of hydrogen – and electrostatic bonding at the mucus-polymer boundary. Rapid hydration in contact with the mucoepithelial surface appears to favor adhesion.

Although the concept of bioadhesion gains increasing interest in alternative routes of administration (e.g., nasal, buccal, ocular, vaginal and rectal), gastroretentive bioadhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach. High turnover rate of the gastric mucous leads to difficulties in retaining a bioadhesive system at site (36, 37).

Furthermore, it is difficult to specifically target the gastric mucus with bioadhesive polymers. In addition, the possibility of esophageal binding might present a challenge regarding safety aspects (38).

B. Size-increasing systems

This approach involves retaining the dosage form in the stomach by increasing its size above that of the pyloric sphincter. Due to significant inter-individual variations, the cutoff size cannot be given exactly, but its diameter was reported to be 12.8 ± 7.0 mm (39).

In order to facilitate swallowing, the dosage form should have an initially small size. Once in the stomach, the dosage forms should quickly increase in size, to prevent premature emptying through the pylorus. In order to avoid accumulation following multiple administrations, the system should be cleared from the stomach after a predetermined time interval (40).

The increase in the system's size can be based on several principles, including expansion due to swellable excipients or unfolding and / or shape modification (to complex geometric shapes) in the stomach.

- **Expanding swellable systems**

Swelling systems are also referred to as plug type system. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT (13).

The accuform technology of depomed is based on a blend of polymers with the API, which forms a gel like substance in the GIT, which prevents the drug from passing through the pyloric opening and releases the drug in a controlled manner.

Glumetza®, a commercially available product by Depomed, Inc., Menlo Park, CA, USA, is a gastric retentive extended-release tablet formulation of 500 or 1000 mg metformin that provides effective, sustained and well tolerated glycemic control with once daily administration (41, 42).

Proquin® XR is another commercially available product by Depomed, based on the accuform technology. It is an antibiotic containing 500 mg ciprofloaxacin and is indicated for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of Escherichia coli and Klebsiella pneumonia (43).

A controlled-release gastric retention system composed of a swellable core, which consisted of the drug, chlorphenamine maleate or riboflavin 5′ phosphate, and the expanding agents polyvinyl pyrrolidone (PVP), Carbopol 934P and calcium carbonate was developed. The tablet core was coated with a permeable coating, consisting of blends of Eudragit RL® 30 D and NE 30 D in different ratios. The tablets swelled to 2- 4 times their original volume, while releasing the drug in a conrolled manner. The optimal ratio of Eudragit® RL 30 D: NE 30 D was found to be 70:30, which was optimum for sufficient elasticity to withstand the pressure of expansion during the initial swelling phase, and allowing the breakdown of the tablet following release of the drug(44).

- **Unfolding and modified shape systems**

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device.

Devices with different geometrical shapes such as continuous solid stick, tetrahedron, ring, cloverleaf, planer disk, string and pellet/sphere were investigated. These systems consist of at least one erodible polymer (e.g., Eudragit® E, hydroxypropyl cellulose (HPC)), one non-erodible polymer (e.g., polyamides, polyolefins, polyurethanes), and a drug dispersed within the polymer matrix.

The devices are compressible to a size suitable for swallowing within a capsule, and are self-expandable to a size, which prevents their passage through the pylorus. Furthermore, they are sufficiently resistant to forces of the stomach to prevent rapid passage through the pylorus for a predetermined period of time, and erode in the presence of gastric juices.

In-vivo studies in beagle dogs have been performed to study the systems physical characteristics, such as size, shape and flexibility on the gastric emptying, after they were folded and placed in a gelatin capsule. The tetrahedron-shaped devices remained in the stomach for longer periods of time than the other shapes, while strings and pellets were eliminated fairly rapidly (45).

C. Density controlled systems

- **High density systems**

These devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice (~1.004 g/cm), the device settles down to the bottom of the stomach, and remains located below the pylorus. This could be accomplished by including a heavy inert material such as zinc oxide, titanium dioxide, iron powder or barium sulphate (46, 47) into the drug containing core pellets or coating drug containing pellets with it. These materials increase density by up to 1.5–2.4 g/cm^3.

However, it has been reported that such devices did not significantly extend the gastric residence time Effectiveness in human subjects was not observed and no system has been marketed (48, 49).

- **Floating systems**

Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (≤ 1.004 g/cm), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations in some cases (50).

  - **Non-effervescent floating drug delivery systems**

Systems with initially low density are highly desired, since they prevent the risk of premature emptying from the stomach. Inherent low density can be provided by entrapment of air or by the incorporation of low density materials, such as fatty substances or oils or foam powder (51, 52).

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharrides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene.

The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration, this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Polycarbonate microspheres by solvent evaporation technique was developed (53). Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated bio fluids as evidenced by scanning electron microscopy (SEM).

High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to- polymer ratio increased both their mean particle size and release rate of drug. Floating tablets of captopril using HPMC (4000 and 15000 cps) and carbopol 934P was developed (54).

In-vitro buoyancy studies revealed that tablets of 2 kg/cm^2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm^2 sank for 3 to 4 min. and then came to the surface. Tablets in both cases remained floating for 24 hr. The tablet with 8 kg/cm^2 hardness showed no floating capability. It was concluded that the buoyancy of the 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 (porosity).

A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24 hr controlled release from the dosage form of captopril was achieved.

Floating alginate beads was prepared by incorporating amoxycillin. The beads were produced by dropwise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved (11).

Single unit floating tablets based on polypropylene foam powder and matrix-forming polymer was prepared. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% w/w foam powder (based on mass of tablet) was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively (55).

Floating micro particles of ketoprofen was prepared by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 with Eudragit RL were used. The formulation containing 1:1 ratio of the 2 above mentioned polymers exhibited high percentage of floating.

Particles in all the examined media as evidenced by the percentage of particles floated at different time intervals. This can be attributed to the low bulk density, high packing velocity, and high packing factor (56).

HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule was developed, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released (57).

- **Effervescent floating drug delivery systems**

This approach provides floating drug delivery systems based on the formation of carbon dioxide (CO_2) gas. It utilizes effervescent components such as sodium bicarbonate ($NaHCO_3$) or sodium carbonate, and additionally citric or tartaric acid (58). Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme.

The CO_2 generating components may be mixed with the tablet matrix components, producing a single layered tablet or compressing the gas generating components in a hydrocolloid containing layer and the drug in another layer formulated for a sustained release effect, thereby producing a bilayer tablet. This concept has also been exploited for floating capsule systems as well as for multiple unit drug delivery systems (59, 60).

Madopar HBS®, an anti-Parkinson's agent, is a commercially available product marketed by Hoffmann-LaRoche. It contains 100 mg levodopa and 25 mg benserazide. It consists of a gelatin capsule, designed to float on the surface of the gastric fluids. After the gelatin shell dissolves, a mucous body is formed that consists of the active drugs and other substances. The drugs diffuse from the hydrated boundary layers of the matrix at the desired rate (61).

Valrease® is another floating capsule, marketed by Hoffmann-La Roche. It contains 15 mg diazepam, which is more soluble at low pH; therefore, absorption is more desirable in the stomach. The drug components form a soft gelatinous mass in the stomach and are released gradually. The HBS system maximizes the dissolution of the drug by prolonging the gastric residence time (62).

Liquid Gaviscon®, a floating liquid alginate preparation, is used to suppress gastroesophageal reflux and alleviate the symptoms of heart burn. The formulation consists of a mixture of alginate, which forms a gel of alginic acid, and a carbonate or bicarbonate component, evolving CO_2 upon reaction with the acidic content of the stomach. The formed gel entraps the CO_2 formed, and consequently floats on the stomach contents (63).

Topalkan® is a third-generation aluminum magnesium antacid, which also contains alginic acid in its formula. It has antipeptic and protective effects with respect to the mucous membrane of the stomach and esophagus, and provides, together with magnesium salts, a floating layer of the preparation in the stomach (64).

Almagate flotcoat® is another novel antacid formulation that confirms a higher antacid potency together with a prolonged gastric residence time and a safe as well as extended delivery of antacid drugs (65). Cifran® OD tablets a gas generating formula containing ciprofloxacin HCl as an active ingredient used as an antibiotic (66).

D. Magnetic systems

This system is based on: the dosage form contains small internal magnet, and a magnet placed on the abdomen over the position of the stomach.

This technique was used in rabbits with bioadhesive granules containing ultrafine ferrite (γ-Fe_2O_3). They guided them to the to the esophagus with an external magnet (~1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 hr (67).

A magnetic tablet containing 50% w/w ultra-ferrite with hydroxypropylmethylcellulose (HPMC) and cinnarizine was formulated. In beagle dogs, the tablet remained in the stomach for 8 h by the application of a magnetic field (1000 to 2600 G). Absorption of cinnarizine was sustained and the area under the plasma concentration-time-curve values (AUC_{0-24}) increased (68).

A method for determining the gastrointestinal transit of magnetic dosage forms under the influence of extracorporeal magnet, using a pH-telemetering capsule (Heidelberg capsule) was developed (69). Small magnets were attached to the capsule and administered to humans. Using an extracorporeal magnet, GRT of the dosage form was less than 6 hr compared with 2.5 hr control. Two years later, the same group proposed oral acyclovir depot tablets with internal magnets.

In-vivo human studies showed that the plasma concentrations of acyclovir were significantly higher after 7, 8, 10 and 12 hr. Furthermore, the
$AUC_{0-24}$was ~2800 ng.h/mL with the external magnet and ~1600 ng.h/mL without(70).

Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise the patient compliance (71, 72)

Aim of work

In this manuscript, novel floating and size increasing compression tablets were formulated for the gastric retention of ofloxacin. We hypothesize that polymers can be utilized for promoting floating of tablets with short lag time. On the other hand, the size increasing tablets will achieve the required swelling of tablets after short period of time. therefore, sustained drug release from tablets will be achieved using different polymers.

To verify this hypothesis, the novel compression tablets were formulated and statistically analyzed by response surface model using Design-Expert® software. Furthermore, the *in-vivo*

performance of the optimized formula was assessed by pharmacokinetic determination in healthy human volunteers and analyzed using SAS®.

The study outcome will provide scientific value for the two developed formulations and may help commercial development, it will ensure safe and clinically reliable management of bacterial infections using interchangeable generic product therefore benefiting society by lowering treatment costs and increase patient compliance.

Summery

Gastric retention is designed to prolong gastric residence time of oral controlled release dosage forms. Prolonged contact time of drug with the gastrointestinal mucosa, leads to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance.

It helps in sustaining drug delivery mainly for drugs that show site specific absorption from the stomach or the upper intestine.

oOfloxacin is a broad-spectrum antimicrobial fluoroquinolone which has activity against a wide range of gram-negative and gram-positive microorganisms. It's an off-white to pale yellow crystalline powder.

Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate <50 mL/min), and dosage adjustment is necessary.

The work in this thesis is divided into three chapters as follows:

Chapter 1: Development and evaluation of ofloxacin floating drug delivery system.

Chapter 2: Development and evaluation of ofloxacin size increasing drug delivery system.

Chapter 3:*In-vivo* comparative study of selected ofloxacin formulations and conventional tablet.

Conclusion

Based on the previous results,

1) the formula B6 that was prepared using Lower concentration of HPMC K100M and higher concentration of sodium bicarbonate was selected for the comparative pharmacokinetic study.
2) the formula B5 that was prepared using lower concentration of PEO wsr303 and low concentration of PVP K30 was selected for the comparative pharmacokinetic study.
3) Based on the results of the *in-vivo* study, the floating preparation had achieved significant enhancement in sustaining ofloxacin.