FORMULATION AND EVALUATION OF FLOATING TABLETS OF CIPROFLOXACIN HCL

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Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation [1]. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery [2]. These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels [3].

Now-a-days most of the pharmaceutical scientists are involved in developing an ideal drug delivery system (DDS). An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period [4].

Controlled release drug delivery systems:

Controlled release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable rate and optimizes the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dosing [2],[4].

In general controlled delivery attempts to [5]:-

a) Sustain drug action at a predetermined rate by maintaining a relatively constant and effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.
b) Localize drug action by spatial placement of controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.
c) Target drug action by using carriers or chemical derivatization to deliver drugs to a particular target cell type.

In practice, very few of the applied systems embrace all of these actions. In most cases the release system creates constant concentration of drug within the body over an extended period of time. In order to maintain a constant drug level in either plasma

or target tissue, release rate from controlled release system should be equal to the elimination rate from plasma or target tissue. The most conventional method to achieve a constant plasma level is the use of intravenous infusion. However, this would be inconvenient for most therapeutic situations so that other non-invasive route such as the oral or transdermal route is preferred.

For conventional drug delivery systems, rate-limiting step in drug availability is usually absorption of drugs across a biological membrane such as the gastrointestinal wall. However in a sustained / controlled release product one aims for release of drug from the dosage form as the rate limiting step. Thus drug availability is controlled by the kinetics of drug release rather than absorption [5].

Advantages of controlled release dosage forms [6]:

Some of the advantages of controlled release (CR) dosage forms (DFs) include,

- Reduction in dosing frequency.
- Reduced fluctuation in circulating drug levels.
- Increased patient compliance.
- Avoidance of night time dosing.
- More uniform effect
- Reduction in gastrointestinal (GI) irritation.
- Reduction in other dose-related side effects.

Disadvantages of controlled release dosage forms:

Controlled release dosage forms (CR-DFs) have several potential disadvantages. They include,

- Cost, Unpredictable, Often poor in vitro – in vivo correlation.
- Dose dumping, reduced potential for dosage adjustment.
- Increased potential for first pass clearance leading to poor systemic availability.
- In general effective drug release period is influenced and limited by GI residence time [6].

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed only in a particular portion of GIT or are absorbed to a different extent in various segments of the GIT. An absorption window exists because of physiological, physicochemical or biochemical factors. The pH dependent solubility and stability level of a drug plays an important role in its absorption. Because most drugs are absorbed by passive diffusion of the unionized form, the extent of ionization at various pH levels can lead to non-uniform absorption or an absorption window. The presence of certain enzymes in a particular region of the GIT also can lead to regional variability in absorption of drugs that are substrates of these enzymes [2].

Drugs having site-specific absorption are difficult to design as oral CRDDS, because the drug released in the region preceding and in close vicinity to the absorption window is only available for absorption. After crossing the absorption window the released drug goes to waste with negligible or no absorption. This drastically decreases the time available for drug absorption after its release and jeopardizes the success of the delivery system [2].

The design of oral controlled drug delivery systems (DDS) is primarily aimed to achieve more predictable and increased bioavailability. However these systems have several physiological difficulties, such as inability to restrain and localize the DDS

within desired regions of the GI tract and highly variable nature of gastric emptying process.

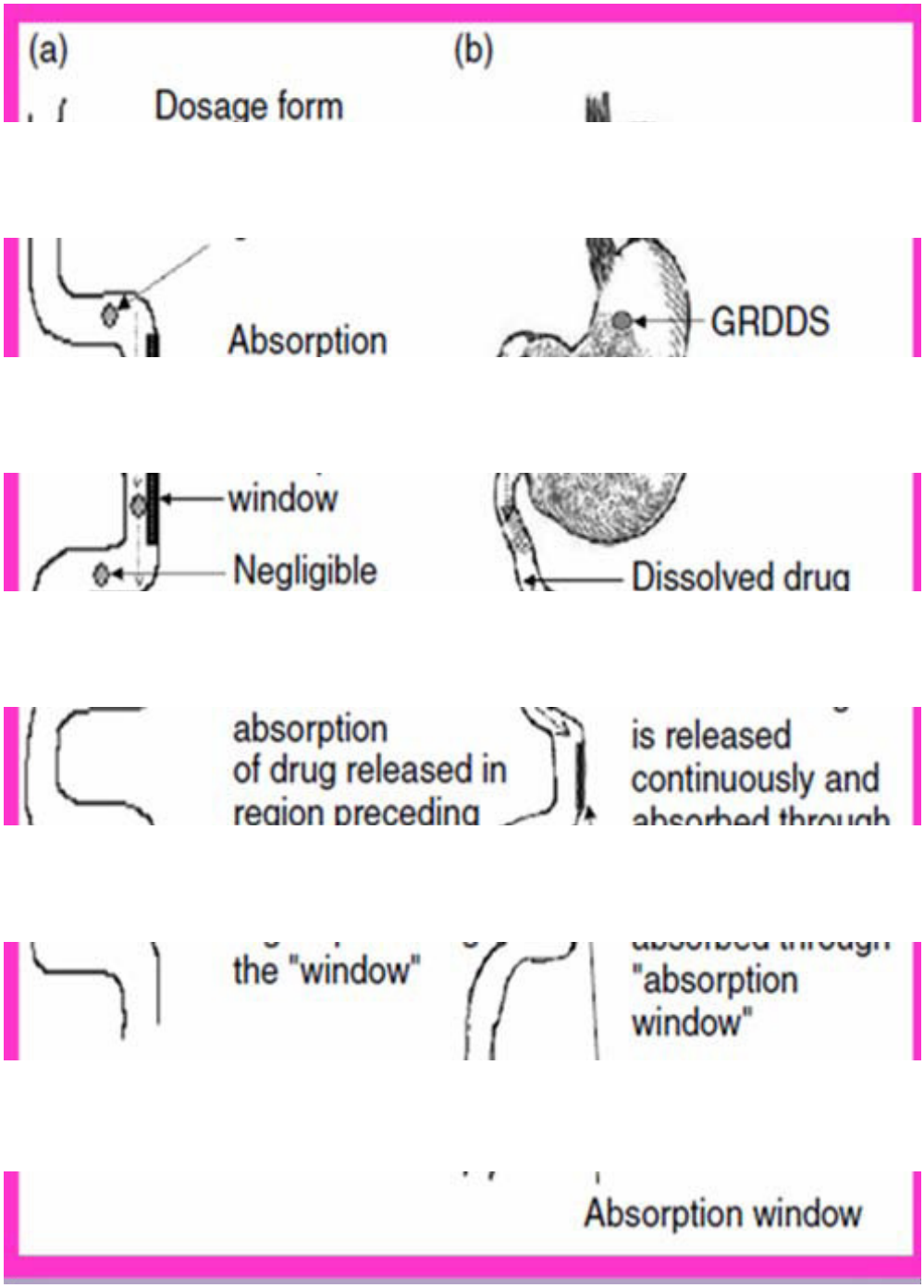
Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release from DDS leading to diminished efficacy of administered dose. The intimate contact of the DDS with absorbing membrane has the potential to maximize drug absorption and may also influence rate of drug absorption. These considerations are development of oral controlled gastro retentive dosage forms [4].

GASTRO RETENTIVE DRUG DELIVERY SYSTEMS:

Dosage form is retained in stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS is improved controlled delivery of drugs and absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability [2].

Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to enhanced absorption properties e.g. large surface area, or enhanced solubility in stomach as opposed to the more distal parts of the GIT [8].

Figure 1: Drug absorption in the case of (a) Conventional dosage forms (b) Gastro retentive drug delivery systems [2].



Certain types of drugs using gastro retentive devices include [7]:-

- Drugs acting locally in stomach e.g. Antacids
- Drugs that are primarily absorbed in stomach e.g. Albuterol
- Drugs that are poorly soluble at an alkaline pH
- Drugs with a narrow window of absorption e.g. drugs that are absorbed mainly from the proximal small intestine e.g. Riboflavin, Levodopa
- Drugs absorbed rapidly from GI tract e.g. Amoxicilin
- Drugs that degrade in colon e.g. Metoprolol.

Longer residence time in stomach could be advantageous for local action in the upper part of small intestine, for example treatment of peptic ulcer disease.

Advantages of Gastro retentive drug delivery systems [9]:

- Enhanced bioavailability.
- Enhanced first-pass biotransformation.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuations of drug concentration.
- Improved selectivity in receptor activation.
- Reduced counter-activity of the body.
- Extended time over critical (effective) concentration.
- Minimized adverse activity at the colon.
- Site specific drug delivery.

Ideal drug candidates for compounding into GRDFs [8]:

a) Drugs stable in gastric milieu.

b) Drugs having narrow absorption window.

c) Drugs to be used for gastro-duodenal local therapy.

Drugs incorporated into GRDFs [8]:

The following are the list of drugs that have been incorporated into GRDFs as microspheres, granules, capsules, tablets or pills.

Acyclovir	Alendronate	Atenolol
Captopril	Cinnarizine	Ciprofloxacin

Cisapride	Furosemide	Glipizide
Ketoprofen	Levodopa	Misoprostol
Nicardipine	Riboflavin	Tetracycline
Verapamil	Diltiazem	

Disadvantages of Gastro retentive drug delivery systems [9]:

- The drugs that may irritate the stomach lining.
- The drugs are unstable in its acidic environment should not be formulated in gastro retentive systems.
- Isosorbide dinitrate are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

Limitations of Gastro retentive drug delivery systems [2]:

- Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
- Requires the presence of food to delay gastric emptying.
- Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.
- In case of bioadhesive systems, the acidic environment, thick mucus as well as high turnover rate of mucous prevents bond formation at the mucous-polymer interface.
- For swellable systems, the dosage form maintaining a size is larger than the aperture of the resting pylorus for required time period.

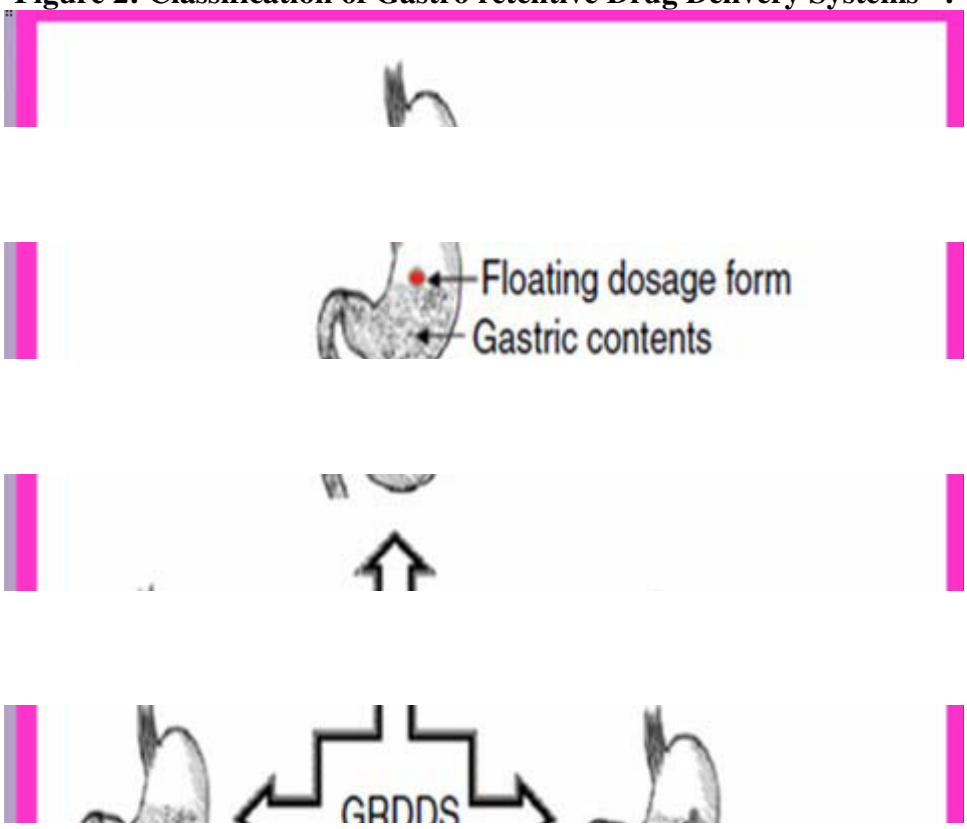
APPROACHES TO GASTRIC RETENTION:

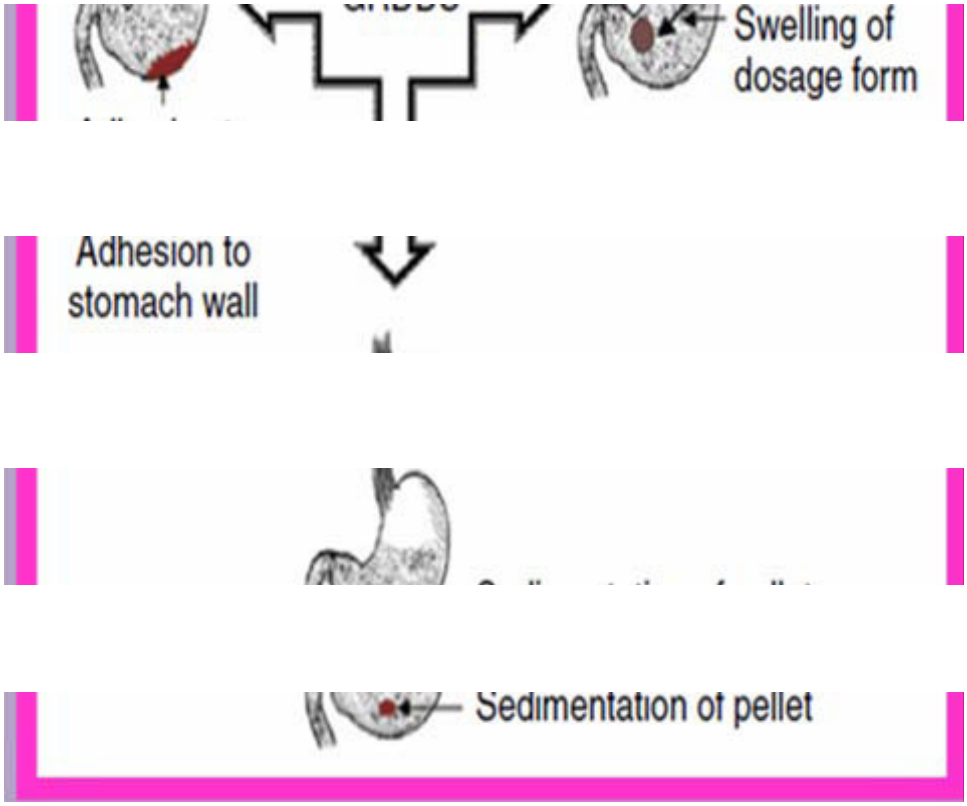
A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These include –

a) Floating systems:

Floating Drug Delivery Systems (FDDS) have a bulk density is lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result is increase in GRT and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two types, non-effervescent system and effervescent systems [1].

Figure 2: Classification of Gastro retentive Drug Delivery Systems [2].





b) Bio/Muco-adhesive Systems [2]:

Bio/muco-adhesive systems are bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending GRT of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

Binding of polymers to mucin/epithelial surface can be divided into three categories:-

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems [2],[4],[8]:

These are dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. This system is named as "plug type system", since they exhibit tendency to remain logged at the pyloric sphincter.

d) High Density Systems [1],[2],[3]:

These systems with a density of about 3 g/cm^3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

e) Incorporation of Passage Delaying Food Agents [10]:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

f) Ion Exchange Resins [11]:

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, sink quickly.

g) Raft Systems [7]:

Incorporated alginate gels that have a carbonate component and upon reaction with gastric acid to give bubbles form in the gel enabling floating.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) [3],[12],[13]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System and

B. Non – Effervescent System.

A. Effervescent Systems:

This effervescent systems are prepared with swellable polymers such as Methocel or polysaccharides e.g., chitosan and effervescent components, e.g. sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature.

The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelyfiedhydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy [3].

The effervescent systems are classified into two types.

I. Gas generating Systems
II. Volatile liquid / Vacuum containing Systems.

I. Gas generating Systems:

1. Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)
2. Intragastric bilayer floating tablets
3. Multiple unit type floating pills

II. Volatile liquid / Vacuum containing Systems:

1. Intragastric floating Gastrointestinal Drug Delivery System
2. Inflatable Gastrointestinal Delivery System
3. Intragastric Osmotically Controlled Drug Delivery System

B. Non – Effervescent Systems [3],[4]:

Used gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid

after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier.

The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release as the drug is slowly released by controlled diffusion through the gelatinous barrier.

Non-effervescent systems include the following:
1. Single layer floating tablets
2. Bilayer floating tablets
3. Alginate Beads
4. Hollow Microspheres

Anatomy and Physiology of Stomach:

The stomach is located in the left upper part of the abdominal hollow under the diaphragm, between the lower end of the oesophagus and the small intestine and is the most dilated part of the GIT [8],[14]. Its opening to the duodenum is controlled by pyloric sphincter. The stomach has four main regions namely cardia, fundus, body and pylorus [14]. Its size varies according to the amount of distention up to 1500 ml following a meal; after food has emptied, a 'collapsed' state is obtained with a resting volume of only 25-50ml [8].

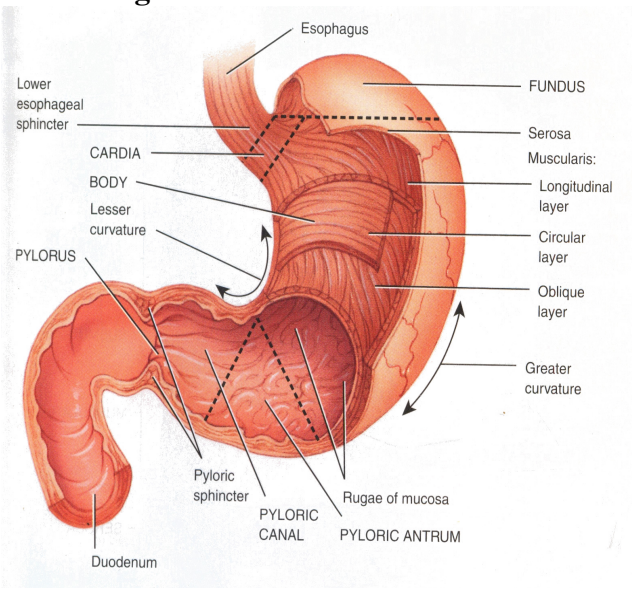
The two major functions of the stomach are [14]:

- To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate.
- To reduce ingested solids to chyme by the action of acid and enzymatic digestion.

Owing to its small surface area compared to the small intestine very little drug absorption occurs in stomach [14]. Storage is the main function of the fundus and body, whereas mixing and grinding takes place in the antrum. The fundus helps to adjust the increased volume during eating by relaxing its fundus muscle fibres and also exerts a steady state pressure on gastric content, pressing them towards distal stomach. To

pass through pyloric valve into the small intestine the particle size should be in the range of 1 to 2mm [4].

Figure 3: Structure of stomach



The stomach has a capacity of approximately 1.5 L, although under fasting conditions it usually contains no more than 50 ml of fluid, which are mostly gastric secretions.

These include [14]:

- Acid secreted by the parietal cells, which maintains pH of the stomach between 1.0 and 3.5 in fasted state.
- The hormone gastrin, which is a potent stimulator of gastric acid production.
- Pepsin, which is secreted by peptic cells.
- Mucus that is secreted by surface mucosal cells and lines the gastric mucosa. In the stomach, mucus protects the gastric mucosa from auto digestion by pepsin-acid combination.

Gastric volume is important for dissolution of dosage form in-vivo. The resulting volume of stomach is 25-50ml. gastric pH affects absorption of drugs from CR-DFs. There is a large volume difference in gastric secretion in normal and achlorohydric individuals. It affects in-vivo dissolution of drugs when administered with 180 ml of water. The pH of stomach in fasted condition is about 1.5 – 2.0 and in fed condition is

2 – 6. The administration of large volume of water with dosage form changes the pH of stomach to the pH of water initially and this does not improve dissolution of basic drugs. Generally basic drugs will have a better change to dissolve in fed condition than in fasted condition [4].

Food buffers and neutralizes gastric acid, thus increasing the pH up to about 6.5. After meal-ingestion is completed, the pH rapidly falls back to below 5.0 and then gradually declines to fasting state values over a period of few hours. The pyloric sphincter has a diameter of 12.8±7 mm in humans and act as a sieve as well as a mechanical stricture to the passage of large particles [8].

Gastric emptying:

The time a dosage form takes to traverse the stomach is usually termed gastric emptying rate. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes and 2 hours, although much longer times (over 12 hours) have been recorded, particularly for large single units [14].

The GI tract is in a state of continuous motility consisting of two modes:

a) Interdigestive motility pattern.
b) Digestive motility pattern

The former is dominant in the fasted state with a primary function of cleaning up the residual content of upper GIT tract [7].

The fasted state is associated with various cycle events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into the following phases.

- Phase I (Basal state):- The quiescent period, lasts from 30-60 minutes and is characterized by lack of secretory, electrical and contractile activity.
- Phase II (Preburst state):- It exhibits intermittent action for 20-40 minutes during which contractile motions increase in frequency and size. Bile enters the

duodenum during this phase, while gastric mucus discharge occurs during the latter part of phase II and throughout phase III.

- Phase III (Burst state):- It is characterized by intense large and regular contractions, termed housekeeper waves, that sweep off undigested food and lasts 10-20 minutes. Maximal pyloric opening, characterizes this phase which enables efficient evacuation of the stomach contents.
- Phase IV is the transition period of 0-5 minutes between phase III and I [2].

This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state repeating every 2-3 hours [2]. Concentration of the hormone motilin in blood controls the duration of the phases. The administration of food rapidly interrupts the MMC cycle and the digestive phase is allowed to take place [7].

The motor activity in the fed state is induced 5-10 minutes after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hours and more typically 3-4 hours. The stomach churns food, while suspended fine particles typically in a size of less than 1mm are emptied through the pylorus into the duodenum [8].

The pyloric sphincter allows liquids and small food particles to empty while other material is retropulsed into the antrum of the stomach and caught up by the next peristaltic wave for further size reduction before emptying. Thus in the fed state liquids, pellets and disintegrated tablets will tend to empty with food, yet large sustained or controlled release dosage forms can be retained in the stomach for longer period of time [14].

When CRDDS are administered in fasted state, the MMC in any of its phases, which can significantly influence total GRT and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it is affect the

time of dosage form spends in the region preceding and around the window. The less time spent in that region the lower the degree of absorption. Therefore the design of GRDDS take into consideration resistance of the dosage form to gastric emptying during phase III of MMC in fasted state and continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS is functional quickly after administration and able to resist the onslaught of physiological events for the required period of time [2].

Emptying of DFs from the stomach:

Non-disintegrating DFs, like other indigestible solids are administered in the fasting state, they typically are not retained in stomach for over 2 hours due to the MMC. On the other hand in fed condition the GRT of non-disintegrating DFs depends mostly on the DF size as well as composition and caloric value of food. In general, GRT of DFs and in particular large DFs is longer in fed state in comparison to fasting state. Large DFs are retropelled from pyloric antrum for further digestion and evacuation at the end of fed state or are retained until arrival of the subsequent 'housekeeper wave'. In such cases GRT is a function of the length of digestive process. Thus theoretically continuous feeding can prolong GRT of DF for more than 24 hours [8].

Gastrointestinal Transit Time [4]:

Food contents remain in each segment of the GIT for different periods of time. The residence time for both liquid and solid foods in each segment of the GIT is reported as follows:

Table 1: Residence time

Segment	Liquid	Solid
Stomach	10 - 30 min	1 – 3 hours
Duodenum	< 60 sec	< 60 sec
Jejunum and Ileum	3 ± 1.5 hours	4 ± 1.5 hours
	-	20 – 50 hours

Colon		

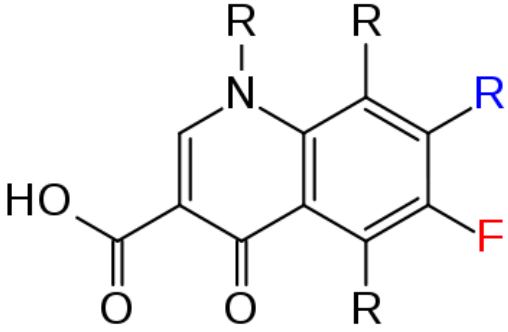
Quinolone:

The quinolones are a family of synthetic broad-spectrum antibiotics. The term quinolone(s) refers to potent synthetic chemotherapeutic antibacterials [15].

The first generation of the quinolones begins with the introduction of nalidixic acid in 1962 for treatment of urinary tract infections in humans. Nalidixic acid was discovered by George Lesher and coworkers in a distillate during an attempt at chloroquine synthesis [16].

Quinolones, in comparison to other antibiotic classes, have the highest risk of causing colonization with Methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile. For this reason, a general avoidance of fluoroquinolones is recommended based on the available evidence and clinical guidelines. The majority of quinolones in clinical use belong to the subset fluoroquinolones, which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7 position [17].

Figure 4: Essential structure of all quinolone antibiotics: the blue drawn remainder of R is usually piperazine; if the connection contains fluorine (red), it is a fluoroquinolone.



The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favorable safety and tolerability profiles. A new four-generation classification of the quinolone drugs takes into account the expanded antimicrobial spectrum of the more recently introduced fluoroquinolones and their clinical indications.

- First-generation drugs (e.g., nalidixic acid) achieve minimal serum levels.
- Second-generation quinolones (e.g., ciprofloxacin) have increased gram-negative and systemic activity.
- Third-generation drugs (e.g., levofloxacin) have expanded activity against gram-positive bacteria and atypical pathogens.
- Fourth-generation quinolone drugs (currently only trovafloxacin) add significant activity against anaerobes.

The quinolones can be differentiated within classes based on their pharmacokinetic properties. The new classification can help family physicians prescribe these drugs appropriately [21].

Classification of Quinolone Antibiotics [21]:

1. First generation
   a. Nalidixic acid (NegGram)
   b. Cinoxacin (Cinobac)
2. Second generation
   a. Norfloxacin (Noroxin)
   b. Lomefloxacin (Maxaquin)
   c. Enoxacin (Penetrex)
   d. Ofloxacin (Floxin)
   e. Ciprofloxacin (Cipro)
3. Third generation
   a. Levofloxacin (Levaquin)
   b. Sparfloxacin (Zagam)
   c. Gatifloxacin (Tequin)
   d. Moxifloxacin (Avelox)
4. Fourth generation
   a. Trovafloxacin (Trovan)

Medical uses:

Fluoroquinolones are broad spectrum antibiotics that play an important role in the treatment of serious bacterial infections, especially hospital acquired infections and others in which resistance to older antibacterial classes is suspected.

Because the use of broad spectrum antibiotics encourages the spread of multi-drug resistant strains and the development of Clostridium difficile infections, treatment guidelines from the Infectious Disease Society of America, the American Thoracic Society, and other professional organizations recommend minimizing the use of fluoroquinolones and other broad spectrum antibiotics in less severe infections and in those in which risk factors for multi-drug resistance are not present.

Adverse effects:

In general, fluoroquinolones are well tolerated, with most side effects being mild to moderate. On occasion, serious adverse effects occur. Some of the serious adverse effects that occur more commonly with fluoroquinolones than with other antibiotic drug classes include CNS and tendon toxicity.

The currently marketed quinolones have safety profiles similar to those of other antimicrobial classes. Fluoroquinolones are sometimes associated with a QTc interval prolongation and cardiac arrhythmias, convulsions, tendon rupture, torsade de pointes and hypoglycemia.

These adverse reactions are a class effect of all quinolones; however, certain quinolones are more strongly associated with increased toxicity to certain organs. For example, moxifloxacin carries a higher risk of QTc prolongation, and gatifloxacin has been most frequently linked to disturbed blood sugar levels, although all quinolones carry these risks.

Some quinolones were withdrawn from the market because of these adverse events (for example, sparfloxacin was associated with phototoxicity and QTc prolongation, thrombocytopenia and nephritis were seen with tosufloxacin and hepatotoxicity with

trovafloxacin). Simultaneous use of corticosteroids is present in almost one-third of quinolone-associated tendon rupture. The risk of adverse events is further increased if the dosage is not properly adjusted, for example if there is renal insufficiency.

Contraindications:

Quinolones are contraindicated if a patient has epilepsy, QT prolongation, pre-existing CNS lesions, CNS inflammation or those who have suffered a stroke. There are safeties concerns of fluoroquinolone use during pregnancy and, as a result, are contraindicated except for when no other safe alternative antibiotic exists.

However, one meta-analysis looking at the outcome of pregnancies involving Quinolone use in the first trimester found no increased risk of malformations. They are also contraindicated in children due to the risks of damage to the musculoskeletal system. Their use in children is not absolutely contraindicated, however. For certain severe infections where other antibiotics are not an option, their use can be justified.

Quinolones should also not be given to people with a known hypersensitivity to the drug. Quinolone antibiotics should not be administered to patients who are dependent on benzodiazepines, since they compete directly with benzodiazepines at the GABA-A receptor, acting as a competitive antagonist and thus possibly precipitating a severe acute and potentially fatal withdrawal effect.

Pharmacology:

The basic pharmacophore, or active structure, of the fluoroquinolone class is based upon the quinoline ring system [18]. The addition of the fluorine atom at C6 is what distinguishes the successive-generation fluoroquinolones from the first-generation quinolones. The addition of the C6 fluorine atom has since been demonstrated to not be required for the antibacterial activity of this class [19].

Various substitutions made to the quinoline ring resulted in the development of numerous fluoroquinolone drugs available today. Each substitution is associated with

a number of specific adverse reactions, as well as increased activity against bacterial infections, whereas the quinoline ring, in and of itself, has been associated with severe and even fatal adverse reactions.

Mechanism of action:

Quinolones and fluoroquinolones are chemotherapeutic bactericidal drugs, eradicating bacteria by interfering with DNA replication. Quinolones inhibit the bacterial DNA gyrase or the topoisomerase II enzyme, thereby inhibiting DNA replication and transcription. Recent evidence has shown eukaryotic topoisomerase II is also a target for a variety of quinolone-based drugs [20].

Quinolones inhibit the bacterial DNA gyrase or the topoisomerase II enzyme, thereby inhibiting DNA replication and transcription. Recent evidence has shown eukaryotic topoisomerase II is also a target for a variety of quinolone-based drugs. Thus far, most of the compounds that show high activity against the eukaryotic type II enzyme contain aromatic substituents at their C-7 positions.

Quinolones can enter cells easily via porins and, therefore, are often used to treat intracellular pathogens such as Legionella pneumophila and Mycoplasma pneumoniae. For many Gram-negative bacteria, DNA gyrase is the target, whereas topoisomerase IV is the target for many Gram-positive bacteria. However, there is debate concerning whether the quinolones still have such an adverse effect on the DNA of healthy cells, in the manner described above, hence contributing to their adverse safety profile. This class has been shown to damage mitochondrial DNA.

Mechanism of toxicity:

The mechanisms of the toxicity of fluoroquinolones has been attributed to their interactions with different receptor complexes such as blockade of the GABAa receptor complex within the central nervous system, leading to excitotoxic type

effects and oxidative stress. The severity of oxidative stress generated by fluoroquinolones has been described as 'enormous' by the authors of one research study and they suggested co-administration of anti-oxidants when using fluoroquinolones to minimise the potential for oxidative related cellular damage.

Interactions:
Theophylline, nonsteroidal anti-inflammatory drugs and corticosteroids enhance the toxicity of fluoroquinolones.

Products containing multivalent cations, such as aluminium- or magnesium-containing antacids and products containing calcium, iron, or zinc, invariably result in marked reduction of oral absorption of fluoroquinolones.

Other drugs that interact with fluoroquinolones include antacids, sucralfate, probenecid, cimetidine, warfarin, antiviral agents, phenytoin, cyclosporine, rifampin, pyrazinamide, andcycloserine.

Many fluoroquinolones, especially ciprofloxacin, inhibit the cytochrome P450 isoform CYP1A2. This inhibition causes an increased level of, for example, antidepressants such as amitriptyline and imipramine, clozapine (an atypical antipsychotic), caffeine, olanzapine (an atypical antipsychotic), ropivacaine (a local anaesthetic), theophylline (a xanthine), and andzolmitriptan (a serotonin receptor agonist).

Antibiotic misuse and bacterial resistance:
Resistance to quinolones can evolve rapidly, even during a course of treatment. Numerous pathogens, including Staphylococcus aureus, enterococci, and Streptococcus pyogenes now exhibit resistance worldwide. Widespread veterinary usage of quinolones, in particular in Europe, has been implicated.

Fluoroquinolones have been recommended to be reserved for the use in patients that are seriously ill and may soon require immediate hospitalization. Though considered

to be very important and necessary drugs required to treat severe and life-threatening bacterial infections, the associated antibiotic misuse remains unchecked, which has contributed to the problem of bacterial resistance. The overuse of antibiotics such as happens with children suffering from otitis media has given rise to a breed of super bacteria that are resistant to antibiotics entirely.

History:

Nalidixic acid is considered to be the predecessor of all members of the quinolone family, including the second, third and fourth generations commonly known as fluoroquinolones. This first generation also included other quinolone drugs such as pipemidic acid, oxolinic acid, and cinoxacin, which were introduced in the 1970s.

They proved to be only marginal improvements over nalidixic acid. Though it is generally accepted nalidixic acid is to be considered the first quinolone drug, this has been disputed over the years by a few researchers who believe chloroquine, from which nalidixic acid is derived, is to be considered the first quinolone drug, rather than nalidixic acid.

Since the introduction of nalidixic acid in 1962, more than 10,000 analogs have been synthesized, but only a handful have found their way into clinical practice.

Social and economic impact:

Increased hospitalizations attributed to adverse drug reactions alone account for billions of dollars each year within the US healthcare system. Severe reactions do occur with the fluoroquinolone class and can add significantly to the cost of care. Antibacterial adverse effects account for nearly 25% of all adverse drug reactions among hospitalized patients.

Patent extensions:

Under the George W. Bush administration (2001–2009), patent extension legislation that allowed Bayer AG, as well as other drug companies, a six-month patent extension

for testing their products for safety in children was signed into law. It has been estimated that Bayer AG's revenue increased an extra $358 million due to ciprofloxacin's pediatric patent extension. The legislation was drafted after extensive lobbying of numerous members of Congress by Bayer AG and others. One of the four sponsors of this legislation was Chris Dodd (D-CT), who, at the time, ranked as one of the top three beneficiaries of campaign contributions by drug companies. Sen. Edward Kennedy (D-MA), who chaired the committee with jurisdiction over the bill, refused to fight over the language that (if it had been included) would have reduced the drug company's profits due to these patent extensions. The reasons for Sen. Edward Kennedy's decision not to fight for the inclusion of this language were not made known.

Ciprofloxacin is a synthetic antibiotic of the fluoroquinoline drug class. It is a second-generation fluoroquinoline antibacterial. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops synthesis of DNA and protein [15].

Ciprofloxacin interacts with other drugs, herbal and natural supplements, a characteristic it shares with other widely used antibacterial drugs such as amoxicillin, trimethoprim, azithromycin, cephalexin and doxycycline [22].

Medical uses:

Ciprofloxacin is used to treat a number of infections including: infections of bones and joints, endocarditis, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, chancroid [23].

Availability:

Ciprofloxacin is available as tablets, intravenous solutions, eye and ear drops.

Bagherwal et al. [24] (2010) formulated floating tablets of Ciprofloxacin Hcl belong to the fluoroquinoline derivatives which is widely used in the long term therapy for treatment of a wide range of infections including anthrax, biliary tract infection, bone and joint infection, gastrointestinal including traveler's diarrhoea and campylobacter enteritis, shiegella, meningococcal meningitis prophylaxis, surgical infection prophylaxis, tuberculosis, leprosy and topically in the treatment of eye infections. Hence there is a potential need for floating tablet as sustained release dosage form for this drug. HPMC and carbomer are the polymers, used as suspending agent, viscosity increasing agent and tablet binder coating agents. In the present study, it was aimed to formulate floating tablet of ciprofloxacin Hcl with HPMC and carbomer in different proportion (4%, 8% and 12%) by direct compression techniques using polymers lactose, Magnesium Stearate, talc with sodium bicarbonate.

Mukhopadhyay et al. [25] (2010) formulated floating-bioadhesive tablets of Ciprofloxacin Hcl is mainly absorbed in the proximal areas of the gastrointestinal tract thus the purpose of our study was formulation of floating-bioadhesive tablets to increase the stay period of drug in its absorption area and decrease the dosing interval by increasing the bioavailability. Floating-bioadhesive tablets were prepared by direct compression technique using polymer like hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), carbopol in different ratios. The effervescent base was prepared by using 1:1 ratio of sodium bicarbonate and citric acid. It was observed that tablet with 5% effervescent base shows greater control in drug release in comparison to that of 10%.

Sahoo et al. [26] **(2007)** formulated floating microspheres of Ciprofloxacin Hcl by cross-linking technique. A polymeric mixture of sodium alginate and hydroxy propyl methyl cellulose (HPMC) was used. Sodium bicarbonate was used as gas forming agent. The solution was dropped to 1% calcium chloride solution containing 10% acetic acid for carbon dioxide release and gel formation. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped morphology and in-vitro release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that sodium bicarbonate had a pronounced effect on various parameters.

Danki et al. [27] **(2010)** studied the development of hydrodynamically balanced system (HBS) of Alfuzosin Hcl as an anti-hypertensive drug designed to increase the gastric residence time, thus prolonging the drug release. HPMC of different viscosity grades to prepared HBS by direct compression technique. The drug polymer ratio, viscosity grades of HPMC, gas generating agents was found to increase drug release and floating property of prepared HBS. All HBS formulation showed good in vitro floating property. It was found that three viscosity grades of HPMC (K4M, K15M, K100M) HPMC K4M along with lactose as diluents were found to be beneficial in improving the drug release rate and floating property.

Chandira et al. [28] **(2010)** formulated floating tablets of Itopride hydrochloride, a novel prokinetic drug, were developed to prolong the gastric residence time and there by increase drug bioavailability. Floating tablets were fabricated; using direct compression method containing Itopride hydrochloride, polymers HPMC K100M, HPMC K15M and carbopol 934 P, along with gas generating agent sodium bicarbonate and citric acid. The results found that tablets containing 125 mg HPMC

K100M, 40 mg HPMC K15M, and 40 mg carbopol provides a better option for 24 hours release action and improved bioavailability

Rao et al. [29] (2009) formulated and optimized the floating drug delivery system of cephalexin. Tablets were prepared by direct compression method incorporating HPMC K4M, xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent. The diffusion exponent of krosmeyer - peppas for optimized formulation was found to be 0.635 which significantly indicated the mechanism of drug release.

Bomma et al. [30] (2009) prepared floating matrix tablets of norfloxcin which were developed to prolong gastric residence time leading to an increase in drug bioavailability by using wet granulation technique using polymers such as HPMC K4M, HPMC K100M and Xanthan gum. The tablets exhibited controlled and prolonged drug release profile while floating over dissolution medium was confirmed as drug release mechanism from these tablets.

Thakkar et al. [31] (2008) formulated and evaluated the levofloxacin hemihydrate floating tablets that were prepared by direct compression method using gelucire 43/01 and HPMC polymers in different ratio. The in-vitro release study revealed the fact that the release rate of drug was decreased by increasing the proportions of gelucire 43/01 by 5 to 40% matrix tablets containing 25% HPMC K4M and 15% gelucire 43/01.

Jaimini et al. [32] (2007) formulated and evaluated famotidine floating tablets. They used Methocel K100 and Methocel K15M with effervescent mixture. It was observed that decrease in the citric acid level increased the floating lag time but tablets floated for longer duration. A combination of sodium bicarbonate (130 mg) and citric acid

(10 mg) was found to achieve optimum in-vitro buoyancy. They reported that tablets prepared with K100 had longer floating time compared with formulations containing Methocel K15M.

Ali et al. [33] (2007) formulated hydrodynamically balanced system for metformin as a single unit floating capsule. The formulation was optimized on the basis of in – vitro buoyancy and in – vitro release in simulated fed state gastric fluid. Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in – vitro percentage release and was taken as the optimized formulation.

Narendra et al. [34] (2006) reported optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. They employed a 2^3 factorial design in formulating the GFDDS with total polymer content-to-drug ratio (X_1), polymer-to-polymer ratio (X_2), and different viscosity grades of HPMC (X_3) as independent variables. The results indicate that X_1 and X_2 – significantly affected the floating time and release properties but the effect of different viscosity grades of HPMC (K4M and K100M) was non-significant.

Rahman et al. [35] (2006) developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and in-vitro dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h in-vitro,

while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the higuchi release model and showed no significant change in physical appearance, drug content, floatability or in-vitro dissolution pattern after storage at 45ºC/75% RH for three months.

Srivastava et al. [36] (2005) prepared floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as HPMC K15M, K4M, Guargum (GG), and sodium carboxy methylcellulose (SCMC), alone or in combination and other standard excipients. Tablets were evaluated for physical characteristics like hardness, swelling index, floating capacity, thickness and weight variation. The effect of effervescent on buoyancy and drug release pattern was also studied. In-vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC- based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

Patel et al. [37] (2005) developed ranitidine floating tablets; in which they optimized types of filler, different viscosity grades of HPMC and its concentration. Two fillers namely Avicel pH 102 and Tablettose 80 were used. Study revealed that type of filler had significant effect on release of drug from hydrophilic matrix tablets (f2 value 41.30) and floating properties. Three different viscosity grades of HPMC namely K100 LV, K4M and K15M were used. Viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties. The drug release from hydrophilic matrices occurred via diffusion mechanisms following square root of time profile. Hardness of tablets had greater influence on floating lag time which

might be due to decreased porosity whereas the position of paddle and types of dissolution medium had no significant effect on drug release.

Dave et al. [38] (2004) reported a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxy propyl methylcellulose were evaluated for gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. They investigated the effect of citric acid and stearic acid on drug release profile and floating properties. They concluded that the proper balance between a release rate retardant and a release rate enhancer could produce a drug dissolution profile similar to a theoretical dissolution profile.

Amin et al. [39] (2004) developed a gastroretentive drug delivery system of ranitidine hydrochloride which was designed using guar gum, xanthan gum and HPMC. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine Hcl from a gastroretentive formulation.

Sangalli et al. [40] (2004) studied the process parameters and in-vitro performances of different HPMC viscosity grades as coating agents for an oral time and site controlled delivery system. Methocel E50 showed the best balance among process time, retarding ability, dimensions of the coated units and possibility of finely tuning the delay duration.

Li et al. [41] (2002) evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived

using 2x3 full factorial designs for calcium delivery. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100LV> E5 LV but different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior.

Aim:

The aim of the present study is to formulation and evaluation of floating tablets of Ciprofloxacin Hcl using HPMC by direct compression techniques.

A rationale for developing Ciprofloxacin Hcl as a gastroretentive dosage form, which is retained in the stomach for prolonged period of time and produces a constant input of drug to the absorption site.

This improves bioavailability of the drug, reduces frequency of dosing, thus minimizing side effects.

Objective:

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria.
It is absorbed completely (91 – 95%) after oral administration and having a biological half-life of 3 to 5 hrs. The drug should be administered twice a day.

The objective of the present study is to formulate the Ciprofloxacin Hcl floating tablets using HPMC (K100M, K4M and E50) in different ratio with sodium bicarbonate and lubricants by direct compression techniques.

Plan of Work:

1. Literature survey
2. Preformulation studies
   - Selection of the drug
   - Analytical characterization of the drug
   - Selection of the excipients
   - Characterization of the excipients
3. Standard calibration curve of drug
4. Formulation development
   - Formulation of the floating tablet
   - Effect of the formulation variables on the drug release, swelling and floating properties
5. Evaluation of tablets
   - Tablet characteristics
   - Floating properties
   - Water uptake
   - In-vitro drug release studies of tablets
6. Treatment of the dissolution data obtained with different kinetic release equations
7. Stability study of the optimized batch.

4.1. MATERIALS AND EQUIPMENTS:

Materials:

Table 2: List of Materials Used

S.No.	Materials	Manufacturer
1	Ciprofloxacin Hcl	Sreepathi Pharmaceuticals Ltd., India.
2	HPMC (K100M, K4M, E50)	Taian Ruitai Cellulose Co. Ltd., China.
3	Sodium bicarbonate	RFCL Ltd., India.
4	Talc	Golcha Group, India.
5	Magnesium stearate	Loba Chemie Pvt. Ltd., India.

Equipments:

Table 3: List of Equipments Used

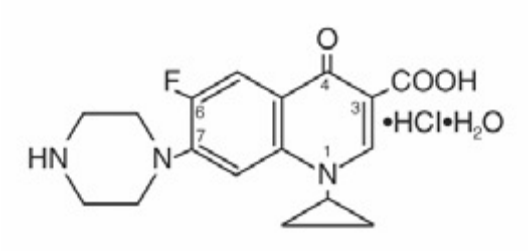
S.No.	Equipments	Manufacturers
1	Electronic Balance	Sartorius, India.
2	UV-VIS Spectrophotometer	Shimadzu, Japan.

3	FTIR Spectrophotometer	Shimadzu, Japan.
4	Rotary Tableting Machine	Fluidpack, India.
5	Dissolution Test Apparatus	Electrolab, India.
6	Vernier Calipers	Mitutoyo, Japan.
7	Hardness Test Apparatus	Monsanto, India.
8	Friability Test Apparatus	Electrolab, India.

4.2. DRUG PROFILE

CIPROFLOXACIN HYDROCHLORIDE [42],[43],[44],[45],[22]:
Ciprofloxacin Hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate.

Structure of Ciprofloxacin Hcl:



Empirical Formula:
$C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$

Molecular Weight: 385.82

Category:
Antibacterial

Dose:
The equivalent of 250 to 750 mg of ciprofloxacin twice daily (116 mg of ciprofloxacin hydrochloride is approximately equivalent to 100 mg of ciprofloxacin).

Description:
Faintly yellowish to light yellow crystalline substance.

Solubility:
Soluble in water; slightly soluble in acetic acid and in methanol; very slightly soluble in ethanol; practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane and in dichloromethane.

Storage:
Store in tightly-closed, light-resistant containers.

Standards:
Ciprofloxacin Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{17}H_{18}FN_3O_3$,Hcl, calculated with reference to the anhydrous substance.

Identification:
A: The infra-red absorption spectrum, Appendix 5.4, is concordant with the reference spectrum of ciprofloxacin hydrochloride or with the spectrum obtained from ciprofloxacin hydrochloride RS.

B: Complies with test B described under Ciprofloxacin using the following solutions in water containing (1) 1.0% w/v of the substance being examined and (2) 1.0% w/v of ciprofloxacin hydrochloride RS.

C: Gives the reactions of chlorides, Appendix 3.1.
Procedure:
Dissolve a quantity of the substance being examined equivalent to about 2 mg of chloride ion in 2 ml of water or use 2 ml of the prescribed solution. Acidify with dilute nitric acid, add 0.5 ml of silver nitrate solution, shake and allow to stand, a

curdy white precipitate is formed, which is insoluble in nitric acid but soluble, after being well washed with water, in dilute ammonia solution, from which is insoluble in nitric acid but soluble, after being well washed with water, in dilute ammonia solution, from which it is reprecipitated by the addition of dilute nitric acid.

pH:
Between 3.0 and 4.5, determined in a 2.5% w/v solution, Appendix 8.11.

Heavy metals:
Not more than 20 ppm, determined on 1.0 g by Method B, Appendix 3.12.

Sulphate:
0.375 g complies with the limit test for sulphates, Appendix 3.15 (400 ppm).

Sulphated ash:
Not more than 0.1%, Appendix 3.22.
Procedure:
Heat a silica or platinum crucible to redness for 10 minutes, allow to cool in a desiccator and weigh. Unless otherwise specified in the individual monograph, transfer to the crucible 1 g of the substance being examined and weigh the crucible and the contents accurately. Ignite, gently at first, until the substance is thoroughly charred. Cool, moisten the residue with 1 ml of sulphuric acid, heat gently until the white fumes are no longer evolved and ignite at 800° ± 25° until all black particles have disappeared. Conduct the ignition in a place protected from air currents. Allow the crucible to cool, add a few drops of sulphuric acid and heat. Ignite as before, allow to cool and weigh. Repeat the operation until two successive weighings do not differ by more than 0.5 mg.

Water:
Between 4.7 and 6.7% w/w, determined on 0.2 g, Appendix 3.24.

Assay:
Carry out the Assay described under Ciprofloxacin using the following solutions in the mobile phase. Solution (1) is a 0.05% w/v solution of the substance being examined. Solution (2) contains 0.05% w/v ciprofloxacin hydrochloride RS. Solution

(3) contains 0.05% w/v each of ciprofloxacin ethylenediamine analog RS and ciprofloxacin hydrochloride RS.

Calculate the content of $C_{17}H_{18}FN_3O_3$,Hcl from the declared content of $C_{17}H_{18}FN_3O_3$,Hcl in ciprofloxacin hydrochloride RS.

Mechanism of action [43]:

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division.

This mechanism can also affect mammalian cell replication. In particular, some congeners of this drug family (for example those that contain the C-8 fluorine) display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and in vivo tumor models. Although quinolones are highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is not known. Quinolone-induced DNA damage was first reported in 1986.

Recent studies have demonstrated a correlation between mammalian cell cytotoxicity of the quinolones and the induction of micronuclei. As such, some fluoroquinolones may cause injury to the chromosome of eukaryotic cells.

There continues to be debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe adverse reactions experienced by some patients following fluoroquinolone therapy.

Clinical Pharmacology [44]:

Absorption:

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin

maximum serum concentrations and area under the curve are shown in the chart for the 250 mg to 1000 mg dose range.

Table 4: Ciprofloxacin dose range of maximum serum concentration and area under curve

Dose (mg)	Maximum Serum Concentration (µg/ml)	Area Under Curve (AUC) (µg•hr/mL)
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1000	5.4	30.8

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 µg/ml respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

Distribution:

The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate.

Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions.

Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism:
Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Excretion:
The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 μg/ml during the first two hours and are approximately 30 μg/ml at 8 to 12 hours after dosing.

The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 ml/minute, exceeds the normal glomerular filtration rate of 120 ml/minute. Thus, active tubular secretion would seem to play a significant role in its elimination.

Adverse Effects [45]:
The serious adverse effects that may occur as a result of ciprofloxacin therapy include irreversible peripheral neuropathy, spontaneous tendon rupture and tendonitis, acute liver failure or serious liver injury (hepatitis), toxic epidermal necrolysis (TEN), and Stevens–Johnson syndrome, severe central nervous system disorders (CNS) and Clostridium difficile associated disease (CDAD: pseudomembranous colitis), as well as photosensitivity/phototoxicity reactions.

Interactions [22]:

The toxicity of drugs that are metabolised by the cytochrome P450 system is enhanced by concomitant use of some quinolones. Quercetin, a flavonol, occasionally used as a dietary supplement, may interact with fluoroquinolones, as quercetin competitively binds to bacterial DNA gyrase. Ciprofloxacin can reduce phenytoin plasma levels, which may, in some cases, result in seizures. Ciprofloxacin may interfere with the levels of thyroid medications resulting in hypothyroidism.

Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug.

Concurrent administration of ciprofloxacin with magnesium or aluminum antacids, sucralfate or products containing calcium, iron, or zinc(including multivitamins or other dietary supplements) may substantially decrease the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired.

Precautions [44]:

General:-

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin.

Central Nervous System:-

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia.

Renal Impairment:-

Alteration of the dosage regimen is necessary for patients with impairment of renal function.

Contraindications [44]:

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.There are only four contraindications found within the 2009 package insert:

- Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug.
- Concomitant administration with tizanidine is contraindicated.
- Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.
- Local I.V. site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions that resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Overdose [45]:

Overdose of ciprofloxacin may result in reversible renal toxicity. Treatment of overdose includes emptying of the stomach via induced vomiting or by gastric lavage. Administration of magnesium, aluminum or calcium containing antacids can reduce the absorption of ciprofloxacin. Hemodialysis or peritoneal dialysis removes only less than 10 percent of ciprofloxacin. Ciprofloxacin may be quantitated in plasma or serum to monitor for drug accumulation in patients with hepatic dysfunction or to confirm a diagnosis of poisoning in acute overdose victims.

4.3. POLYMER PROFILE

HYDROXYPROPYL METHYL CELLULOSE [46]:

Non-proprietory Names:

BP: Hypromellose
USP: Hydroxypropyl methyl cellulose 2208, 2906, 2910

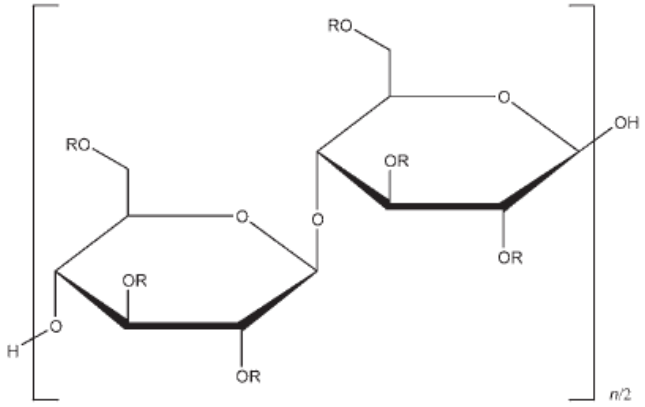
Synonyms:

Methyl hydroxypropyl cellulose, Methocel, Methyl cellulose propylene glycol ether.

Chemical Name and CAS Registry Number:
Cellulose Hydroxypropylmethyl ether [9004–65–3]

Molecular weight:
Approximately 10,000 to 15,00,000

Structural formula:



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category:
Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation:
Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations

between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.

High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use.

Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.

Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

Description:
An odorless and tasteless, white or creamy-white fibrous or granular powder.

Solubility:
Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

Acidity/alkalinity:
pH = 5.0–8.0 for a 2% w/w aqueous solution.

Viscosity:
HPMC K100M: 1,00,000 mPa-s
HPMC K4M: 4,000 mPa-s
HPMC E50: 50 mPa-s

Stability and Storage Conditions:
Very stable in dry conditions. Solutions are stable at pH 3.0 – 11.0. Stored in a well closed container, in a cool, dry place.

Incompatibilities:
Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Method of Manufacture:
A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce swollen alkali cellulose that is chemically more reactive than untreated cellulose.

The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

Handling Precautions:
Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in

nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

4.4. EXCIPIENT PROFILE

SODIUM BICARBONATE [46]:

Functional Category:
USP: Alkalizing agent
BP: Antacid; systemic alkalinizing substance

Synonyms:
Sodium hydrogen carbonate, sodium acid carbonate, baking soda

Chemical Name and CAS Registry Number:
Carbonic acid monosodium salt [144-55-8]

Empirical Formula: $NaHCO_3$

Molecular weight: 84.01

Applications in Pharmaceutical Formulation:
Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.

Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anesthetic solutions, and total parenteral nutrition (TPN) solutions. In some parenteral formulations, e.g. niacin, sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility.

Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes.

Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol, and improve the stability of levothyroxine. Sodium bicarbonate has also been included in formulations of vaginal bioadhesive tablets and in carbon dioxide releasing suppositories.

Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids; it has also been suggested as a means of preventing radiocontrast-induced nephrotoxicity. Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

Table 5: Uses of sodium bicarbonate

Use	Concentration (%)
Buffer in tablets	10–40
Effervescent tablets	25–50
Isotonic injection/infusion	1.39

Description:

An odorless, white crystalline powder with a slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

Acidity/alkalinity:

pH = 8.3 for a freshly prepared 0.1Maqueous solution at 258C; alkalinity increases on standing, agitation, or heating.

Solubility:
Water: 1 part in 11 parts (20ºC), 1 part in 4 parts (100ºC), Ethanol (95%; 20ºC): insoluble; Ether (20ºC): practically insoluble.

Melting point:
270ºC with decomposition.

Hygroscopicity:
At relative humidities below 80%, the moisture content is less than 1%. Above 85% relative humidity, it rapidly absorbs excessive amounts of water and may start to decompose.

Stability and Storage Conditions:
Upon heating at 250ºC to 300ºC, sodium bicarbonate decomposes and is converted into anhydrous sodium carbonate. Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

Incompatibilities:
Sodium bicarbonate reacts with acids, acidic salts and many alkaloidal salts, with the evolution of carbon dioxide. It can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum.

Method of Manufacture:

Sodium bicarbonate is manufactured either by passing carbon dioxide into a cold saturated solution of sodium carbonate, or by the ammonia–soda (Solvay) process, in which first ammonia and then carbon dioxide is passed into a sodium chloride

solution to precipitate sodium bicarbonate while the more soluble ammonium chloride remains in solution.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (chewing gums; ear drops; eye lotions; oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, soluble tablets, orodispersible tablets, and tablets; suppositories and suspensions) licensed in the UK.

TALC [46]:

Non-proprietory Names:
BP: Purified Talc
USP: Talc

Synonyms:
Hydrous magnesium calcium silicate; Hydrous magnesium silicate; Magnesium hydrogen metasilicate; Powdered talc; Talcum.

Chemical Name and CAS Registry Number:
Talc [14807-96-6]

Empirical Formula:
$Mg_6(Si_2O_5)_4(OH)_4$

Functional Category:
Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.

Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Table 6: Uses of talc

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

Description:
Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Acidity/alkalinity:
pH = 7–10 for a 20% w/v aqueous dispersion.

Solubility:
Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage Conditions:
Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. Stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

MAGNESIUM STEARATE [46]:

Synonyms:
Dibasic magnesium stearate; Magnesium distearate; Magnesium octadecanoate; Octadecanoic acid magnesium salt; Stearic acid magnesium salt.

Chemical Name and CAS Registry Number:
Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.24

Functional Category:
Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation:
Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description:
Magnesium stearate is a very fine, light white, impalpable powder, faint odor of stearic acid. The powder is greasy to the touch and readily adheres to the skin.

Solubility:
Practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions:
Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities:
Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Method of Manufacture:
Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

Handling Precautions:
Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

Regulatory Acceptance:
GRAS listed. Accepted as a food additive in the USA and UK. Included in the FDA Inactive Ingredients Database (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations; intravitreal implants and injections).

4.5. PREFORMULATION STUDIES [42],[47]:

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included description, solubility, pH, and compatibility studies.

a) **Description:**
Description of Ciprofloxacin Hcl was determined.

b) **Solubility:**
Solubility of Ciprofloxacin Hcl in water, 0.1N Hcl, acetone, acetonitrile and dichloromethane.

c) **pH:**
pH of Ciprofloxacin Hcl was determined to IP studies. Between 3 to 4.5 in a 2.5% w/v solution.

d) **Compatibility Studies:**

The compatibility of the drug and polymer under experimental conditions is an important prerequisite before formulation. It is necessary to confirm that the drug does not react with the polymer and affect the shelf life of the product. This can be confirmed by carrying out infrared spectroscopy studies.

Procedure: The obtained drug and polymer were subjected to IP studies. In the present study potassium bromide disc (pellet) method was employed and the obtained IR spectra were analysed comparatively, with reference spectrum of Ciprofloxacin Hcl.

4.6. METHODOLOGY [24]:

Floating tablets of Ciprofloxacin Hcl were prepared by direct compression technique using varying ratio of polymer such as HPMC (K100M, K4M and E50) with sodium bicarbonate as gas generating agent. The composition of each formulation is given in Table 7. The formulated tablets are given in Figure 5.
HPMC (K100M, K4M and E50) ratio used in the formulations F_1 is 1:2:3, F_2 is 1:3:2, F_3 is 1:1:1, F_4 is 2:1:3, F_5 is 2:3:1, F_6 is 3:1:2 and F_7 is 3:2:1.

Sifting:
Ciprofloxacin Hcl was passed through sieve no. 20 and collect in a clean bowl. HPMC K100M, HPMC K4M, HPMC E50 and sodium bicarbonate were passed through sieve no. 40 and collect in a clean bowl. Talc was passed through sieve no. 60 and collect in a clean bowl. Finally magnesium stearate was passed through sieve no.60 and collect in a separate clean bowl.

Mixing:
Ciprofloxacin Hcl was geometrical mixed with HPMC K100M, HPMC K4M, HPMC E50 and sodium bicarbonate for 10 minutes. Then talc was added and further mixed for 5 minutes.

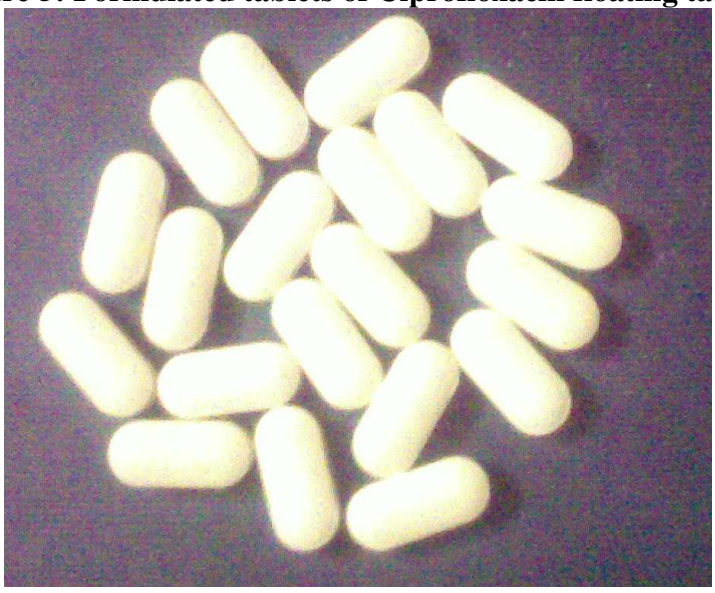
Lubrication:
After sufficient mixing of drug as well as other component, magnesium stearate was added and further mixed for additional 2 minutes.

Compression:
The lubricated granules were compressed by Rotary tableting machine. The weight of the tablet was kept constant for all formulations.

Table 7: Composition of Ciprofloxacin floating tablets

Ingredients (mg/tablet)	Batch Code						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Ciprofloxacin Hcl	500	500	500	500	500	500	500
HPMC K100M	20	20	40	40	40	60	60
HPMC K4M	40	60	40	20	60	20	40
HPMC E50	60	40	40	60	20	40	20
Sodium bicarbonate	100	100	100	100	100	100	100
Talc	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5
Total	730	730	730	730	730	730	730

Figure 5: Formulated tablets of Ciprofloxacin floating tablets



4.7. EVALUATION PARAMETERS:

A) Pre-Compression Parameters [48]:

i) Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighted amount of sample (5 gm) was transferred into a 25 ml measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 100 times on a plane hard wooden surface and the tapped volume of packing was recorded. LBD and TBD were calculated by the following formula:

$$\text{LBD (Loose bulk density)} = \frac{\text{Weight of granules}}{\text{Volume of packing}}$$

$$\text{TBD (Tapped bulk density)} = \frac{\text{Weight of granules}}{\text{Tapped volume of packing}}$$

ii) Compressibility Index:

Percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula:

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

iii) Hausner Ratio:

Hauser ratio was calculated by the following formula:

$$\text{Hausner ratio} = \frac{\text{TBD}}{\text{LBD}}$$

iv) Angle of Repose (θ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

Where θ = Angle of repose

h = height of the heap

r = radius of the heap

Table 8: Scale of flow property

Flow property	Angle of Repose (θ in degrees)	Compressibility Index (CI in %)	Hausner Ratio
Excellent	25 – 30	< 10	1.00 – 1.11
Good	31 – 35	11 - 15	1.12 – 1.18
Fair	36 – 40	16 – 20 1.19 – 1.25	
Possible	41 – 45	21 - 25	1.26 – 1.34
Poor	46 – 55	26 – 31	1.35 – 1.45
Very Poor	56 – 65	32 – 37	1.46 – 1.59
Very, very poor	> 66	> 38	> 1.60

B) Post-Compression Parameters:

The tablets were evaluated for the various parameters enlisted below:-

1. Appearance
2. Weight variation
3. Thickness
4. Hardness
5. Friability
6. Drug content
7. Tablet density
8. Floating test
9. Swelling study
10. In-vitro dissolution studies
11. Kinetics of drug release
12. Stability studies

1) Appearance:

The compressed tablets were examined under the magnifying lens for its appearance.

2) Weight Variation:

The procedure described in IP 1996 was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed to determine the average weight and were compared with individual

tablet weight. The percentage deviation was calculated and checked for weight variation [49].

Table 9: Percentage deviation of Average weight

Average weight of tablet	Percentage deviation
80 mg or less	± 10%
More than 80 mg but less than 250 mg	± 7.5%
250 mg or more	± 5%

3) Thickness:

The tablet thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The thickness of the tablets was measured using vernier caliper. It is expressed in mm. 5 tablets of each batch were picked randomly and its thickness were measured individually. The thickness of the tablet is mostly related to the tablet hardness [48].

4) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Mansanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked from each batch and the hardness of the tablets was determined.

5) Friability:

Friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100

revolutions, and then the tablets were weighed again (W_{final}). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability.

% Friability was then calculated by:-

$$F = \frac{W(initial) - W(final)}{W(initial)} \times 100$$

% Friability of less than 1% is considered acceptable.

6) Drug Content:

Ten tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed in a 100 ml volumetric flask and dissolved in a suitable quantity of 0.1 N Hcl. Then the volume was made upto 100ml with 0.1 N Hcl and filtered. 2 ml of filtrate was transferred to a 100 ml volumetric flask and volume was made with 0.1 N Hcl. The absorbance of the resulting solution is measured by UV spectrophotometer at 276nm.

7) Tablet Density [50]:

Tablet density is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004 g/cm^3). The density was determined using following relationship.

V = lbh
d = m/V
V = volume of tablet (cc)
l = length of tablet (cm)
b = width of tablet (cm)
h = crown thickness of tablet (cm)
m = mass of tablet (g)
d = density of tablet (g/cc)

8) Floating Test [38]:

The tablets were placed in a 100 ml beaker containing 0.1 N Hcl. The time between introduction of dosage form and its buoyancy on 0.1 N Hcl, and the time during which the dosage form remains buoyant were measured. The time taken for the dosage form to emerge on surface of medium is called Floating Lag Time

(FLT) or Buoyancy Lag Time (BLT) and total duration of time during which the dosage form remains buoyant is called Total Floating Time (TFT).

9) Swelling Study [2]:

The swelling behavior of a dosage form is measured by studying its weight gain or water uptake (WU). The study was done by immersing the dosage form in 0.1 N Hcl at 37°C and determining these factors at regular intervals up to a period of 8 hours. Water uptake was measured in terms of percent weight gain, as given by the equation.

$WU = (W_t - W_o) \times 100 / W_o$

W_t = Weight of the dosage form at time t.

W_o = Initial weight of the dosage form.

10) In-vitro Dissolution Studies:

Standard calibration curve [42]:

Weighed accurately 100 mg of Ciprofloxacin Hcl and dissolved in a suitable quantity of 0.1 N Hcl in a 100ml volumetric flask. Then the volume was made upto 100ml with 0.1 N Hcl, which gives 1000 µg/ml concentration.

The standard stock solution was then serially diluted with 0.1 N Hcl to get 5, 10, 15, 20, 25 and 30 µg/ml of Ciprofloxacin Hcl. The absorbance of the solutions was measured against 0.1 N Hcl as blank at 276 nm using spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Cumulative % drug release:

In-vitro drug release profile of Ciprofloxacin Hcl was evaluated using (paddle, 900 ml 0.1 N Hcl, 37±0.5°C, 50 rpm). One tablet was placed in each of the six dissolution vessels and the system was run.

Aliquots of samples were withdrawn after 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th hour. Fresh dissolution medium was replaced to maintain the original volume. The

withdrawn aliquots were filtered, suitably diluted with 0.1 N Hcl to obtain concentration of 10µg/ml, and its absorbance measured spectrophotometrically at 276 nm to determine drug release.

11) Kinetics of Drug Release [51]:

The data obtained from in-vitro dissolution studies was subjected in order to determine release kinetics of the formulations.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage from that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = Kt \text{ --------- (1)}$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form,
W_t = amount of drug in the pharmaceutical dosage form,
t = time,
K = Proportionality constant.

The pharmaceutical dosage form following this profile release the same amount of drug by unit of time and in this model can be explained by following equation:

$$Q_t = Q_0 + K_0 t \text{ ---------- (2)}$$

Where, Q_t = Cumulative amount of drug release at time "t",
Q_0 = Initial amount of drug in solution,
K_0 = Zero order rate constant.
t = time in hours.

OR,

$$W = K.t \text{ ---------- (3)}$$

Where W is percentage drug release at time t,
K is the release rate constant.

It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

A graph is plotted between the time taken on x-axis and the cumulative % of drug release on y-axis and it gives a straight line.

First order kinetics:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner. The dissolution phenomena implies a surface action, as can be seen by Noyes – Whitney equation,

$$\frac{dc}{dt} = K(C_s - C) \text{ ---------- (4)}$$

Where, C = Concentration of solute in time t,
C_S = solubility in equilibrium at experience temperature.
k =First order proportionality constant
Hixson and Crowell adapted the above equation as

$$\frac{Dw}{dt} = KS(C_s - C) \text{ ---------- (5)}$$

Where, w = amount of solute in solution at time t,
S = Solid area accessible to dissolution.

$$\log Q_t = \log Q_0 + K_1.t / 2.303 \text{ --------- (6)}$$

Where, Q_t = amount of drug release in time t,
Q_0 = initial amount of drug in solution,
K_1 = First order release constant.
Above equation also represents this model.

The pharmaceutical dosage form following this dissolution profile, such as those containing water soluble drugs in porous matrices release drug in a way that is proportional to amount of drug remaining in its interior in such a way that amount of drug released by unit of time diminish.

OR, In (100 – W) = In 100 – k t ---------- (7)

Here, the drug release rate depends on its concentration.

A graph is plotted between the time taken on x-axis and the log cumulative % of drug remaining to be released on y-axis and it gives a straight line.

Higuchi Model / Higuchi's square Root of time Equation (Diffusion model):

Higuchi developed mathematical expressions for drugs particles dispersed in a uniform matrix behaving as diffusion media. To study the dissolution form a planar system having a homogeneous matrix, the relation obtained was

$$ft = Q = \sqrt{(2C - C_S)C_S t} \quad \text{---------- (8)}$$

Where, Q = Amount of drug released in time t per unit area.
C = Drug initial concentration
C_S = drug solubility in matrix media
D = Diffusivity of drug molecules in matrix substance.

The solid line represents the variation of drug concentration in the pharmaceutical system after time t. To distance h, the concentration gradient will be constant, provided C>> Cs. The linearity order follows the Fick's law.

$$Q = \sqrt{tDC_S(2C - C_S)} \quad \text{---------- (9)}$$

Relation is valid during all time except when the total depletion of drug in therapeutic system is achieved. Higuchi developed other models for release from heterogeneous matrix, when the drug concentration in matrix is lower than its solubility and the release occurs through pores in matrix, the obtained relation is:

$$\text{ft} = Q = \sqrt{\frac{DE}{T}(2C - \varepsilon C_S)C_S t} \quad \text{---------- (10)}$$

Where, Є = matrix porosity.

Or,

$$Q = K_H t^{1/2} \text{----------} (11)$$

Q = Cumulative amount of drug release at time t,
K_H = Higuchi constant.

The Higuchi equation suggests that the drug release by diffusion.
A graph is plotted between the square root of time taken on X-axis and the cumulative % of drug release on Y –axis and it gives a straight line.

Korsmeyer And Peppas Model:
This equation is useful to study the diffusion / relaxation release of dosage form as well zero order release kinetics. The equation can be described as

$$F = (M_t / M) = K_m t^n \text{----------} (12)$$

Where, F = fraction of drug released at time t,
M_t = Amount of drug released at time t
M = Total amount of drug in dosage form
K_m = Kinetic constant
n = Diffusion or release exponent.
t = Time in hours

If n = 0.45 for Fickian diffusion,
0 .45 <n< 0.89 for anomalous diffusion or non Fickian diffusion.
n = 0.89 and above for case -2 relaxation or super case transport – 2.

A graph is plotted between the log time taken on x-axis and the log cumulative % of drug release on y-axis and it gives a straight line.

In order to study the drug release kinetics of the examined tablets, the dissolution profiles of formulations were analyzed according to zero-order, first order, Higuchi's square root and Korsmeyer - Peppas equations.

12) Stability studies [52], [53], [54]:

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and pack profile.

The prepared floating tablets of Ciprofloxacin Hcl were placed in plastic tubes containing dessicant and stored at ambient humidity conditions, at room temperature, oven temperature (40±2°C) and in refrigerator (2-8°C) for a period of 60 days.

The samples kept for stability were evaluated for the following physicochemical parameters after 15, 30, 45 and 60 days for F_2, F_5, F_6 and F_7 batches.

Parameters evaluated:

i) Appearance
ii) Hardness
iii) Friability
iv) Floating test
v) Drug content
vi) In-vitro dissolution

Hydrodynamically balanced tablets of Ciprofloxacin Hcl were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its bioavailability.

In the present study, seven formulations were prepared and the compositions of all the batches are shown in Table 7. The formulated tablets are shown in Figure 5. The tablets were characterized for various physicochemical parameters.

I. **PREFORMULATION STUDIES:**

a) **Description:**
Description of Ciprofloxacin Hcl was found to be faintly yellowish to light yellow crystalline substance.

b) Solubility:
Ciprofloxacin Hcl was found to be soluble in water, 0.1N Hcl and practically insoluble in acetone, acetonitrile and dichloromethane.

c) **pH:** pH of Ciprofloxacin Hcl was found to be 3.6

d) **Compatibility Studies:**
Compatibility studies were performed using FT-IR spectrophotometer and the FTIR spectrum of the obtained drug and drug with polymers were studied. The characteristic absorption peaks of Ciprofloxacin obtained at 3335.03cm^{-1}, 3084.28cm^{-1} were seen in the FT-IR spectrum of drug with polymers, indicating compatibility of drug with polymer components. The FT-IR spectrum of the drug and drug with polymers are shown in Figure 6 and 7 respectively.

Figure 6: FT-IR spectrum of pure drug Ciprofloxacin Hcl

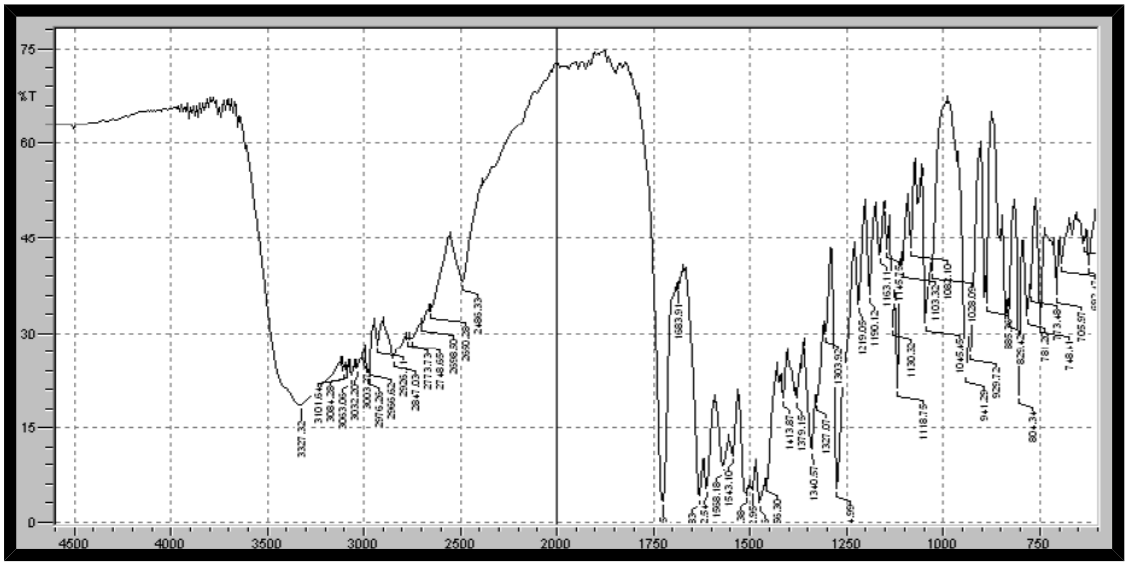


Figure 7: FT-IR spectrum of Ciprofloxacin Hcl with HPMC (K100M, K4M and E50)

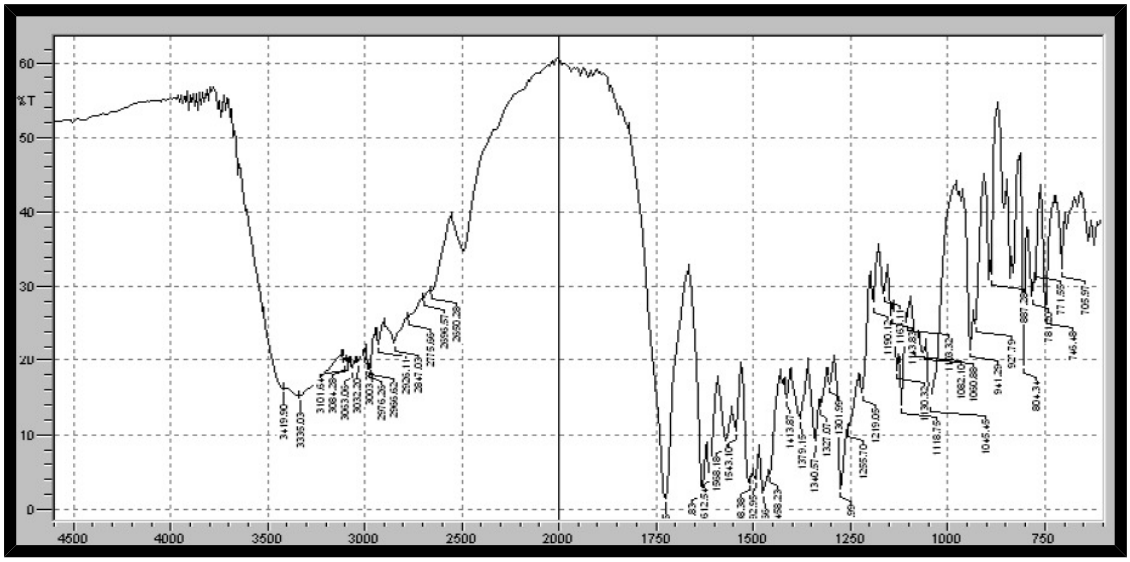


Table 10: FT-IR spectra data of pure drug Ciprofloxacin Hcl

Groups and mode of vibrations	**Frequency (in cm^{-1})**	
	Drug	**Expected Range**
NH stretching	3327.32	3500-3300

C-N stretching	1327.07	1350-1000
C-F stretching	1379.15	1400-1000
C=C stretching	1712.54	1720-1708
C=O carboxylic stretching	1728.33	1730-1700
C-H stretching	3084.28	3050-3010
O-H carboxylic stretching	2976.26	3400-2400

II. EVALUATION OF FLOATING TABLETS OF CIPROFLOXACIN HCL:

A) Pre-Compression parameters:

The bulk density of granules value is used for determination of compressibility index and hausner ratio.

Compressibility index of formulations F_1, F_3 and F_4 values are 16.84%, 18.19% and 17.01% respectively indicate the pair flow property. Formulation F_2, F_5, F_6 and F_7 values are 14.23%, 12.60%, 13.20% and 14.23% respectively indicate the good flow property.

Hausner ratio of formulations F_1, F_3 and F_4 values are 1.20, 1.22% and 1.21% respectively indicate the pair flow property. Formulation F_2, F_5, F_6 and F_7 values are 1.16, 1.14, 1.15 and 1.16 respectively indicate the good flow property.

Angle of repose of formulations F_1, F_3 and F_4 values are 31.24, 32.65 and 31.37 respectively indicate the good flow property. Formulation F_2, F_5, F_6 and F_7 values are 28.42, 29.14, 27.34 and 28.30 respectively indicate the excellent flow property.

Table 11: Pre-Compression Parameters

Parameters	Formulation

	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Loose Bulk Density (gm/ml)	0.454	0.476	0.454	0.400	0.416	0.434	0.476
Tapped Bulk Density (gm/ml)	0.546	0.555	0.555	0.482	0.476	0.500	0.555
1.161.221.211.141.151.16Compressibility Index (%)	16.84	14.23	18.19	17.01	12.60	13.20	14.23
Angle of Repose (θ)1.20 Hausner Ratio	31.24	28.42	32.65	31.37	29.14	27.34	28.30

B) Post-Compression parameters:

1) Appearance:

Microscopic examination of tablets from each batch showed white, caplet shape, biconvex, uncoated tablets plain on both sides.

2) Weight variation:

The percentage weight variations of all formulations are shown in Table 12. The tablets passed weight variation test as % weight variation was within pharmacopoeial limits of ±5% of the average weight.

3) Thickness:

The thickness of all seven formulations values obtained from 5.58 mm to 5.64 mm.

The thickness of tablets are consumer acceptance and to maintain tablet to tablet uniformity. It's mostly related to tablet hardness.

4) Hardness:

The hardness of formulations F_3 value is 5.6 kg/cm^2. Formulation F_1 and F_4 values are same 3.5 kg/cm^2. Formulation F_2, F_5, F_6 and F_7 values obtained from 4.5 kg/cm^2 to 5.0 kg/cm^2.

The hardness of formulations F_3 is highest value compare to other formulations. Formulation F_1 and F_4 is lowest value compare to other formulations.

5) Friability:

% friability values obtained were less than 1% ensuring that the tablets were mechanically stable.

6) Drug content:

The percentage drug content of the seven batches were found to be between 97.43% to 99.90%, which is within acceptable limits indicating dose uniformity in each batch.

Table 12: Physicochemical Properties of Ciprofloxacin Floating Tablets

Parameters	Formulation						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Weight Variation (gm)	0.733± 0.019	0.729± 0.016	0.728± 0.022	0.731± 0.021	0.731± 0.014	0.733± 0.015	0.732± 0.013
Thickness (mm)	5.62	5.60	5.58	5.64	5.62	5.58	5.60
Hardness (kg/cm^2)	3.5	4.5	6.5	3.5	4.5	5.0	5.0
Friability (%)	0.94	0.52	0.32	0.92	0.52	0.56	0.54
Drug Content (%)	99.90	98.67	97.43	99.63	98.12	98.82	99.09

7) Tablet density:

In order to have good floating behavior in the stomach, density of the system should be less than that of the gastric contents. All seven batches showed density in the range of 0.92 – 0.94 g/cm^3.

In the study it was clearly observed that the tablets of all batches showed good floating characteristics after buoyancy lag time. This indicated that when the tablet comes in contact with test medium, it expanded (because of swellable polymer) and also there was formation of CO_2 gas (because of effervescent agent).

The tablet floated as density dropped below 1.0 due to the expansion of polymer and upward force of CO_2 gas generation.

Table 13: Tablet Density of Ciprofloxacin Floating Tablets

Parameters	Formulation						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Thickness (cm)	0.562	0.560	0.558	0.564	0.562	0.558	0.560
Length (cm)	1.716	1.720	1.716	1.718	1.722	1.720	1.716
Width (cm)	0.814	0.818	0.814	0.816	0.820	0.818	0.814
Tablet Density (gm/cc)	0.93	0.93	0.94	0.93	0.92	0.93	0.94

8) Floating test:

Carbon dioxide is formed within the tablet containing effervescent agent when it is brought in contact with acidic medium (0.1 N Hcl).

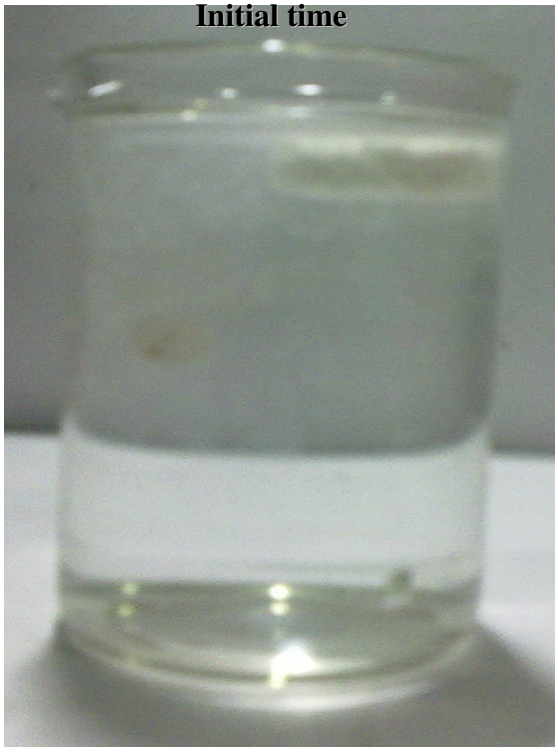
On immersion in 0.1 N Hcl at 37°C, the tablets floated and remained buoyant without disintegration. The results of floating lag time of all seven formulations within 1 minute. Total floating time of F_1 and F_4 formulations are more than 6 hours. Total floating time of F_2, F_3, F_5, F_6 and F_7 formulations are more than 10 hours. Figure 8 shows buoyancy character of formulated tablets.

Table 14: Floating Test of Ciprofloxacin Hcl Tablets

Parameters	Formulation						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Floating Lag Time or Buoyancy Lag Time (sec)	12	30	50	10	35	15	20
Total Floating Time (hrs)	>6	>10	>10	>6	>10	>10	>10

Figure 8: Buoyancy character of formulated tablets

Initial time



After 20 sec time

9) Swelling study:

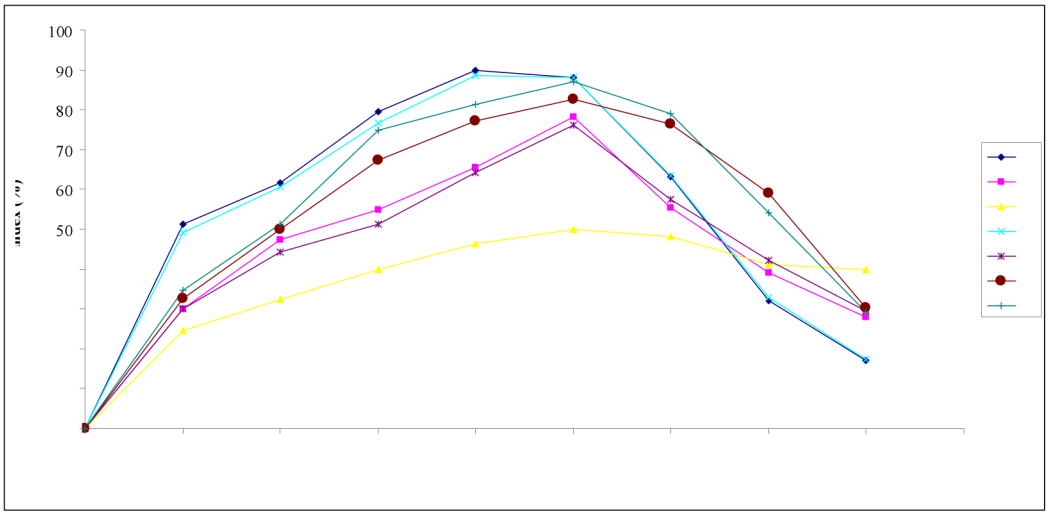
Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure,

hydrophilicity and ionization of the functional groups. Swelling study was performed on all the batches for 8 hours. The study showed that swelling of tablet increased up to 4-5 hours for all formulations but after that it decreased. The results of swelling index are given in Table 15, while the plot of swelling index against increases with time because polymer gradually absorbs water due to its hydrophilicity. The outermost layer of polymer hydrates, swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

Table 15: Swelling Index of Ciprofloxacin Floating Tablets

Time (hrs)	Swelling Index (%)						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	51.38	30.14	24.54	49.27	30.06	32.55	34.68
2	61.77	47.33	32.51	60.51	44.18	49.92	51.33
3	79.56	54.83	39.83	76.81	51.34	67.37	74.92
4	89.92	65.44	46.41	88.56	64.29	77.11	81.29
5	88.21	78.33	50.10	88.17	76.14	82.54	87.16
6	63.11	55.42	48.23	63.43	57.55 76.44	79.13	
7	32.15	39.22	41.11	32.98	42.18	59.15	54.24
8	17.18	27.93	39.87	17.26	29.46	30.29	29.35

Figure 9: Swelling Index of Ciprofloxacin Floating Tablets



10) In-vitro Dissolution study:

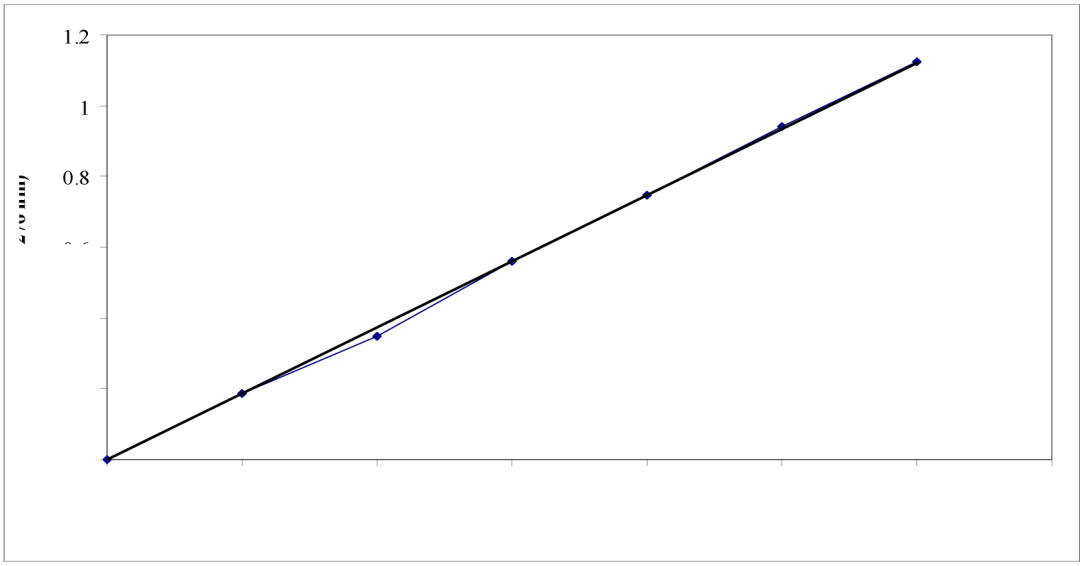
Standard calibration curve of ciprofloxacin Hcl:

The λmax of Ciprofloxacin Hcl in 0.1 N Hcl was found to be 276 nm. The absorbance values are tabulated in Table 16. Ciprofloxacin Hcl obeyed Beer's law in the concentration range of 5-30 µg/ml with regression coefficient of 0.9993. The standard calibration curve of Ciprofloxacin Hcl is shown in Figure 10.

Table 16: Absorbance of standard solutions of Ciprofloxacin Hcl

S.No.	Concentration (µg/ml)	Absorbance (276 nm)
1	5	0.186
2	10	0.349
3	15	0.562
4	20	0.747
5	25	0.942
6	30	1.124

Figure 10: Standard calibration curve of Ciprofloxacin Hcl



Cumulative % drug release:

In-vitro drug release profile of tablets from each batch using USP dissolution apparatus Type II are shown in Table 17. The plot of % cumulative drug released Vs. time (hr) was plotted for all formulations and depicted as shown in Figure 11.

In the present study HPMC used was hydrophilic in nature, drug release involves (1) hydration and swelling of polymer and dissolution of active ingredients (2) transfer of the dissolved drug and soluble components into the bulk.

The results of formulation F_3 used HPMC (K100M, K4M and E50) for the ratio of 1:1:1 was slow drug release of 79.98% within 10 hours.

Formulation F_1 ratio is 1:2:3 and F_4 ratio is 2:1:3 were faster drug release of 99.82% and 99.34% respectively within 6 hours.

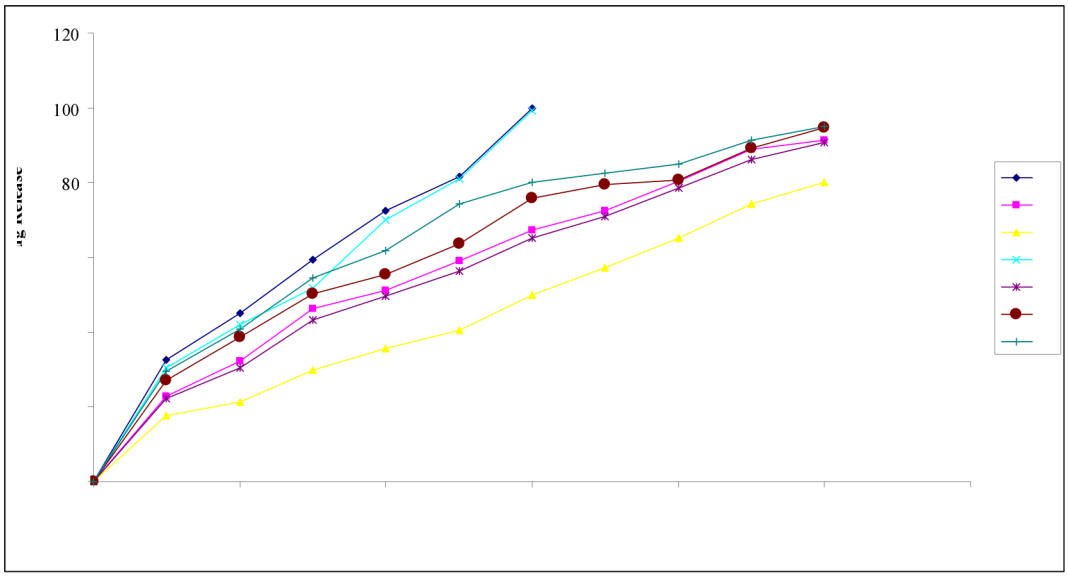
Formulations F_2, F_5, F_6 and F_7 used HPMC (K100M, K4M and E50) for the ratio of 1:3:2, 2:3:1, 3:1:2 and 3:2:1 for drug release were 91.38%, 90.66%, 94.65% and 95.10% respectively.

The formulations F_2, F_5, F_6 and F_7 are found to be satisfactory with the dissolution profile results. Hence these formulations are kept for future studies.

Table 17: In-vitro Dissolution study of Ciprofloxacin Floating Tablets

Time (hrs)	Cumulative % Drug released						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	32.69	22.93	17.72	30.39	22.12	27.25	29.40
2	45.08	32.20	21.45	42.16	30.55	38.71	40.85
3	59.26	46.25	29.83	51.73	43.14	50.22	54.62
4	72.37	51.07	35.76	69.98	49.72	55.34	61.73
5	81.61	59.14	40.41	80.93	56.43	63.66	74.43
6	99.82	67.31	49.92	99.34	65.18	75.76	80.17
7		72.43	57.33		70.92	79.38	82.59
8		80.27	65.04		78.71	80.70	85.10
9		88.79	74.37		86.12	89.26	91.48
10		91.38	79.98		90.66	94.65	95.10

Figure 11: In – vitro Dissolution study of formulated tablets



11) Kinetics of drug release:

The results of dissolution data were fitted to various drug release kinetic equations. Regression coefficient (R^2) value was highest for korsmeyer – peppas release equation in formulations F_2, F_5, F_6 and F_7.

The kinetics of drug release of R^2 values obtained for formulations F_2, F_5, F_6 and F_7 are tabulated in Table 18. The drug release kinetics obtained for formulations F_2, F_5, F_6 and F_7 are tabulated in Table 19, 20, 21 and 22.

Formulation F_2 plots of Zero order, First order, Higuchi matrix, Korsmeyer - Peppas and are depicted in Figure 12, 13, 14 and 15. Formulation F_5 plots of Zero order, First order, Higuchi matrix, Korsmeyer - Peppas and are depicted in Figure 16, 17, 18 and 19. Formulation F_6 plots of Zero order, First order, Higuchi matrix, Korsmeyer - Peppas and are depicted in Figure 20, 21, 22 and 23. Formulation F_7 plots of Zero order, First order, Higuchi matrix, Korsmeyer - Peppas and are depicted in Figure 24, 25, 26 and 27.

The Zero order drug release graph is plotted between the time taken on x-axis and the cumulative % of drug release on y-axis.

First order drug release graph is plotted between the time taken on x-axis and the log cumulative % of drug remaining on y-axis.

Higuchi's square root graph is plotted between the square root of time taken on x-axis and the cumulative % of drug release on y-axis.

Korsmeyer – Peppas drug release graph is plotted between the log time taken on x-axis and the log cumulative % of drug release on y-axis.

The results of kinetic drug release of formulation F_2, F_5, F_6 and F_7 in the R^2 values was highest for korsmeyer – peppas model. The 'n' value obtained from 0.521 to 0.633 indicates the non Fickian diffusion.

Table 18: Kinetics of drug release of R^2 value for F_2, F_5, F_6 and F_7

Batch No.	Regression Coefficient (R^2)				
	Zero Order	First Order	Higuchi	Korsmeyer - Peppas	
				R^2	n
F2	0.9860	0.9511	0.9930	0.9944	0.612
F5	0.9920	0.9514	0.9928	0.9958	0.633
F6	0.9727	0.9342	0.9918	0.9940	0.542
F7	0.9366	0.9701	0.9837	0.9899	0.521

Table 19: Drug release kinetics of formulation F2

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
1	0	1	22.93	1.36	77.07	1.89
2	0.30	1.41	32.20	1.51	67.80	1.83
3	0.48	1.73	46.45	1.67	53.55	1.73
4	0.60	2	51.07	1.71	48.93	1.69
5	0.70	2.24	59.14	1.77	40.86	1.61
6	0.78	2.45	67.31	1.83	32.69	1.51
7	0.85	2.65	72.43	1.86	27.57	1.44
8	0.90	2.83	80.27	1.90	19.73	1.30

9	0.95	3	88.79	1.95	11.21	1.05
10	1	3.16	91.38	1.96	8.62	0.94

Figure 12: Zero order drug release kinetics of formulation F2

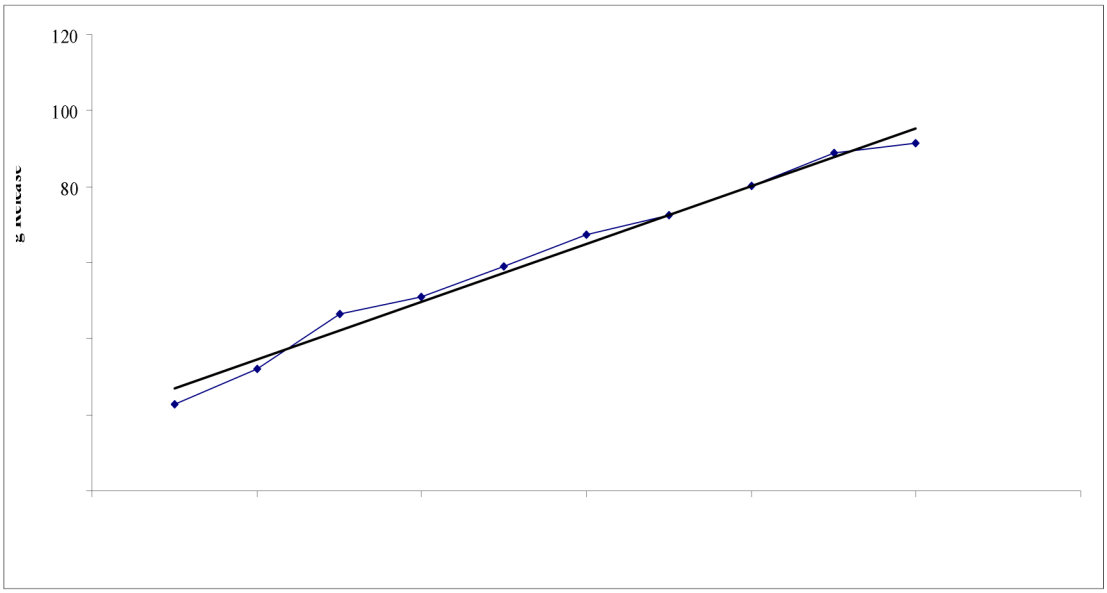


Figure 13: First order drug release kinetics of formulation F2

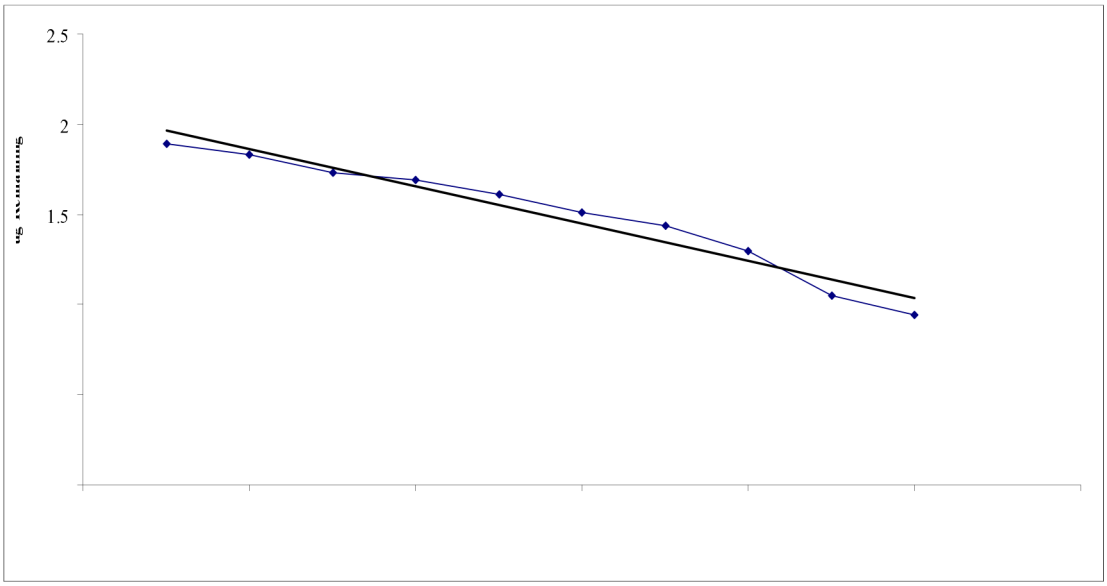


Figure 14: Higuchi drug release kinetics of formulation F2

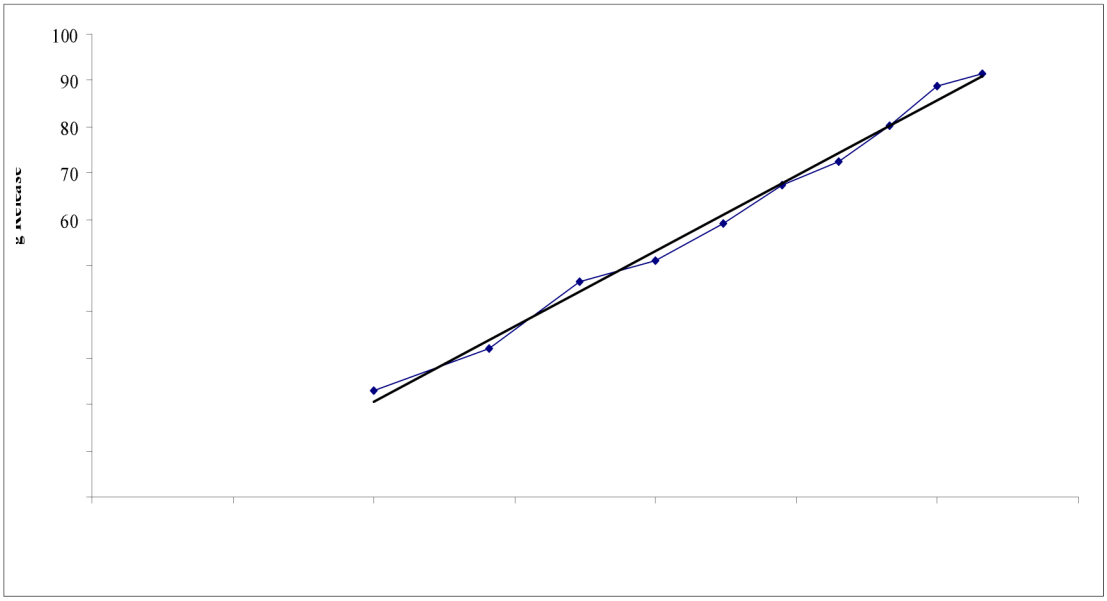


Figure 15: Korsmeyer - Pepps drug release kinetics of formulation F2

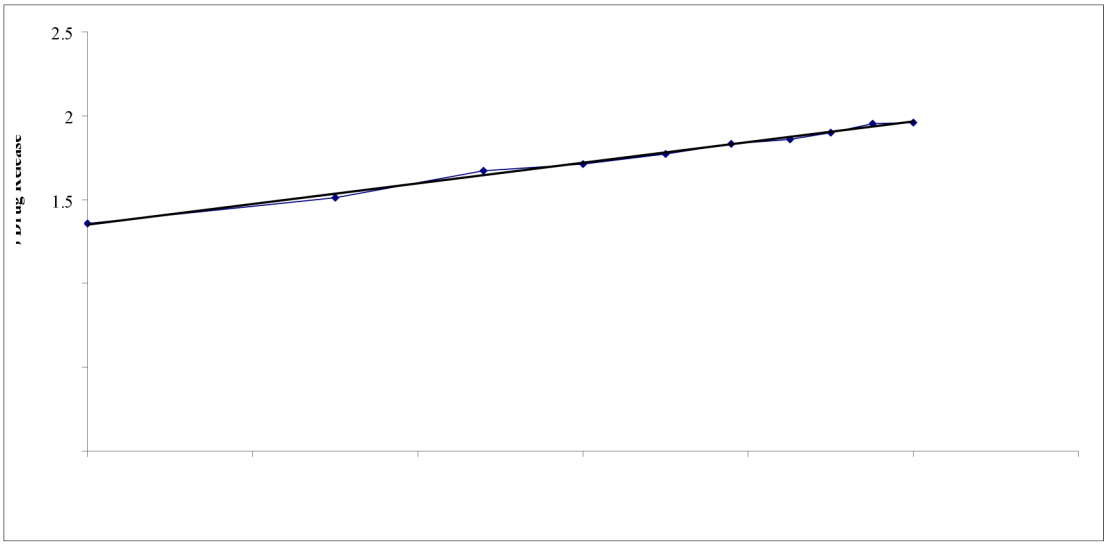


Table 20: Drug release kinetics of formulation F5

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
1	0	1	22.12	1.34	77.88	1.89

2	0.30	1.41	30.55	1.49	69.45	1.84
3	0.48	1.73	43.14	1.63	56.86	1.75
4	0.60	2	49.72	1.70	50.28	1.70
5	0.70	2.24	56.43	1.75	43.57	1.64
6	0.78	2.45	65.18	1.81	34.82	1.54
7	0.85	2.65	70.92	1.85	29.08	1.46
8	0.90	2.83	78.71	1.90	21.29	1.33
9	0.95	3	86.12	1.94	13.88	1.14
10	1	3.16	90.66	1.96	9.34	0.97

Figure 16: Zero order drug release kinetics of formulation F5

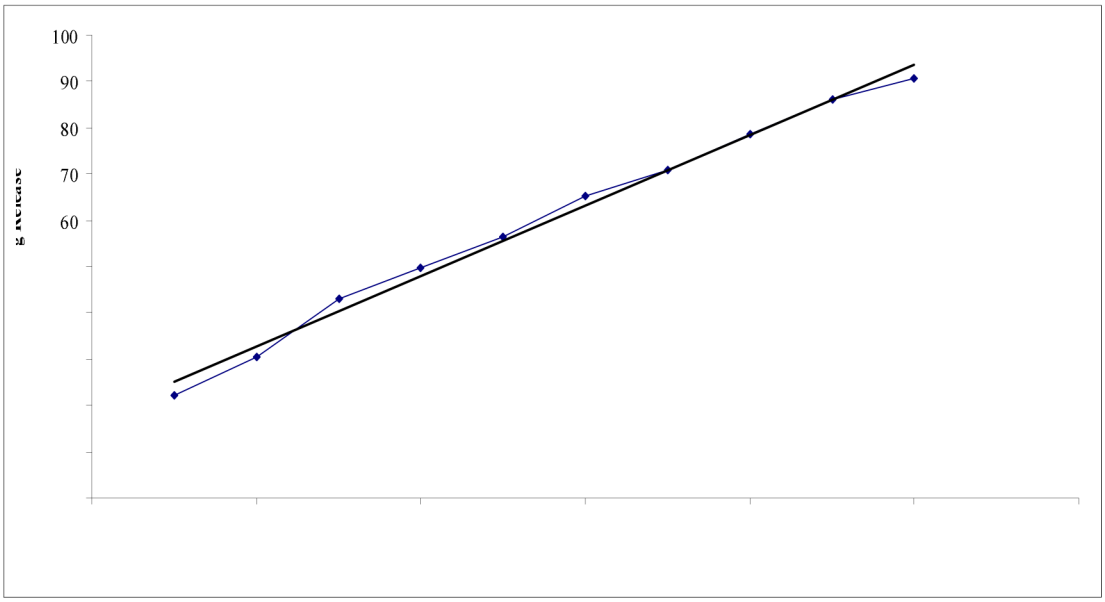


Figure 17: First order drug release kinetics of formulation F5

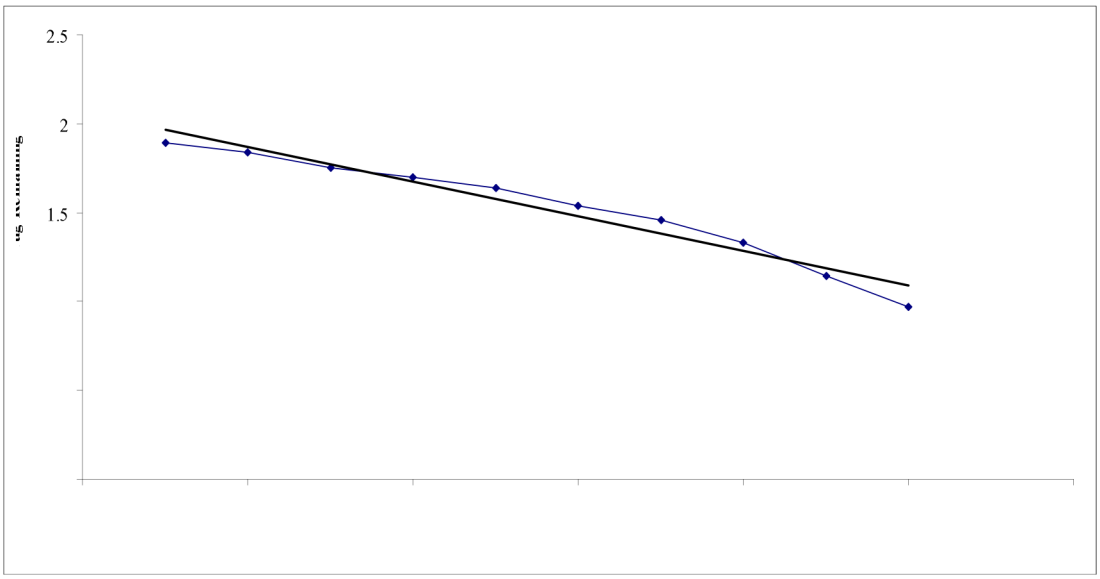


Figure 18: Higuchi drug release kinetics of formulation F5

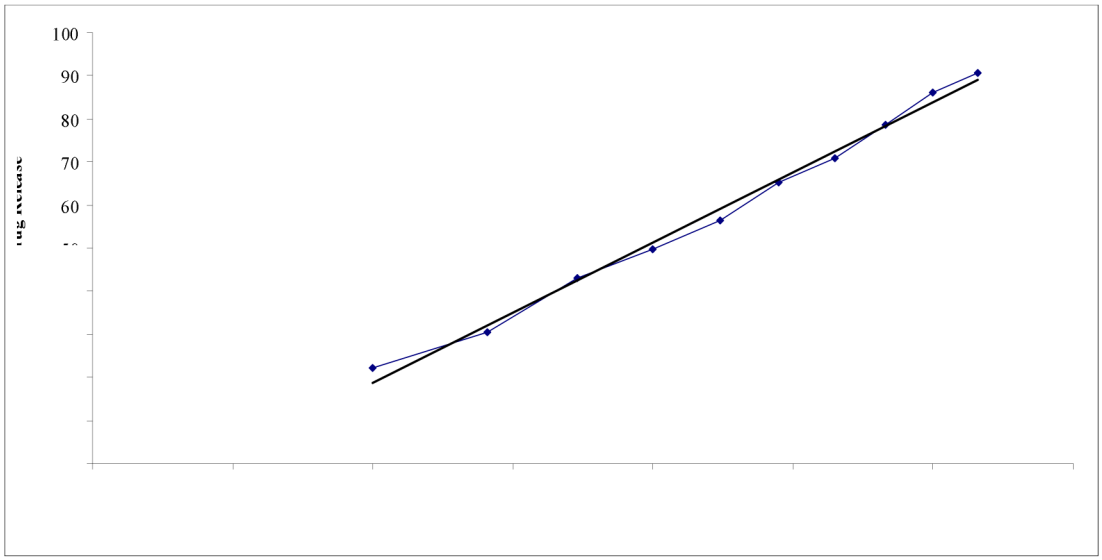


Figure 19: Korsmeyer - Pepps drug release kinetics of formulation F5

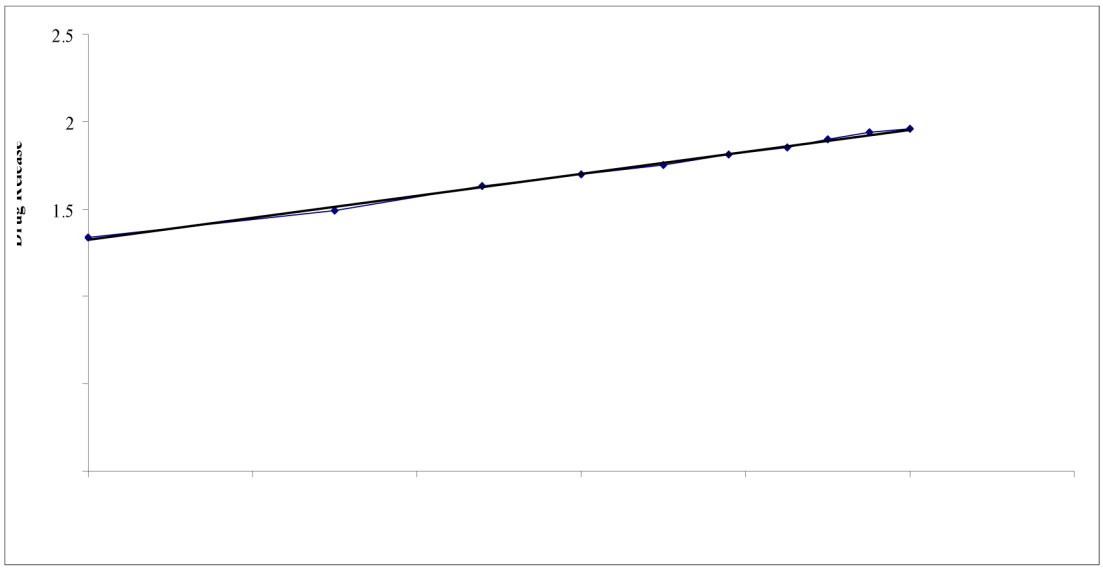


Table 21: Drug release kinetics of formulation F6

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
1	0	1	27.25	1.44	72.75	1.86
2	0.30	1.41	38.71	1.59	61.29	1.79
3	0.48	1.73	50.22	1.70	49.78	1.70
4	0.60	2	55.34	1.74	44.66	1.65
5	0.70	2.24	63.66	1.80	36.34	1.56
6	0.78	2.45	75.76	1.88	24.24	1.38
7	0.85	2.65	79.38	1.90	20.62	1.31
8	0.90	2.83	80.70	1.91	19.30	1.29
9	0.95	3	89.26	1.95	10.74	1.03
10	1	3.16	94.65	1.98	5.35	0.73

Figure 20: Zero order drug release kinetics of formulation F6

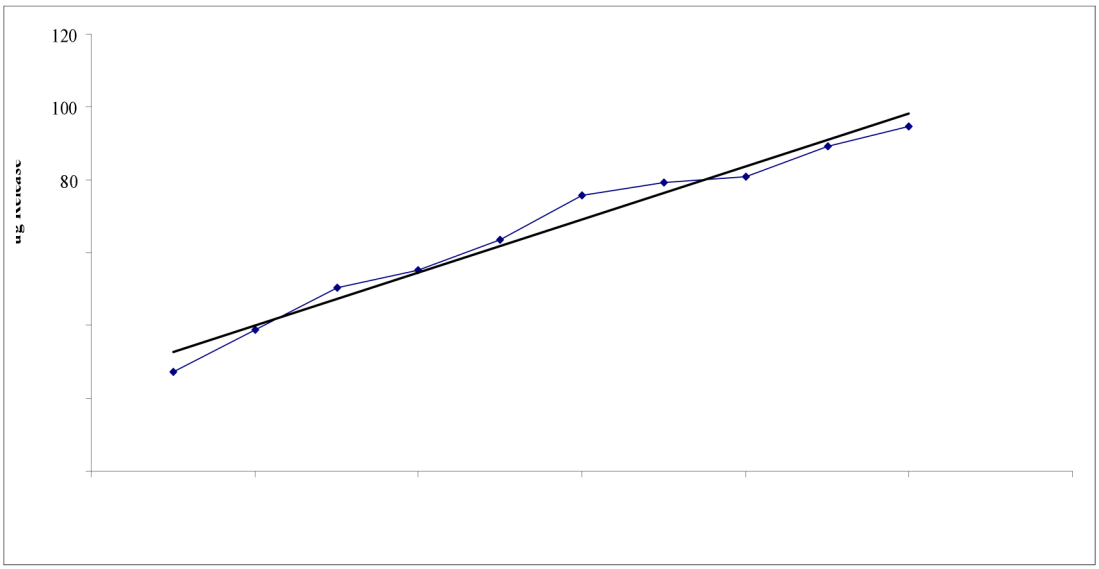


Figure 21: First order drug release kinetics of formulation F6

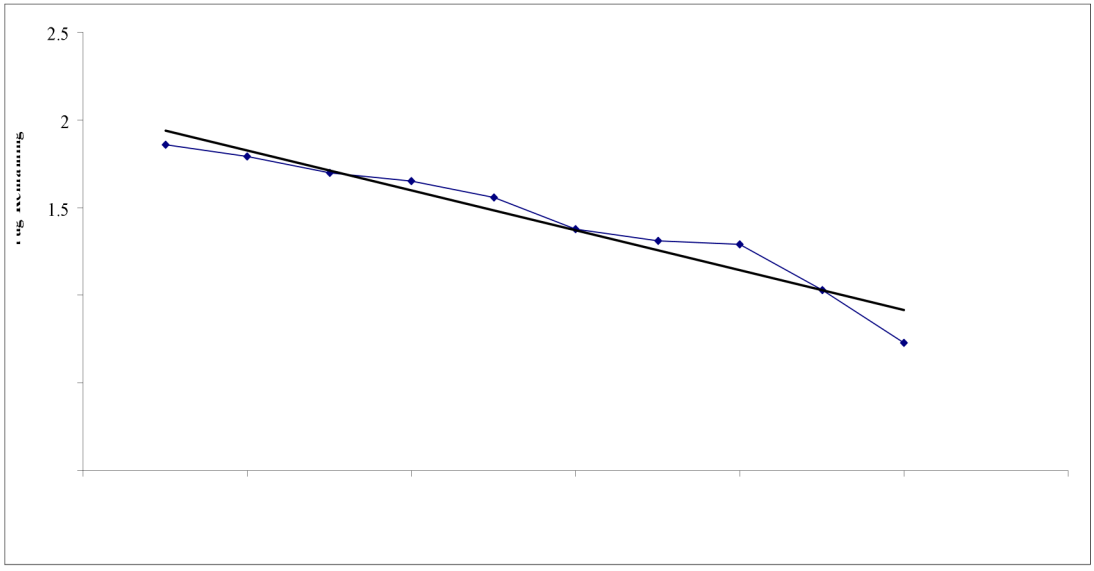


Figure 22: Higuchi drug release kinetics of formulation F6

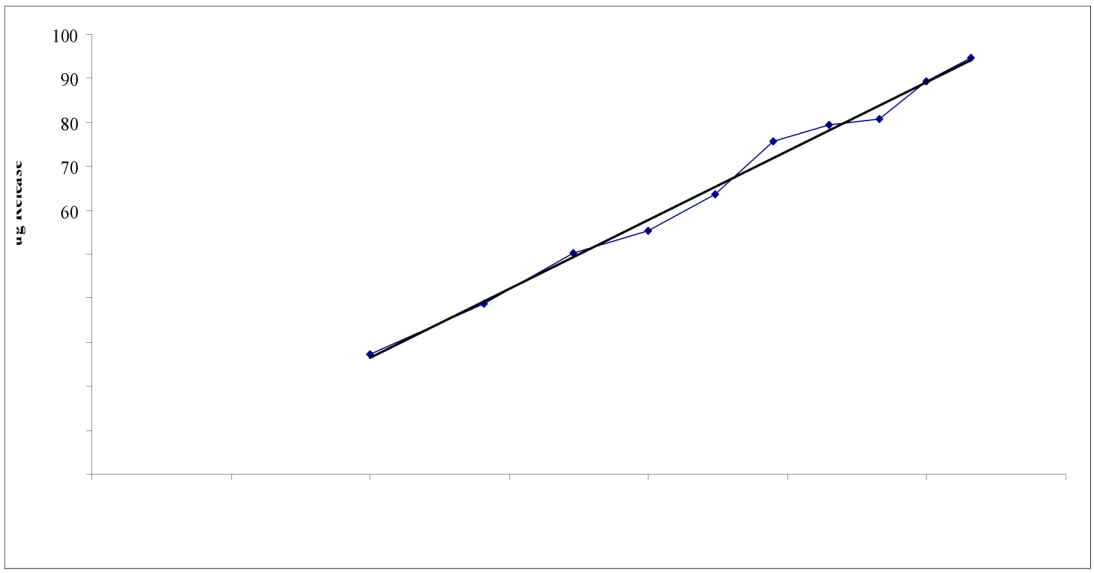


Figure 23: Korsmeyer - Pepps drug release kinetics of formulation F6

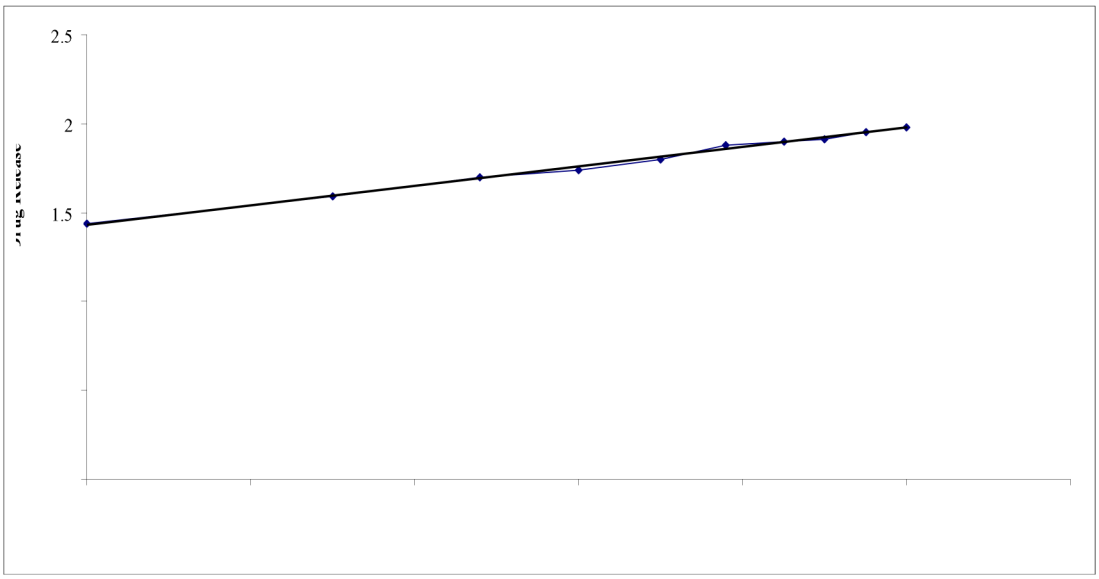


Table 22: Drug release kinetics of formulation F7

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
1	0	1	29.40	1.47	70.60	1.85
2	0.30	1.41	40.85	1.61	59.15	1.77

3	0.48	1.73	54.62	1.74	45.38	1.66
4	0.60	2	61.73	1.79	38.27	1.58
5	0.70	2.24	74.43	1.87	25.57	1.41
6	0.78	2.45	80.17	1.90	19.83	1.30
7	0.85	2.65	82.59	1.92	17.41	1.24
8	0.90	2.83	85.10	1.93	14.90	1.17
9	0.95	3	91.48	1.96	8.52	0.93
10	1	3.16	95.10	1.98	4.90	0.69

Figure 24: Zero order drug release kinetics of formulation F7

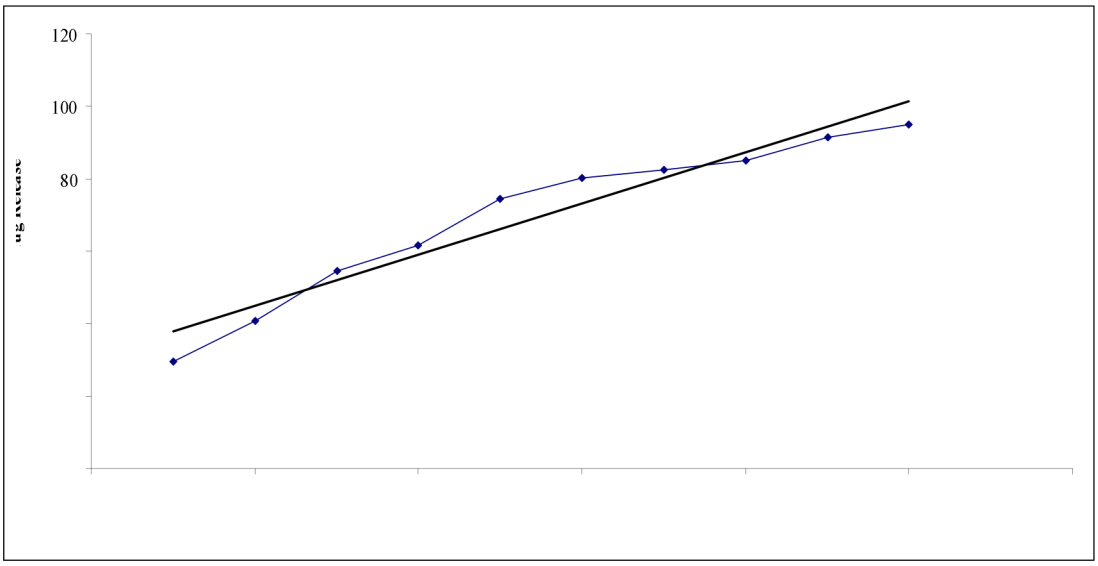


Figure 25: First order drug release kinetics of formulation F7

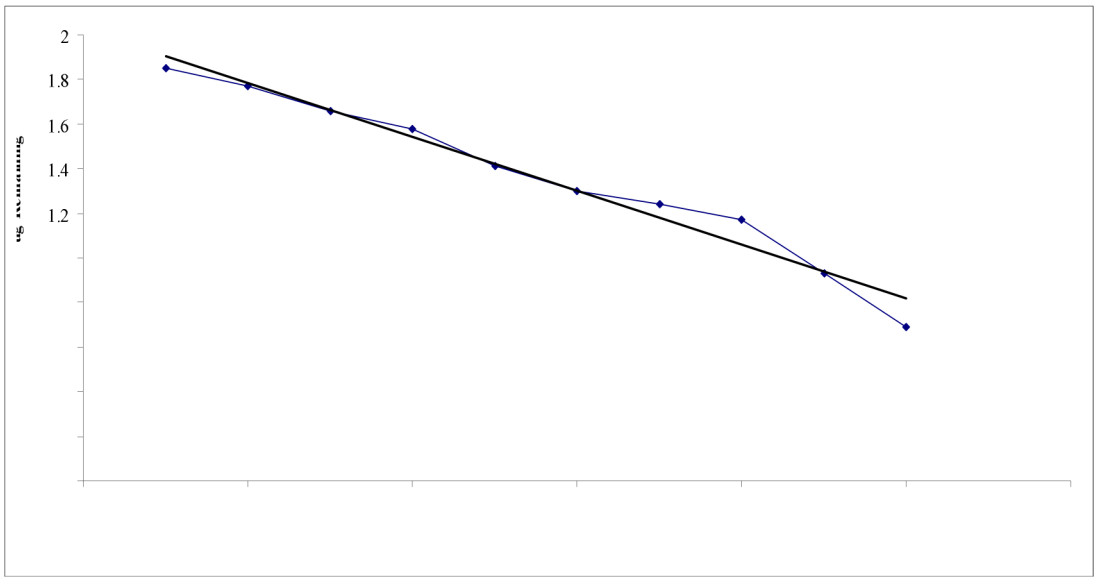


Figure 26: Higuchi drug release kinetics of formulation F7

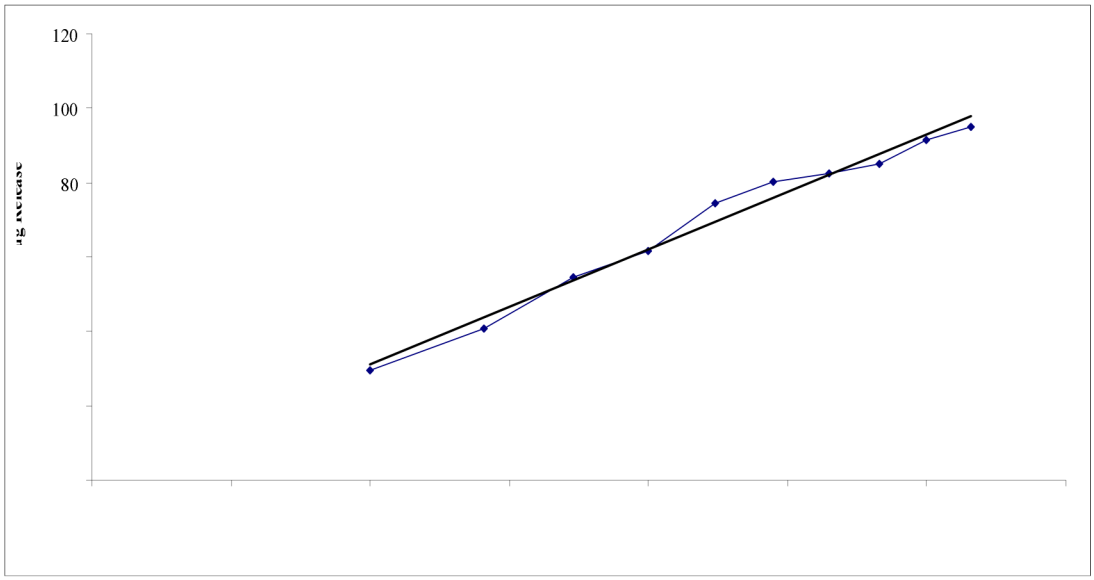
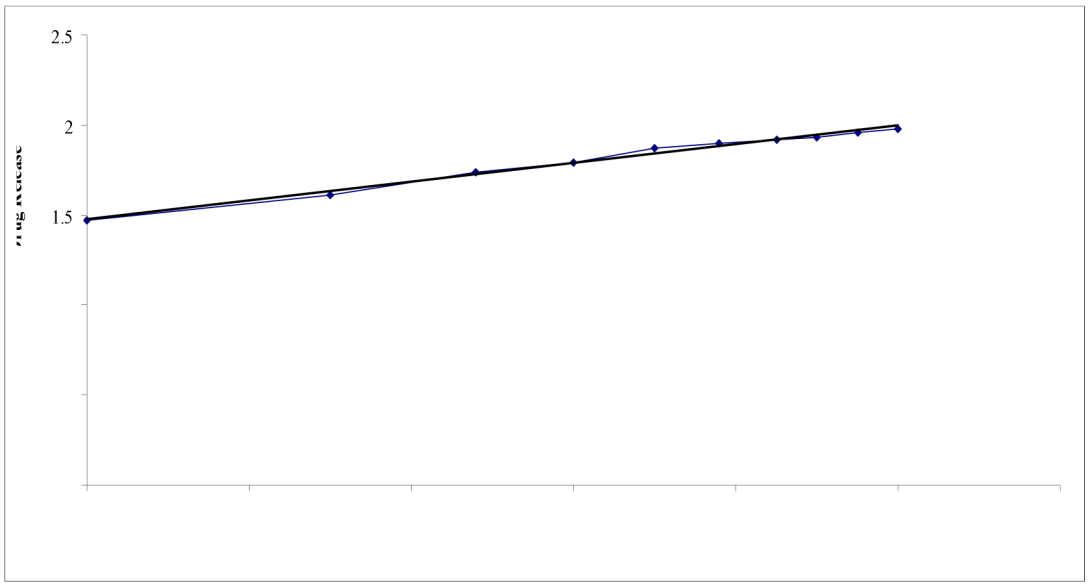


Figure 27: Korsmeyer - Pepps drug release kinetics of formulation F7



12) Stability studies:

Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°C and in refrigerator for a period upto 60 days. The samples were withdrawn after a period of 15 days, 30 days, 45 days and 60 days and were analyzed for its appearance, hardness, friability, floating test, drug content and in-vitro release.

The results obtained are tabulated in Table 23, 24, and 25. Results reveal no significant changes in appearance, floating test and drug content. There was no much variation either in hardness, friability and drug release in F_2, F_5, F_6 and F_7 formulations kept at the three storage conditions. Thus from the tables it is evident that F_2, F_5, F_6 and F_7 formulations were stable at all three storage conditions up to a period of 30 days. However F_2, F_5, F_6 and F_7 showed a decrease in hardness after a period of 30 days, with subsequent increase in friability and in-vitro drug release, for samples stored at prevailing room

temperature (34±2ºC) and at 40ºC, whereas there was no significant change in F_2, F_5, F_6 and F_7 formulations stored in refrigerator. Thus from the above results it can be concluded that Ciprofloxacin floating tablets are stable when stored at 2 to 8ºC.

Table 23: Formulations F2, F5, F6 and F7 stored at Room Temperature

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content (%)	Cum. % Drug Released (in 10th hours)
				BLT (sec)	TFT (hrs)		
F2	15	4.5	0.52	30	>10	98.46	91.21
	30	4.5	0.53	30	>10	98.21	90.76
	45	4.4	0.53	31	>10	97.82	90.54
	60	4.4	0.56	32	>10	97.53	90.07
F5	15	4.5	0.52	35	>10	98.06	90.47
	30	4.5	0.52	35	>10	97.86	90.18
	45	4.4	0.53	37	>10	97.59	89.74
	60	4.3	0.54	38	>10	97.16	89.35
F6	15	5.0	0.56	15	>10	98.63	94.28
	30	4.9	0.56	15	>10	98.31	94.02
		4.9	0.57	16	>10	98.11	93.88

	45 60	4.8	0.58	17	>10	97.88	93.57
F7	15	4.5	0.54	20	>10	98.94	95.02
	30	4.5	0.54	20	>10	98.67	94.85
	45	4.4	0.55	21	>10	98.39	94.43
	60	4.3	0.55	22	>10	98.04	94.17

Table 24: Formulations F2, F5, F6 and F7 stored at 40°C

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content (%)	Cum. % Drug Released (in 10th hours)
				BLT (sec)	TFT (hrs)		
F2	15	4.5	0.52	30	>10	98.38	91.17
	30	4.4	0.53	31	>10	98.17	90.68
	45	4.3	0.54	32	>10	97.65	90.42
	60	4.2	0.57	34	>10	97.48	90.01
F5	15	4.5	0.52	35	>10	97.96	90.28
	30	4.4	0.54	36	>10	97.69	90.03
	45	4.4	0.55	37	>10	97.37	89.69
	60	4.3	0.56	38	>10	96.85	89.27
F6	15	5.0	0.56	15	>10	98.59	94.15
	30	4.9	0.58	16	>10	98.27	93.94
	45	4.8	0.58	16	>10	98.07	93.56

	60	4.7	0.59	17	>10	97.65	93.31
F7	15	4.5	0.54	20	>10	98.82	94.89
	30	4.4	0.55	21	>10	98.59	94.64
	45	4.3	0.56	21	>10	98.17	94.37
	60	4.3	0.58	22	>10	97.84	94.12

Table 25: Formulations F2, F5, F6 and F7 stored in Refrigerator (2-8ºC)

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content (%)	Cum. % Drug Released (in 10th hours)
				BLT (sec)	TFT (hrs)		
F2	15	4.5	0.52	30	>10	98.62	91.28
	30	4.5	0.52	30	>10	98.47	90.81
	45	4.5	0.53	31	>10	98.16	90.69
	60	4.4	0.53	31	>10	97.94	90.41
F5	15	4.5	0.52	35	>10	98.07	90.52
	30	4.5	0.52	35	>10	97.91	90.37
	45	4.5	0.53	36	>10	97.73	89.99
	60	4.4	0.53	37	>10	97.62	89.63
F6	15	5.0	0.56	15	>10	98.76	94.47
	30	4.9	0.56	15	>10	98.49	94.18
	45	4.9	0.56	16	>10	98.25	94.02
	60	4.9	0.57	16	>10	98.18	93.86

F7	15	4.5	0.54	20	>10	99.02	95.06
	30	4.5	0.54	20	>10	98.93	94.97
	45	4.4	0.54	20	>10	98.74	94.75
	60	4.4	0.55	21	>10	98.51	94.53

SUMMARY

- Compounding drugs having narrow absorption window in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs.
- After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and prolonged manner, so that the drug is supplied continuously to its absorption sites in the upper gastrointestinal tract.
- In the present study an attempt was made to formulate Ciprofloxacin as floating drug delivery system in order to enhance its bioavailability and to localize drug at the absorption site.
- Floating tablets of Ciprofloxacin Hcl were formulated using sodium bicarbonate as gas generating agent and HPMC as water swellable polymer by direct compression technique.
- FT-IR spectral studies revealed that the drug and polymer used were compatible.
- These formulations were subjected to various evaluation parameters like weight variation, thickness, hardness, friability, drug content, tablet density, floating test, swelling index, in-vitro release studies and stability studies.
- The results of all these parameters are tabulated and depicted graphically in the result and discussion section.

- Evaluation parameters viz. tablet weight variation, thickness, friability and drug content were within acceptable limits for all seven formulations.

- All seven formulations showed satisfactory results for tablet density, floating test and swelling studies.
- Results of in-vitro release using USP dissolution apparatus Type II method indicated that the drug release of formulations F_2, F_5, F_6 and F_7 are satisfactory.
- The results of kinetic drug release of formulation F_2, F_5, F_6 and F_7 in the R^2 values was highest for korsmeyer – peppas model.
- Stability studies showed F_2, F_5, F_6 and F_7 to be stable at room temperature, 40°C and 2-8°C for a period of 60 days. F_2, F_5, F_6 and F_7 formulations were stable at all three storage conditions up to a period of 30 days. However F_2, F_5, F_6 and F_7 showed a decrease in hardness after a period of 30 days, with subsequent increase in friability and in-vitro drug release, for samples stored at prevailing room temperature (34±2°C) and at 40°C. No significant change was observed in F_2, F_5, F_6 and F_7 formulation stored in refrigerator. This suggested that the most suitable storage temperature for Ciprofloxacin floating tablets is 2-8°C.

CONCLUSION

- Hydrodynamically balanced tablets of Ciprofloxacin Hcl can be formulated with an approach to increase gastric residence and thereby improve drug bioavailability.
- An attempt to develop floating tablets of Ciprofloxacin Hcl, using sodium bicarbonate as gas generating agents and HPMC as hydrophilic polymer by direct compression technique was achieved.

- The formulated tablets showed compliance for various physiochemical parameters viz. tablet dimensions, total floating time, tablet density and drug content.
- The dissolution studies formulations of F_2, F_5, F_6 were good release and F_7 formulation was excellent.
- Data obtained from kinetic treatment revealed F_2, F_5, F_6 and F_7 formulations follow Korsmeyer – peppas model. The 'n' value obtained from 0.521 to 0.633 indicates the non Fickian diffusion.
- The results of stability studies indicated that the most suitable storage temperature for Ciprofloxacin floating tablets was 2-8^{o}C for a period of 60 days.

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