"DESIGN OF A MUCOADHESIVE-FLOATING DRUG DELIVERY SYSTEM FOR SUSTAINED GASTRIC RELEASE OF CEFDINIR TO ENHANCE BIOAVAILABILITY"

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ABSTRACT:

The increasing prevalence of gastric infections and the rising challenge of antibiotic resistance necessitate the development of novel drug delivery systems that enhance therapeutic efficacy while minimizing systemic side effects. Floating drug delivery systems (FDDS) provide gastric retention, prolonged drug release, and improved local action, making them ideal for antibiotics used in the treatment of *Helicobacter pylori* and other gastric infections. The present study aims to formulate and evaluate a floating drug delivery system containing a selected antibiotic. The formulation was developed using gas-generating excipients, polymers with controlled release properties, and optimized to achieve buoyancy, sustained drug release, and enhanced bioavailability. Preformulation studies, drug–excipient compatibility tests, and physicochemical characterizations were carried out to ensure stability. The prepared formulations were evaluated for floating lag time, total floating duration, swelling index, drug content uniformity, in-vitro release kinetics, and stability under accelerated conditions. Preliminary results indicated that the optimized batch demonstrated rapid buoyancy with prolonged gastric retention and sustained antibiotic release over 12 hours. Such a system offers the potential for targeted delivery at the site of infection, reduced dosing frequency, improved patient compliance, and may contribute to overcoming challenges in conventional antibiotic therapy. This innovative approach highlights the promise of floating drug delivery systems as a platform for more effective and reliable antibiotic treatment.

Keywords: Floating drug delivery system, gastric retention, antibiotic, sustained release, Helicobacter pylori, bioavailability.

INTRODUCTION :

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems (Arora, S *et al*., 2005). Controlled Release Drug Delivery Systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. CRDDS is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period, enhancement of activity of duration for short half-life drugs, reducing frequency of dosing and wastage of drugs, eliminating or minimizing the side effects, optimized therapy and better patient compliances (Chien, YW 1989 & 1992; Neha Narang, 2010).

The successful development of oral CRDDS requires an understanding of the three aspects of the system, namely.

- The physiochemical characteristics of the drug.
- Anatomy and physiology of Gastro Intestinal Tract (GIT)
- Characteristics of dosage form (Hetangi Rathod, *et al*., 2010).

Orally taken drug will get absorbed and entered into systemic circulation and that formulation, which stayed in the therapeutic range for longer duration may be a successful formulation. In that aspect the drug level with respect to time for the different formulations of oral solid dosage forms were given in Figure 1.1.

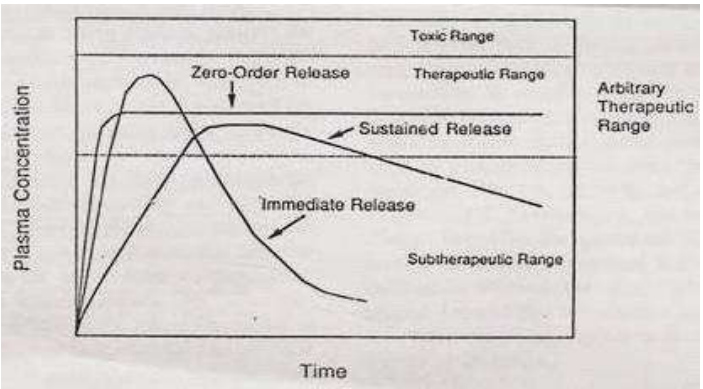

Figure 1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to regulate the gastrointestinal transit time of a drug through Floating Drug Delivery System (FDDS) to get maximal gastrointestinal absorption of drugs and site specific delivery (Koner, P 2007).

GASTROINTESTINAL RETENTION:

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment (Praveen Kumar, et al., 2014). It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better bioavailability of new products with new therapeutic possibilities and substantial benefits for patients (Koner, P 2007).

To successfully modulate the gastrointestinal transit time of a drug delivery system through FDDS. For maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT (Arora, S *et al*., 2005).

STOMACH ANATOMY

The main function of the stomach is to process and transport of food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly (Kandharkar, SU *et al*., 2013). Substantial enzymatic digestion is started in stomach, particularly for proteins. Vigorous contractions of gastric smooth muscle the foodstuffs are mixed and grind with gastric secretions, which results in liquefaction of food. As food is liquefied in the stomach, it is gradually released into the small intestine for further processing (Wilson, CG and Washington, N 1989).

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, but the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Desai, SA 1984).

It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15, but when food comes into the stomach, the pH may rise 3.0 to 4.0 levels due to the buffering capacity of proteins. Whereas, in fasted state, basal gastric secretion in women is slightly lower than that of men (Davis, SS *et al*., 1986).

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states (Sisode, NR *et al*., 2014). During the fasting state an inter- digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours (Mihir Patel, *et al*., 2013). This is called the inter-digestive myloelectric cycle or Migrating Myloelectric Cycle (MMC), which is further divided into following 4 phases are described and the motility pattern is illustrated in Figure 1.2.

- **PHASE I (BASAL PHASE):**
- lasts from 30 to 60 minutes with rare contractions.
- **PHASE II (PRE-BURST PHASE):**

- lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase step forward the intensity and frequency also increases gradually.
- **PHASE III (BURST PHASE):**
- lasts for 10 to 20 minutes. It also includes intense and regular contractions for short period, which is due to the wave, that all the undigested material is swept out of the stomach down to the small intestine. It is also called as the housekeeper wave.
- **PHASE IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

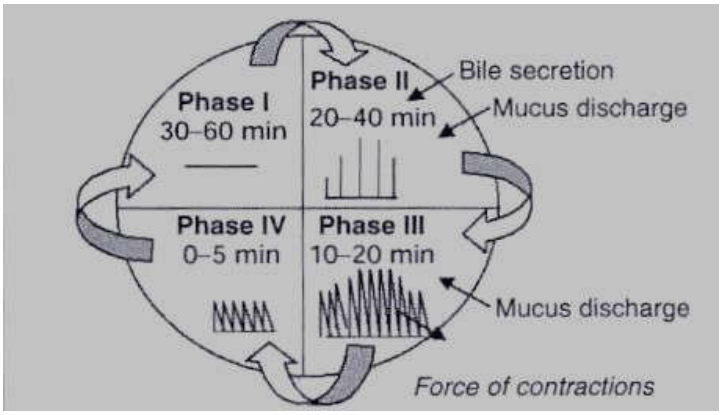

Figure 2: Motility pattern in GIT

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

1. FORMULATION FACTORS

➢ SIZE OF TABLETS

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets or granules are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves (Oth, M *et al*., 1992) Floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found to be that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach (Timmermans, J 1989). Floating units away from the

gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase (Timmermans, J 1989).

- **DENSITY OF TABLETS**

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period (Gergogiannis, YS *et al.*, 1993). A density of less than 1.0 g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities (Gergogiannis, YS *et al.*, 1993).

- **SHAPE OF TABLETS**

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, string, pellet, cloverleaf, and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2 cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 h (Cargill, R et al., 1988).

- **VISCOSITY GRADE OF POLYMER**

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity (Li, S *et al.,* 2003).

2. IDIOSYNCRATIC FACTORS

- **GENDER**

Women have slower gastric emptying time than do men. Mean ambulatory Gastric Residence Time (GRT) in meals (3.4±0.4 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface (Koner, P *et al*., 2007).

✧ **AGE**

Low gastric emptying time is observed in elderly than do in younger subjects. Intra-subject and inter-subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT (Mojaverian, P *et al*., 1988).

✧ **POSTURE**

- **UPRIGHT POSITION**

An upright position protects floating forms against postprandial emptying, because the floating forms remains above the gastric contents irrespective of its size. Floating dosage forms shows extended and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from, where they are expelled through the pylorus by antral peristaltic movements (Timmermans, J and Moes, AJ 1994).

- **SUPINE POSITION**

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects (Chawla, G *et al*., 2003).

- **CONCOMITANT INTAKE OF DRUGS**

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI motility decreasing drugs can increase gastric emptying time (Chawla, G *et al*., 2003).

- **FEEDING REGIMEN**

GRT increases in the presence of food, which leads to increased drug dissolution of the dosage form at the most favourable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins (Muller Lissner, SA and Blum, AL 1981).

● SUITABLE DRUGS FOR GASTRO RETENTION

Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release dosage form in the stomach is also useful for therapeutic agents, which the stomach does not readily absorb, since sustained release dosage form prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited (Richa Joshi and Sayantan Mukhopadhyay 2014). Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

- Narrow absorption window in GIT, e.g., levodopa and riboflavin.
- Basically absorbed from stomach and upper part of GIT, e.g., cinnarazine and chlordiazepoxide.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
- Locally active in the stomach, e.g., misoprostol and antacids.
- Drugs that degrade in the colon, e.g., metronidazole and ranitidine HCl.

APPROACHES TO GASTRO RETENTION

Several techniques are reported in the literature to increase the gastric retention of drugs (Singh, BN and Kim, KH, 2000; Shah, SH *et al*., 2009).

❖ HIGH DENSITY SYSTEMS

These systems, which have a density of ~3g/cm^{3,} are retained in the rugae of stomach and capable of withstanding its peristaltic movements that was through an image and presented in Figure 1.3 (Devereux, JE *et al*., 1990). The only major drawback with these systems are it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm^3. Diluents such as barium sulphate (density= 4.9), titanium oxide, zinc oxide, and iron powder must be used to manufacture such high density formulation (Chawla, G *et al*., 2003).

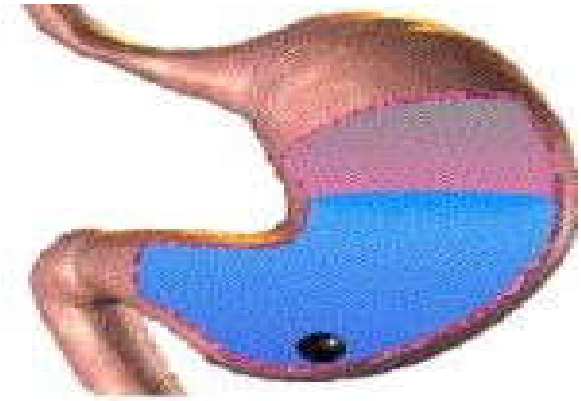

FIGURE 3: HIGH DENSITY SYSTEMS

❖ SWELLING AND EXPANDING SYSTEMS

These systems are also called as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state (Bolton, S and Desai, S 1989). The movement of the process in the stomach was given in Figure 1.4

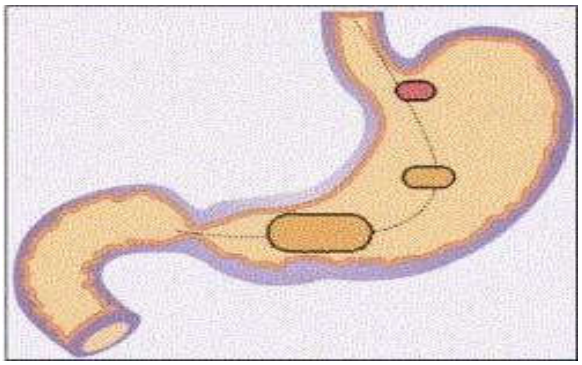

Figure 4: Swellable tablet in stomach

By selection of polymer with the proper swelling properties and molecular weight, sustained and controlled drug release can be achieved. Upon coming in contact with gastric fluid, the polymer absorbs water and swells. The voluminous swelling of these polymers is a result of the presence of physico-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of the polymer and thus maintain the physical integrity of the dosage forms. A high degree of cross linking retards the swelling property of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in

voluminous swelling followed by the rapid dissolution of polymer (Gupta, P *et al*., 2002).

❖ INCORPORATING DELAYING EXCIPIENTS

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a led stage thereby reducing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system (Groning, R and Heun, G 1984).

❖ MODIFIED SYSTEMS

Systems with non-disintegrating geometric shape moulded from silastic elastomers or extruded from polyethylene blends, that extend the GRT depending on shape, size and flexural modules of drug delivery device (Kedzierewicz, F *et al*., 1999).

❖ MUCOADHESIVE & BIOADHESIVE SYSTEMS

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site- specific manner. This way involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients, which have been used commonly in these systems include polycarbophil, chitosan, lectins, carbopol, Carboxy Methyl Cellulose (CMC) and gliadin, etc (Patel, R 2007 and Asane, GS 2007).

❖ FLOATING SYSTEMS

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach, by not affecting the gastric emptying rate for a prolonged period of time. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the dosage form system, which was shown in Figure 1.5. After release of drug, the residual system is emptied from the stomach (Mayavanshi, AV and Gajjar, SS 2008). Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with air, inert gas, or vacuum.

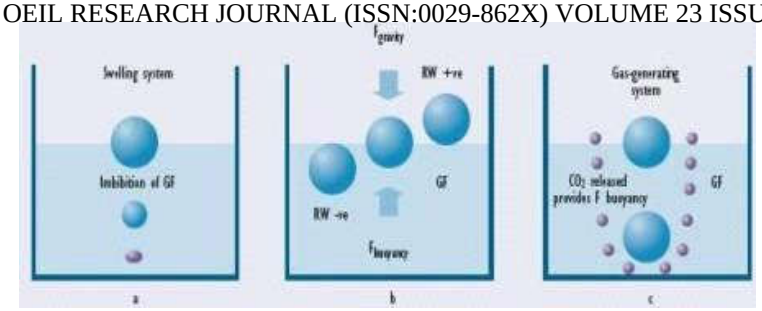

Figure 5: The mechanism of floating systems

CLASSIFICATION OF FDDS BASED ON MECHANISM OF BUOYANCY

- **SINGLE UNIT**

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract (Whitehead, L *et al*., 1998).

- **NON-EFFERVESCENT SYSTEMS**

One or more gel forming, highly swellable, cellulosic hydrocolloids (hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose (HPMC) and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers (polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules (Hilton, AK Desai, PB 1992 and Sheth, PR and Tossounian, JL 1978). For the preparation of these types of systems, the gel-forming hydrocolloid and the drug are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The swollen formed gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

- **EFFERVESCENT SYSTEMS OR GAS GENERATING SYSTEMS**

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. tartaric acid, citric acid, and sodium bicarbonate. They are formulated in such a way that, when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped

in swollen hydrocolloids, which provides buoyancy to the dosage forms (Ahmed, OAA 2013). The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 (Amit Kumar Nayak *et al*., 2013).

- **MULTIPLE UNITS**

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the inter-subject variability in absorption and the probabilities for dose dumping is lower (Kawashima, Y *et al*., 1998).

- **NON-EFFERVESCENT SYSTEMS**

A little or no much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit Hydrodynamically Balanced System (HBS) containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug with chitosan and acetic acid is extruded through a needle, and the exudates is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

- **EFFERVESCENT SYSTEMS**

A multiple unit system comprises of calcium alginate core and calcium alginate/ Polyvinyl Alcohol (PVA) membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is prepared and added drop wise into the aqueous solution of calcium chloride solution, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behaviour of radio labelled floating beads and compared with non-floating beads

in human volunteers using gamma scintigraphy. Prolonged GRT of more than 5.5 h was observed for floating beads. The non-floating beads had a shorter residence time with a mean onset emptying time of 1 h (Iannuccelli, V *et al*., 1998).

- **FLOATING MICROSPHERES**

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties are mainly depending on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit RS and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer-plasticizer ratio (Gholap, SB *et al*., 2010).

- **RAFT FORMING SYSTEMS**

The basic mechanism involved in the raft formation includes, the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called as raft (Deepika, K *et al*., 2014). The raft floats, because of the buoyancy created by the formation of Carbon-di-oxide (CO_2) and act as a barrier to prevent the reflux of gastric contents like Hydro Chloric Acid (HCl) and enzymes into the esophagus. Normally, the system contains formation of a gelling agent and alkaline carbonates or bicarbonates that are responsible for the formation of, to get the system less dense and float on the gastric fluids (Paterson, RS 2008). Reckitt and Colman Products Ltd., have come out with such formulation in the treatment for *H.pylori* infections of GIT.

ADVANTAGES OF FLOATING DOSAGE FORM

- These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., furosemide and riboflavin.
- The continuous change in plasma drug concentration is minimized, and concentration-dependent adverse effects, which are associated with peak concentrations, can be prevented. This special feature importance for drugs with a

narrow therapeutic index.

- The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
- Complete absorption of the drug from the floating drug delivery or dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in the gastric fluid occurs and dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.
- Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhoea. Under such situations, it may be advantageous to some extent to keep the drug in floating condition in stomach to get a relatively increased response.
- Drugs that have poor bioavailability since it have the site specific absorption property, which from the upper part of the gastrointestinal tract are the potential drug candidates can be formulated as floating drug delivery systems, thereby maximizing or improving their absorption. A considerable increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available Lasix® tablets (33.4%) and enteric-coated Lasix® long product (29.5%).

LIMITATIONS OF FDDS

- A high level of fluid in the stomach is essential for drug delivery to float and work effectively.
- Drugs which have solubility problems and stability in GIT are not suitable candidates for these types of systems.
- Drugs that under goes first pass metabolism may not be desirable for the preparation of these types of systems.
- Drugs that are irritant to gastric mucosa are also not desirable.
- The drug substances, which are unstable in the acidic environment of the stomach are not suitable drug candidates that to be incorperated in the system.

METHODOLOGY

PRIMARY CHARACTERIZATION OF ACTIVE INGREDIENT AND ADDITIVES

DESCRIPTION OF CEFDINI

mg of sample was taken in a Petri dish and was spread carefully and recorded its colour, odour and texture.

IDENTIFICATION TEST

To confirm the identity of all the ingredients used in the research work these following tests were carried out. The procedure was presented in Table 4.3.

INGREDIENTS	PROCEDURE
Carbopol	A 1% dispersion of Carbopolpolymer is neutralized to form viscous mucilage. With the addition of a 10% solution of calcium chloride, it forms a white precipitate immediately.
Hydroxy propyl methyl cellulose	To 5 ml of a 0.5% solution of the sample, 5 ml of a 5% solution of copper sulfate or of aluminium sulfate was added. No precipitate appears. This test permits the distinction of sodium hydroxy propyl methylcellulose from other cellulose ethers.
Poly vinyl pyrrolidone	To 5 ml of a 1 in 50 solution of the sample, 5 ml of dilute hydrochloric acid is added. To that 5 ml of water and 2 ml of 1 in 10 solution of potassium dichromate was added. A yellow precipitate forms.

Table 4.3: Identification test

PREFORMULATION STUDY OF CEFDINIR

Preformulation studies were carried out in order to find out of the drug excipients interactions. Compatibility studywas performed using DSC and FTIR to find out the interaction between the drug and excipients. The specific identification tests were carried out in order to find out the drug excipients interactions (Bhise *et al.,* 2007).

FTIR STUDIES OF CEFDINIR

Infrared spectrum obtained for pure Cefdinir. Physical mixture of drug and different polymers were used to verify the chemical compatibility of drug with the excipients used in the formulation development. IR Spectrum, which was taken for the identification, and it was prepared by pellet technique with 2-3 mg of sample and potassium bromide (dried at 40- 50ºC). A portion of the mixture was taken and compressed under 10 ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by FT-IR spectrophotometer.Using a FTIR spectrometer and the sample was scanned from 4000- 400cm^{-1}. The selection of excipients was performed as represented in the schematic diagram, which was presented in Figure 5.

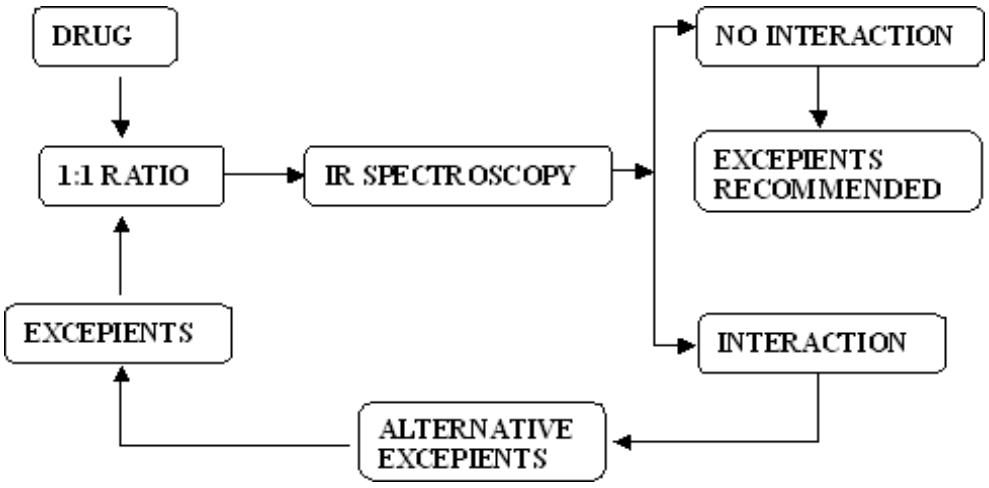

Figure 6: Schematic representation of compatibility studies

DIFFERENTIAL SCANNING CALORIMETRY STUDIES OF CEFDINIR

Differential Scanning Calorimetry (DSC) was performed to study the physical and chemical interaction between the drug and excipients that were used. DSC spectra of pure drug and drug composite mixture were recorded on DSC-60 instrument. The drug-excipient mixture was scanned in the temperature range of 50-400 ˚C under an atmosphere of nitrogen. Aluminium pans and lids were used for all samples. The heating rate was 20°C/min and the obtained thermograms were observed for any type of interaction.

MELTING POINT DETERMINATION

Melting point of Cefdinir was determined by capillary method(Akash Jain, 2004). Fine powder of cefdinir was filled in a glass capillary tube (previously sealed on one end). The drug filled capillary tube was inserted into the melting point apparatus and observed the temperature at which drug started to melt by using the thermometer.

ANGLE OF REPOSE

Angle of repose is the angle of inclination, formed to the flat surface by the bulk of granules, when it is allowed to flow under gravitational force from a fixed height (Bodhmage A, 2006).It is a characteristic of granule flow properties and is calculated by using the formula.

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

Where, Θ - Angle of repose; h - Height of granule above flat surface and r - Radius of circle formed by the granule pile. The limit has been presented in Table 4.

Flow ability	Angle of repose
Excellent	<25
Good	25-30
Passable	30-40
Poor	>40

Table 4: Limits of angle of repose

BULK DENSITY

The bulk density was determined by pouring perceived drug excepients blend into a graduated cylinder and measuring the volume and weight (TardosGI, 1996). It is expressed in g/ml and is given by

$$D_b = M/V_o$$

Where, M is the mass of powder and Vo is the bulk volume of powder

TAPPED DENSITY

It was determined by placing a graduated cylinder containing a known mass of drug excipients blend, on mechanical tapping apparatus (Cain J, 2002). The tapped volume was measured by tapping the powder to constant volume is expressed in g/ml and is given by

$$Dt = M/Vt$$

Where, M is the mass of powder and Vt is the tapped volume of powder

CARR'S COMPRESSIBILITY INDEX

It is also a characteristic of granule flow properties. The bulk density and tapped density was measured and compressibility index (Carr, 1965) was calculated using the formula,

$$C.I. = \{(Pt - P0) / Pt\} \times 100$$

Where, P_t is the tapped density and P_0 is the bulk density, the limit is given in Table 5.

Carr's Index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 5: Limits of Carr's Compressibility index

HAUSNER'S RATIO:

Tapped density and bulk density were measured and the hausner ratio (BellTA, 2001) was calculated using the formula,

$$\text{Hausner's ratio} = P_t / P_0$$

Where, P_t is the tapped density and P_0 is the bulk density.

DETERMINATION OF ΛMAX OF CEFDINIR

Two different stock solutions of drug sample were prepared by dissolving 100 mg of drug in 100 ml of 0.1 N HCl were further diluted and analyzed spectrophotometrically to determine λ_{max}.

PREPARATION OF CALIBRATION CURVE OF CEFDINIR IN 0.1 N HCL

Cefdinir was quantitatively analyzed by various techniques. In the current study, Cefdinir was quantified by UV spectrophotometry method. Stock solution was prepared by dissolving 100 mg of Cefdinir in 100 ml of 0.1N HCl solutions, which was further diluted to get the solutions of concentration 5, 10, 15, 20, 25, and 30 µg/ml respectively. Absorbance of these solutions were observed and measured using UV spectrophotometer at 264 nm and plotted in a graph, where wavelength against the concentration to get the standard curve.

FORMULATION OF FLOATING TABLETS OF CEFDINIR BY DIRECT COMPRESSION TECHNIQUE

Floating tablets of each containing 250 mg Cefdinir drug was prepared by direct compression technique. The preparation of the tablet was processed as presented in Figure 7. The composition of various formulations of the tablets with their codes are listed in the Table 6. Accurately weighed quantities of Micro Crystalline Cellulose (MCC) and polymer for each batch were taken in a mortar and mixed geometrically, to this required amount of Cefdinir was added and mixed slightly with pestle. Accurately weighed quantity of citric acid and sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is

passed through sieve # 40 and mixed with the Cefdinir blend which was also passed through sieve # 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and blendedfor 2 minutes, further the talc was added and mixed for 2 minutes.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
Cefdinir	250	250	250	250	250	250	250
HPMC K15M (Hydrophilic Polymers)	100	100	-	-	100	40	40
HPMC K 100 M (Hydrophilic Polymers)	50	-	100	-	50	110	120
Carbopol 934 P (Hydrophilic Polymers)	40	-	-	100	-	50	40
Sodium bicarbonate (Effervescent agent)	-	60	60	60	60	60	60
Citric acid (Effervescent agent)	-	30	30	30	30	30	30
PVP K 30	10	10	10	10	10	10	10
Micro crystalline cellulose(Filler)	100	100	100	100	50	-	-
Aerosol	5	5	5	5	5	5	5
Magnesium stearate (Lubricant)	3	10	10	10	10	10	10
Talc (Antiadherant)	3	5	5	5	5	5	5

Table 6: Composition of Cefdinir floating tablets

POST-COMPRESSION PARAMETERS

✓ DETERMINATION OF DRUG CONTENT

To evaluate tablets potential for efficacy, the quantity of drug per tablet needs to be checked from tablet to tablet, and batch to batch. To carry out this test, ten tablets from each batch was weighed and powdered. Powder equivalent to average weigh of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of 0.1N HCl. The solution was filled up to the mark and mixed well. A portion of the sample solution was filtered and analyzed by a UV spectrophotometer at 264 nm.

✓ WEIGHT VARIATION TEST

20 tablets were selected at random and weighted individually. The average weight of tablet was calculated. Individual weights of the tablets were compared for deviation with the average weight. Because of the tablets weighed over 100 mg, IP specifies that the tablets pass the test, if not more than two of the individual weights deviated from the average weight by more than 5% (IP, 2006).

✓ HARDNESS

Tablet hardness has been defined as the force required for breaking or cracking or crushing a tablet in a diametric compression test. A tablet was placed in between two anvils of the hardness tester (Monsanto type), force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded (Lachman, L*et al*., 1991).

✓ FRIABILITY

Tablets require a certain amount of strength, or resistance and hardness to friability, to withstand mechanical shocks of handling while in manufacture, packaging and also shipping. Pre-weighed tablet samples (20 tablets) were placed in the friabilator, which was then allowed to operate for 100 revolutions and dropping the tablets a distance of 6 inches with each revolution. The percentage friability was calculated using the formula (Lachman, L*et al*., 1991).

✓ *IN VITRO* BUOYANCY STUDY

The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) and duration of time by which the dosage form constantly emerge on surface of medium called Total Floating Time.(TFT).The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP.The temperature of the medium was maintained at 37±2ºC. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium was noted (Rosa, M*et al*., 1994). The floating behavior of Cefdinir tablet was presented in Figure 4.3.

✓ *IN VITRO* DISSOLUTION STUDY

Dissolution of the tablet of each batch was carried out using USP type I apparatus (Basket type) (Rasool Bazigha, KA and Sahar, AF2013).Nine hundred ml of 0.1 N HCl was filled in the dissolution vessel and the temperature of the medium was set at 37±0.5ºC. Tablet was placed in each dissolution vessel and rotational speed of basket was set at 50 rpm. The 5 ml of sample was withdrawn at pre-determined time interval for 12 h and same volume of fresh medium was replaced. The samples were analyzed or quantified for drug content against 0.1 N HCl as blank at λ_{max} of 264 nm using double beam UV visible spectrophotometer. The amount or content of drug was calculated using the equation generated from standard curve. The percentage cumulative drug release was calculated.

✓ STUDY OF SWELLING BEHAVIOR (WATER UPTAKE STUDIES)

Swelling of tablet/beads with excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle might be due to saturation of capillary spaces within the particles or hydration of macromolecule(Hassan Kawsar*et al*., 2011). The liquid enters the particles through pores and bind with the large molecule, breaking the hydrogen bond that result in the swelling of particle. Approximately one tablet/100mg of beads was taken in a dissolution basket and weighed(W1) the baskets along with the beads were immersed in simulated gastric fluid. The weight (W2) of the basket along with the beads was determined after 4th h and 8th h.

RESULTS AND DISCUSSION

PRIMARY CHARACTERIZATION OF ACTIVE INGREDIENT AND ADDITIVES

DESCRIPTION OF CEFDINIR

Description of the active ingredient was analyzed as described in 4.6.1.1. The observations were presented in Table 9. The color, odor, and texture of Cefdinir was complies as per IP specifications (IP, 2006).

S. No.	Components	Cefdinir
1	Color	Light Yellow
2	Odor	Odorless
3	Texture	Powder

Table 9: Description of active ingredient

IDENTIFICATION TEST

Identification tests were carried out as described in 4.6.1.2. The observed results were presented in Table 10. Additives that were used in our preformulation studies, for which identification tests were, performed (IP, 2006). Ugwoke et al., 2005 states that before the development of formulation excipients quality is must be identified.

Sl. No.	Ingredients	Observation	Inference
1	Carbopol	A white precipitate immediately forms.	Carbopol may be confirmed.
2	Hydroxy Propyl Methyl Cellulose	No precipitate appears.	Hydroxy Propyl Methyl Cellulose may be confirmed.
3	Poly vinyl pyrrolidone	A yellow precipitate forms.	Poly vinyl pyrrolidone may be confirmed.

Table 10: Identification test for additives

PREFORMULATION STUDY OF CEFDINIR

FTIR STUDIES OF CEFDINIR

The active component Cefdinir and physical mixture with different polymers were taken for FTIR as described in 4.6.2.1. The FTIR spectrum of Cefdinir was presented in Figure 9. The FTIR spectrum of HPMC K15M was presented in Figure 10. The FTIR spectrum of Cefdinir and HPMC K100M was presented in Figure 11. The FTIR spectrum of Cefdinir and Carbopol 934P was presented in Figure 12. The FTIR spectrum of Cefdinir and PVP K30 was presented in Figure 13. The FTIR spectrum of Cefdinir and Microcrystalline cellulose was presented in Figure 14.

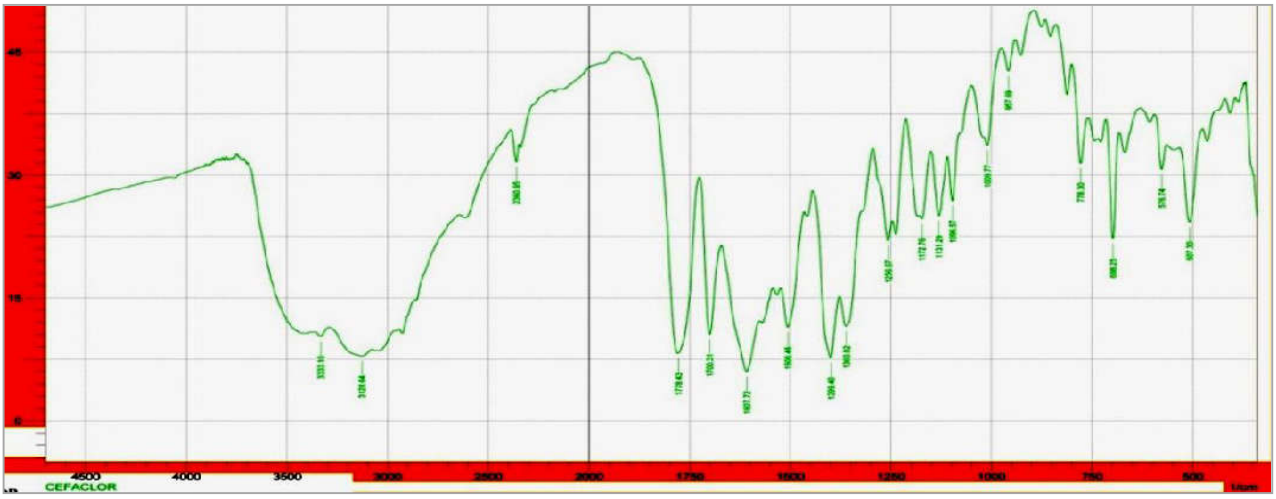

Figure 9: FTIR Spectrum of Cefdinir

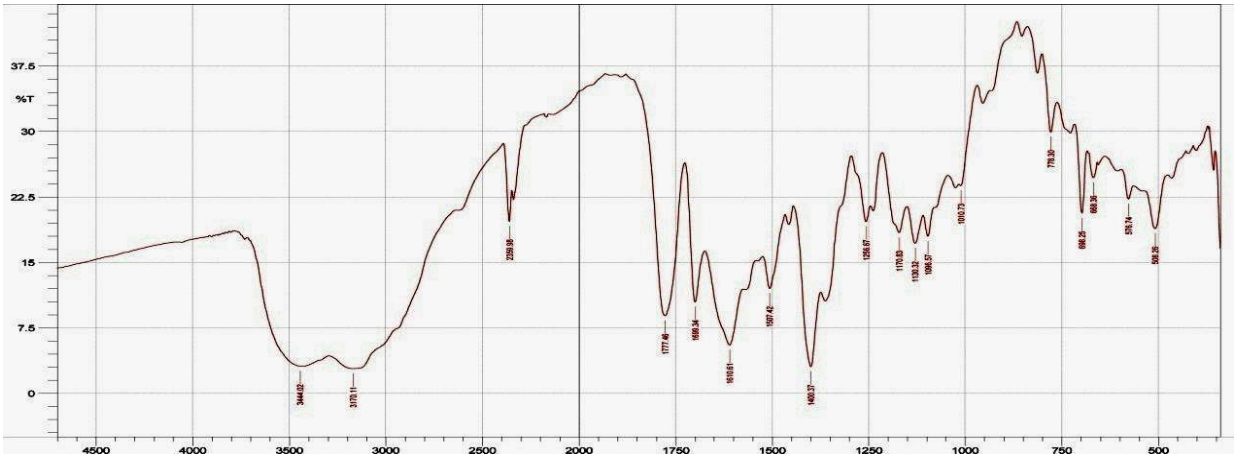

Figure 10: FTIR Spectrum of Cefdinir with HPMC K15M

Figure 11: FTIR Spectrum of Cefdinir with HPMC K100M

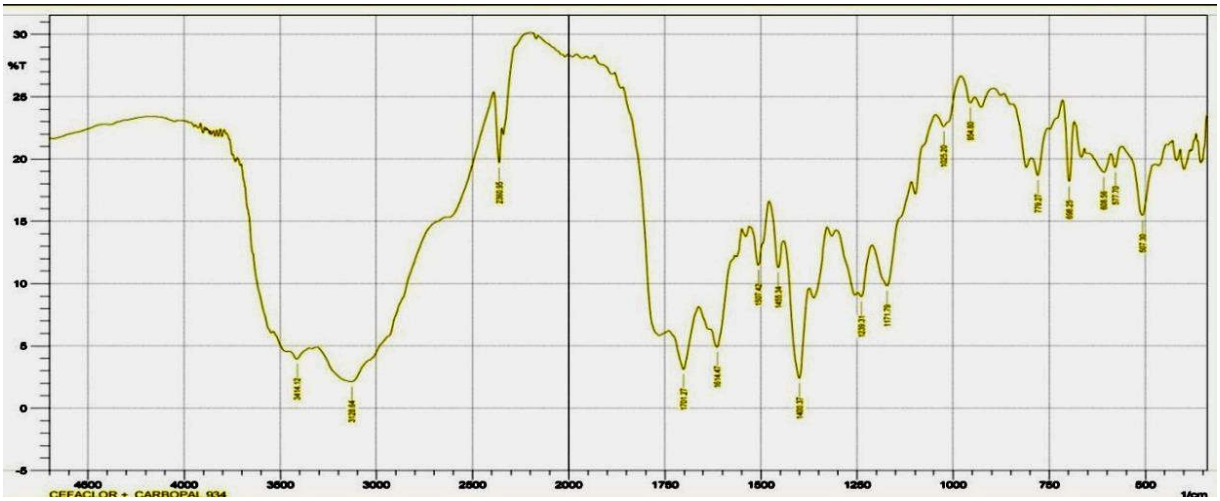

Figure 12: FTIR Spectrum of Cefdinir with Carbopol 934P

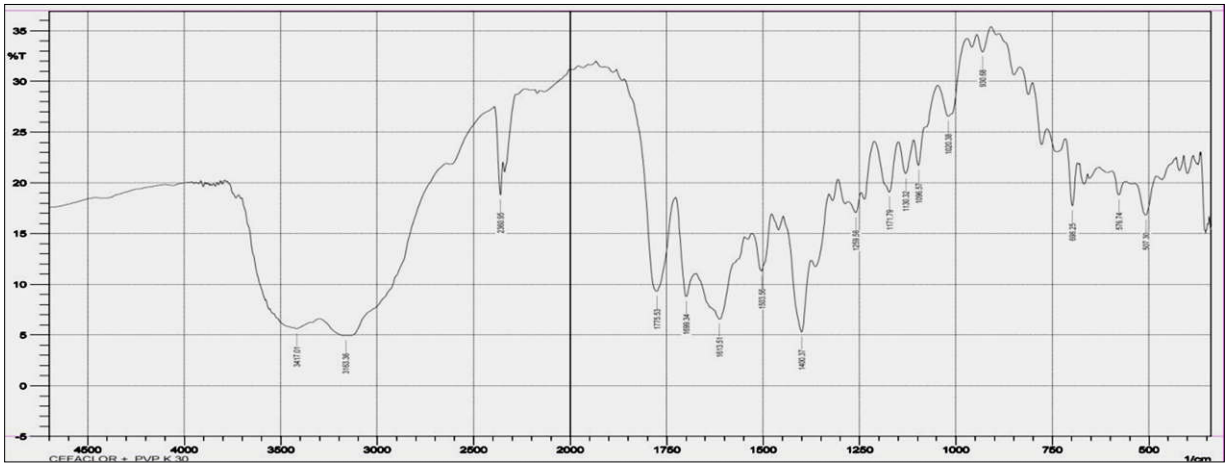

Figure 13: FTIR Spectrum of Cefdinir with PVP K30

In an effort to investigate the possible chemical interaction of drug with polymer, that have been analyzed (a) Cefdinir; (b) HPMC K15M; (c) HPMC K100M; (d) Carbopol 934P; and (e) PVP K30. Cefdinir has shown a characteristic peak at 1778.43 cm^{-1}, which shows C=C, broad band at 3333.10 cm^{-1}, shows a characteristic peak at 3128.64 cm^{-1}, which is responsible for C-NH, a sharp peak at 1360.62 cm^{-1} due to the presence of C-N, a sharp peak at 1399.40 cm^{-1} due to the presence of C-OH, a sharp peak at 1700.31 cm^{-1} due to the presence of C=O, a sharp peak at 776.30 cm^{-1} due to the presence of C-Cl and a sharp peak at 576.74 cm^{-1} due to the presence of C-S.

CHARACTERISTICS OF FINAL BLEND OF CEFDINIR FLOATING MATRIX TABLETS

Formulations	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index or Carr's Index	Hausner's ratio
F1	21°.32'	0.372	0.399	13.53	1.138
F2	22^0.15′	0.351	0.407	13.79	1.159
F3	21^0.23′	0.353	0.410	13.98	1.161
F4	23^0.36′	0.341	0.394	13.45	1.154
F5	24^0.18′	0.355	0.401	12.31	1.130
F6	21^0.22′	0.343	0.411	16.32	1.195
F7	22^0.38′	0.365	0.423	11.25	1.140

Table 10: Identification test for additives

These indicate that the chemical stability of Cefdinir was good after formulation. From results, it was concluded that there was no interference in the functional group as the principle peaks of Cefdinir were found to be unaltered in the drug polymer physical mixture.

DIFFERENTIAL SCANNING CALORIMETRY STUDIES OF CEFDINIR

Differential Scanning Calorimetry (DSC) study of Cefdinir was performed as described in 4.6.2.2. Thermograms were obtained for pure Cefdinir and mixed matrix

floating tablet containing Cefdinir with other excipients. Pure powdered Cefdinir showed a melting endotherm at 327.30 °C, found in Figure 15. There was no significant difference in the melting point of drug in both samples. It indicates that the drug was present in its characteristic physical and chemical form. It was compatible with all the excipients present in the tablet and there was no major interaction of the drug with the excipients which were presented in Figure 16-20.

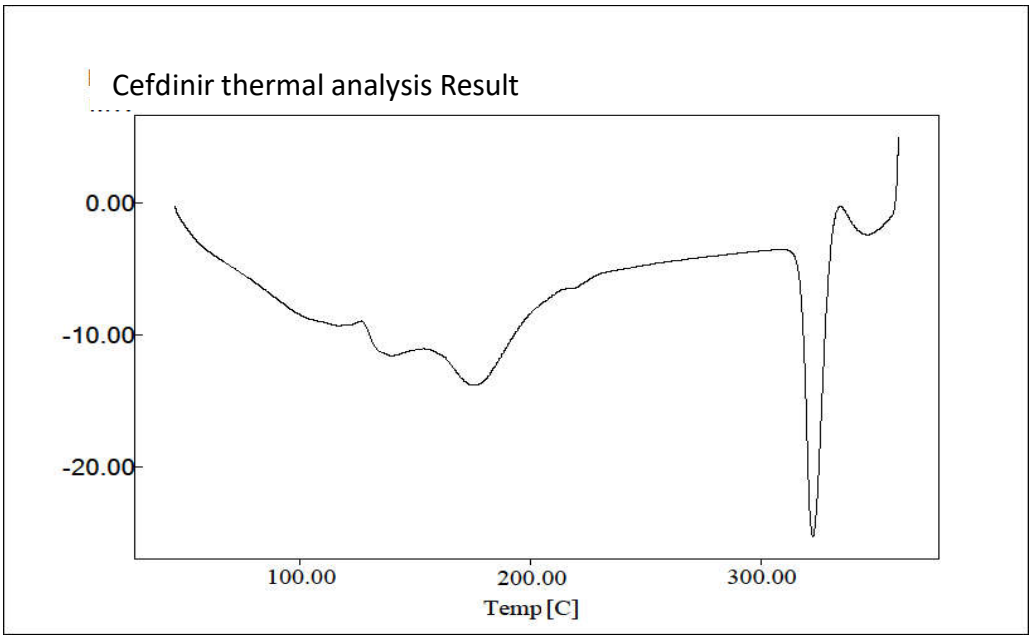

Figure 15: DSC thermogram of Cefdinir

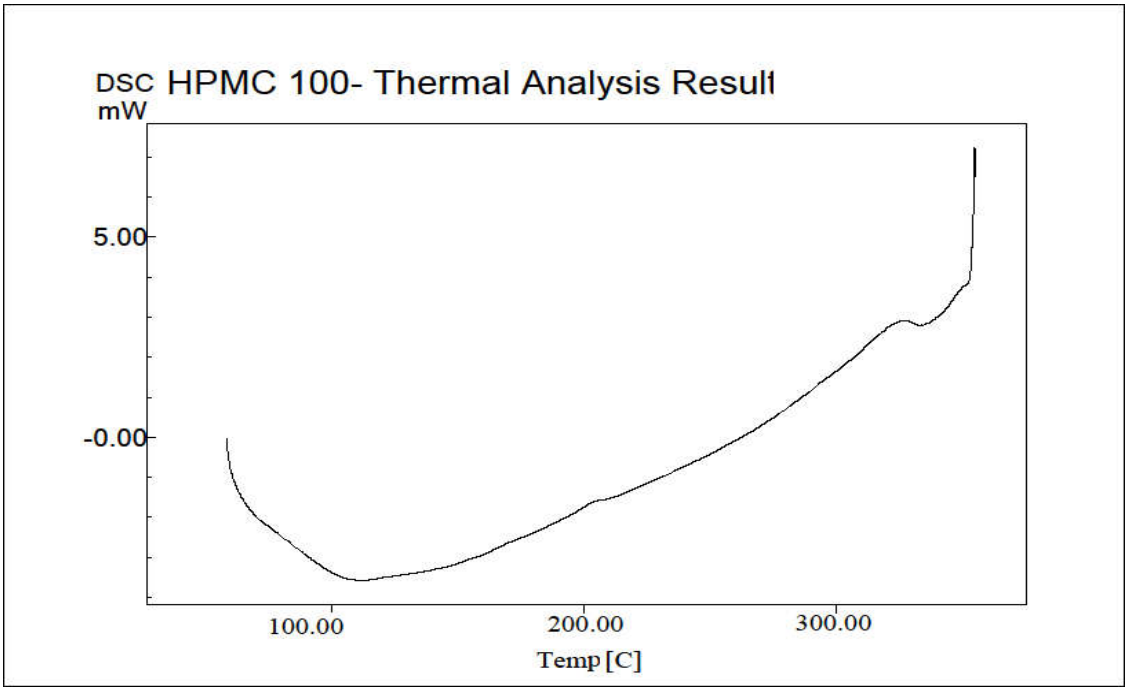

Figure 16: DSC thermogram of HPMC 100

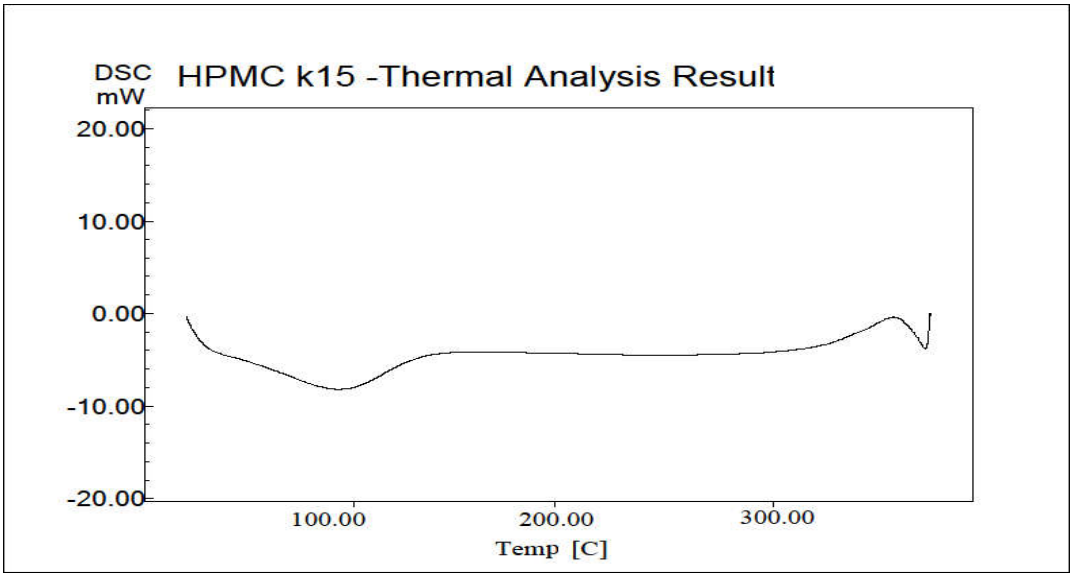

Figure 17: DSC thermogram of HPMC K15

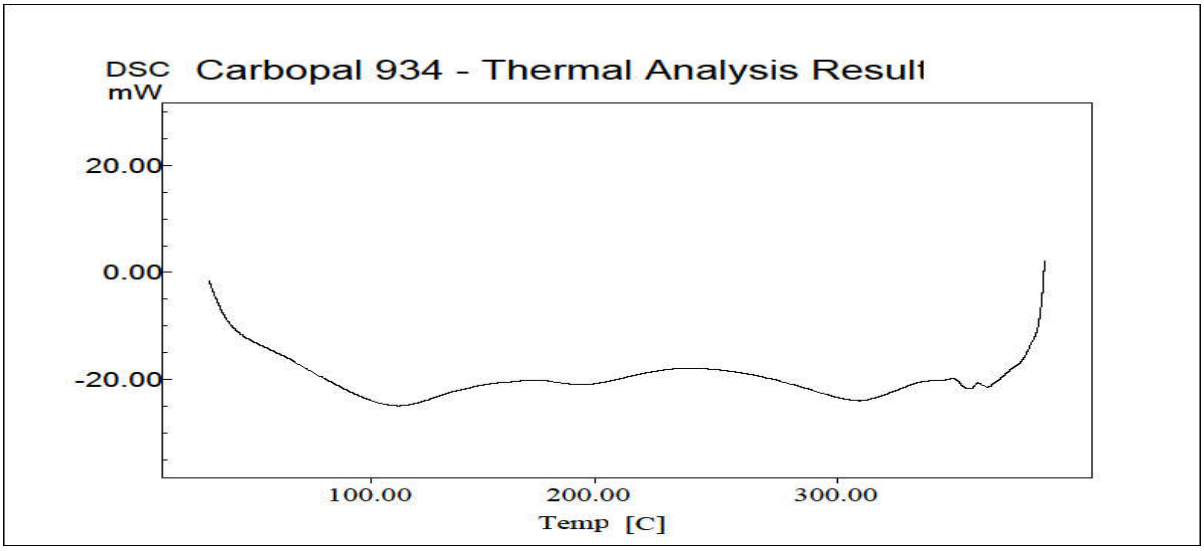

Figure 18: DSC thermogram of carbopal

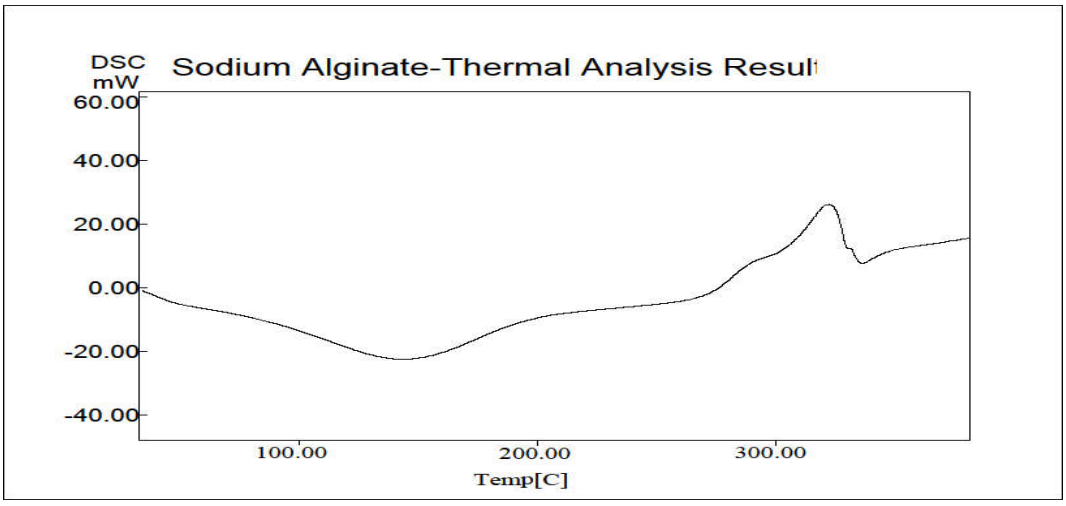

Figure 19: DSC thermogram of sodium alginate

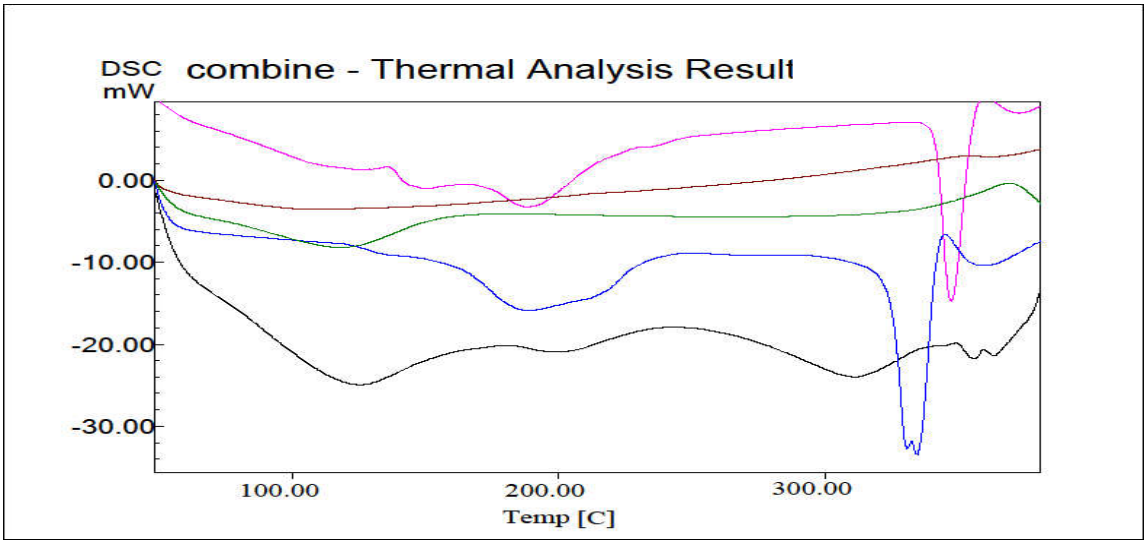

Figure 20: DSC thermogram of Cefdinir and polymers

- **MELTING POINT DETERMINATION**

Melting point of Cefdinir was determined as described in 4.6.2.3 and was found to be >180^{o}c

- **ANGLE OF REPOSE**

Angle of repose was determined as described in 4.6.2.4. Angle of repose of the different formulations were found to be less than <25$^{o}\theta$, which is excellent in the flow property. The observed values are presented in the Table 11.

- **BULK DENSITY**

The bulk density was determined as described in 4.6.2.5. It was found to be that, the bulk density of the different formulations lies between 0.353 and 0.372 g/ml, which is ideal. The observed values are presented in the Table 11.

- **TAPPED DENSITY**

Tapped density of the different formulations was determined as described by 4.6.2.6.It was found to be that the bulk density of the different formulations lies between 0.394 and 0.423 g/ml, which is ideal. The observed values are presented in the Table 11.

- **CARR'S COMPRESSIBILITY INDEX**

Compressibility index was calculated for the different formulations were determined as described by 4.6.2.7. It was found to be that, the compressibility index of the different formulations lies between 11.25 and 16.32, which is ideal (5 – 16). The observed values are presented in the Table 11.

- **HAUSNER'S RATIO**

Hausner´s ratio was calculated for the different formulations were determined as described by 4.6.2.8. It was found to be that the Hausner ratio of the different formulations lies between 1.130 and 1.195, which is ideal (< 1.25). The observed values are presented in the Table 11.

- **DETERMINATION OF λMAX OF CEFDINIR**

The absorption maximum was found by adopting the methodology as described in 4.6.2.9. It was found to be that the λ_{max} was found to be at 264 and 210 nm. Among the two wavelengths 264 nm that have been selected for further analysis, because 210 nm is the solvent peak of HCl. The spectrum of the Cefdinir was presented in Figure 21.

- **PREPARATION OF CALIBRATION CURVE OF CEFDINIR**

Cefdinir was quantitatively analyzed by various techniques. In the present study, Cefdinir was estimated by UV spectrophotometry method. The calibration curve was prepared as described in 4.6.2.10.

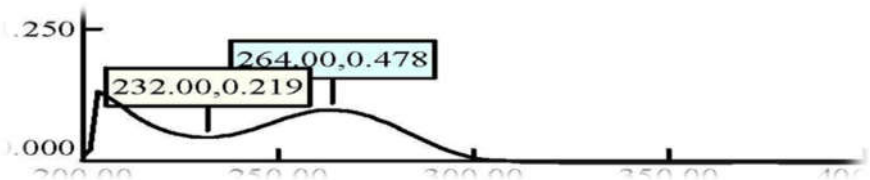

Figure 21: Absorption spectrum of Cefdinir

From the spectrum of the drug using 0.1 N HCl, it was concluded that the drug had λ_{max} at 264.0 nm and was recorded. It was observed that the drug obeys Beer-Lambert's law in the concentration range of 5-30 µg/ml. It shows a linear graph and the regression coefficient of the curve was found to be 0.9976. The data was presented in Table 12 and the linear curve was presented in Figure 22.

Concentration(µg / ml)	Absorbance
5	0.129
10	0.248
15	0.357
20	0.469
25	0.586
30	0.690

Table 12: Linearity profile of Cefdinir

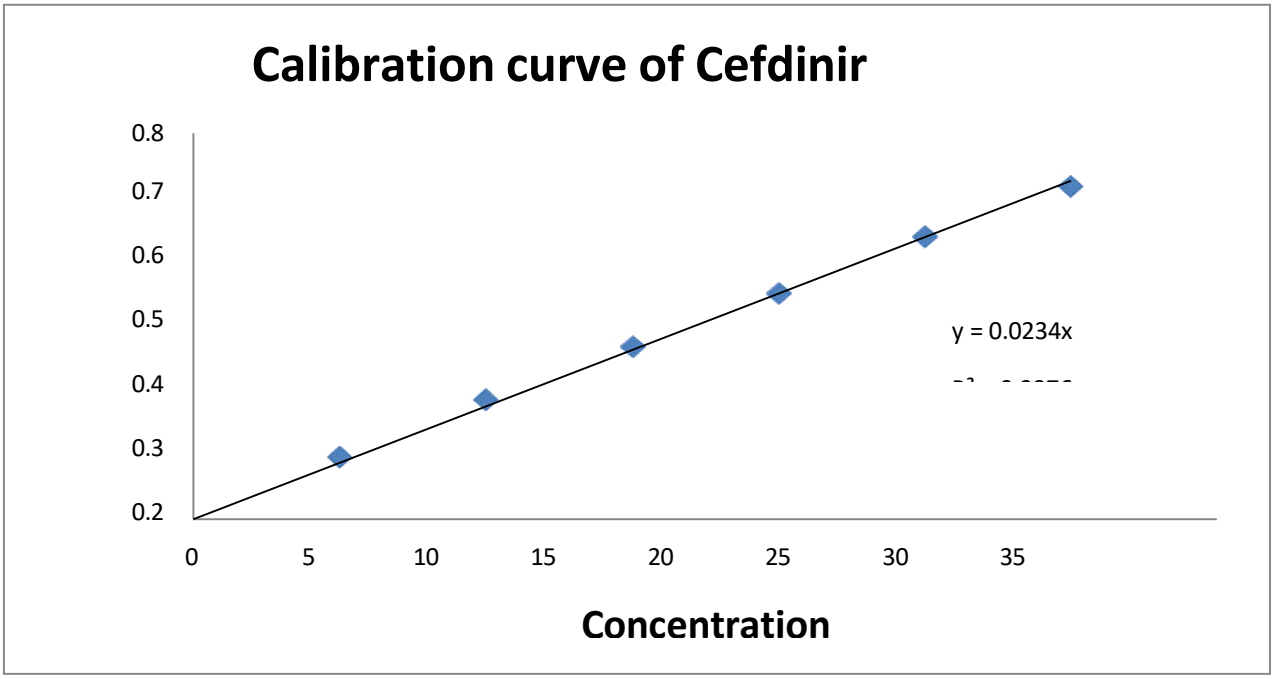

Figure 22: Calibration curve of Cefdinirin 0.1 N HCl

POST-COMPRESSION PARAMETERS (EVALUATION OF TABLETS)

DETERMINATION OF DRUG CONTENT

The floating tablets were formulated as described in 4.6.3, was evaluated for drug content as described in 4.6.4.1 and the results were presented in Table 12. It was found to be that, the drug content in the different formulations was lies between 93.5 and 100.1%.

WEIGHT VARIATION TEST

The floating tablets were formulated as described in 4.6.3, was evaluated for weight variation test as described in 4.6.4.2 and the results were presented in Table 12. It was found to be that, the weight variation of the different formulations was lies between 567±5 and 571±5 mg, which were within the limit as per IP (2006).

HARDNESS

The floating tablets were formulated as described in 4.2.3, was evaluated for hardness test as described in 4.6.4.3 and the results were presented in Table 13. It was found to be that, the hardness of the different formulations was lies between 10.2 and 11.1kg/cm^2, which were within the limit as per IP (2006).

FRIABILITY

The floating tablets were formulated as described in 4.6.3, was evaluated for friability test as described in 4.6.4.4 and the results were presented in Table 13. It was found to be that, the friability of the different formulations was lies between 0.205 and 0.325%, which were within the limit as per IP (2006).

***IN VITRO* BUOYANCY STUDY**

The floating tablets were formulated as described in 4.6.3, was evaluated for *In vitro* buoyancy study as described in 4.6.4.5. The time taken for the tablet to emerge on surface of medium and the duration of time by which, the tablet constantly remain on the surface of medium was noted and the results were presented in Table 14. From the floating behavior studies, it was found to be that as the concentration of effervescent mixture increase, the floating lag time, floating duration and matrix integrity

decreased and vice versa was observed through results. A reverse trend was observed on increasing the polymer concentration. The Initial batch is prepared without sodium bicarbonate did not show any sign of floating. Hence, sodium bicarbonate has been used as a gas generating agent in order to float the tablet, where the sodium bicarbonate induces CO2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration o thepolymer, thus decreasing the density of the tablet below 1g/ml, and the tablet become buoyant. To study the effect of sodium bicarbonate concentration on floating lag tie batches F1 to F7 were selected. It was found that, as the amount of polymer increases the floating lag time decreases. Thus sodium bicarbonate 60 mg and citric acid 30mg was essential to achieve optimum *in vitro* buoyancy (i.e. floating lag time of 4-5 minutes and floating duration of 12 h). Further increase in the concentration of sodium carbonate does not show any significant effect of floating behavior. The increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid drug release. Hence 60 mg concentration of sodium bicarbonate and citric acid was kept constant for batches, which showed floating lag time between 4 and 5 min and remained floating for more than 12 h. The relationship between the amounts of gas generating agents and floating lag time as well as the duration of floating are shown in table. It was observed that floating lag time for this system in the range of 4 to 54 min and flotation was achieved maximum at gas generating quantity of 60 mg and 30mg with in 4 min as shown in the Table 14.

Batch code	Floating lag time (min)	Total floating time (h)
F1	Did not float	Did not float
F2	54	>5
F3	25	>6
F4	17	>9
F5	12	>10
F6	4	>12
F7	4	>12

Table 14: *In vitro* buoyancy study of Cefdinir floating tablets

IN VITRO DISSOLUTION STUDY

The floating tablets were formulated as described in 4.6.3, was evaluated for *in vitro* dissolution study as described in 4.6.4.6. The dissolution profile of the formulated tablets was noted and the results were presented in Table 15 and Figure 23 & 24.

S.NO	Time (h)	F1	F2	F3	F4	F5	F6	F7
1	1	22.68	23.15	23.01	23.12	23.90	25.11	25.92
2	2	31.41	30.68	31.39	34.98	36.73	39.23	39.71
3	4	45.63	47.41	48.96	40.91	42.98	43.72	43.89
4	6	58.29	59.78	57.81	59.64	59.10	62.39	62.93
5	8	75.42	77.39	80.30	68.73	68.83	71.23	71.74
6	10	87.83	90.36	91.24	78.41	79.02	82.14	82.92
7	12	90.15	92.45	92.59	92.90	93.56	94.10	94.91

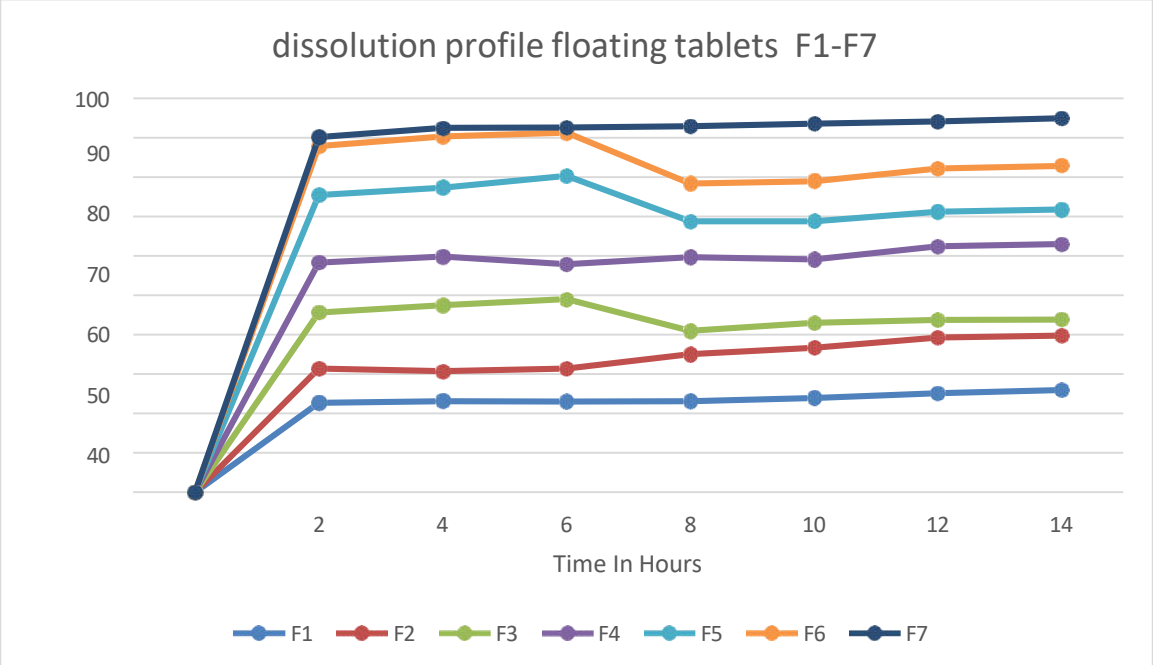

Figure 23: *In vitro* dissolution profile of Cefdinir floating tablets (F1-F5)

The percentage drug release from batch F1 to F7 vary from 90.15 to 94.91%. In formulation F1 without sodium bicarbonate the *in vitro* result shows 90.15% and from formulations F2 –F7 with only one polymer were showed 92.45, 92.59 and 92.90% at the end 12th h, and formulations F5 to F7 without filler, but different ratio of polymers shows the *in vitro* results of 93.99, 94.10 and 94.91. The drug released from the formulations diffusion coupled with erosion. Formulation, F7 is selected as optimized formulation among all the formulations showing 94.91 % sustained release at the end of 12 h as shown in Table 14.

SUMMARY AND CONCLUSION

Drug delivery system plays a pivotal role in the therapeutic efficacy of any drug therapy. This work was aimed to prepare and evaluate a novel drug delivery system of a therapeutically effective and proven drug. In this work, floating drug delivery administration has been selected because floating drug delivery administration appears to be an ideal for the systemic drug delivery.Cefdinir is an effective simple antibiotic drug. Therefore the objective of this thesis was to develop a new floating drug delivery system of Cefdinir, which can be administered through the oral route, particularly to achieve rapid relief by fast onset of action; to increase bioavailability and to avoid the second dose of administration.The work started with the preformulation followed by different trials of formulations. The compatibility study observations showed that, chemically Cefdinir remained unaffected by excipients.This project of final blend of Cefdinir floating matrix tablets were studied for angle of repose, tapped density, bulk density, compressibility index and Hausner’s ratio. The value of Carr’s Index from 5-16 indicates excellent to good flow of powder. Similarly value of Hausner ratio (< 1.25) and Angle of repose (< 25º) indicates good flow

properties of drug.The absorption maximum of Cefdinir was studied using UV spectrophotometry and found at 264 nm as the **max**. Using the absorption maxima, linearity was performed and plotted from the concentrations of 5-30 µg/ml was performed and the regression coefficient of the curve was found to be 0.9976.Seven batches of floating tablet were formulated using Cefdinir 250 mg with hydrophilic polymers, effervescent agent, filler, lubricant and anti-adherent with or without different proportions.Various formulations show good flow properties. Results of angle of repose (210.22′ – 240.18′), Bulk density (0.357-0.372), tapped density (0.391-0.423), Carr's index (11.25- 16.33) and Hausner's ratio (1.130-1.195) shows satisfactory results, which is need for better bioavailability. Evaluation results for hardness of various batches of prepared formulations (10.2 –11.1 kg / sq cm) and friability (0.205 – 0.325 %) indicates that the floating tablets having sufficient strength to withstand the physical abrasion. Tablets of all the batches were passed in the weight variation test as per the limits prescribed in IP (5% deviation is allowed for average weight of tablet X ≥ 250 mg).*In vitro* buoyancy study of Cefdinir floating tablets F1 to F7 was found to be satisfactory. It was observed that as the amount of polymer increases the floating lag time decreases. *In vitro* dissolution study Formulation F7 is selected as optimized formulation among all the formulations, which shows 94.91 % sustained release at the end of 12 h. Formulation F7 is selected as optimized formulation among all the formulations, which swelled to 121.38 % at the end of 8 hours.In the present study the floating tablets of Cefdinir showed better gastric cytoprotection when compared with conventional dosage form. This may be due to its extended duration of release and action.Floating drug delivery of Cefdinir has been an equivalent dose of Cefdinir and the target concentration achieved more rapidly and with less variability in plasma concentrations compared with eternal formulations.

REFERENCES

1. Akash Jain,Gang Yang, and Samuel H. Yalkowsky. Estimation of Melting Points of Organic Compounds. *Industrial and Engineering Chemistry Research*2004;43 (23): 7618-7621.

2. Arora S, Ali A, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review.AAPS PharmSciTech 2005; 6(3): E372- E390.

3. Asane GS. Mucoadhesive gastrointestinal drug delivery system: An overview. 2007; www.pharmainfo.net.
4. Amit Kumar Nayak, Ruma Maji, Biswarup Das. Gastro retentive drug delivery systems: A review. Asian Journal of Pharmaceutical and Clinical Research, 2010; 3(1): 1-10.
5. Amrinder Singh, Jha KK, Prabh Simran Singh and Anuj Mittal. Formulation and evaluation of Cefixime floating beads. International Journal of Research in Pharmacy and Chemistry, 2011; 1(4): 922-924.
6. Anil Patel, Janki Prasad Rai, Deepak Kumar Jain and Jitendra Banweer. Formulation, development and evaluation of Cefaclor extended release matrix tablet. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(4): 355-357.
7. Ahmed OAA, Shaimaa MBE and Tarek AA. Kinetic study of the *in vitro* release and stability of theophylline floating beads. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(1): 179-184.
8. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL, Editors. The Theory and Practice of Industrial Pharmacy, 3rd (Ed.), Mumbai: Varghese Publishing House; 198
9. Bolton S and Desai S, Floating sustained release therapeutic compositions, US Patent, 1989, 4,814,179.
10. Barbhaiya RH, Shukla UA, Gleason CR, Shyu WC, Wilber RB and Pittman KA.Comparison of cefprozil and cefaclor pharmacokinetics and tissue penetration. Antimicrobial Agents and Chemotherapy,1990; 34(6): 1204-1209.
11. Baumgartner S, Kristl J, Vrecer F. Optimization of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics 2000; 195: 125-135.
12. Bell TA. Flowability measurement and interpretation in industry. Handbook of Conveying and Handling of Particulate Solids, 10th (Ed.), 2001, p. 3-13.
13. Bhise SB and Rajkumar M. Controlled Nasal Drug Delivery of Ondansetron hydrochloride. Indian Journal of Pharmaceutical Education and Research 2006; 2(7): 229-235.
14. Bodhmage A. Correlation between physical properties and flowability indicators

for fine powders. Department of Chemical Engineering, University of Saskatchewan, 2006.

15. Beata Medenecka, Anna Jeli Ska, Marianna Zaj, Magdalena Ba Dyka Krzysztof Juszkiewicz and Irena Oszczapowicz. Stability of the crystalline form of Cefaclor monohydrate and its pharmaceutical preparations. Acta Poloniae Pharmaceutica, 2009; 66(5): 563-569.
16. Bharathi A, Kalyana Srinivas N, Ramana Reddy G, Veeranjaneyulu M, Sirisha A, Kamala P. Formulation and *in vitro* evaluation of Diclofenac Sodium sustained release matrix tablets using melt granulation technique. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(2): 788-808.

17. Carr RL. Evaluating flow properties of solids. Chemical Engineering 1965; 18: 163-168.
18. Cargill R, Cadwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric emptying: I. Effects of physical properties on gastric residence times of non- disintegrating geometric shapes in beagle dogs. Pharmaceutical Research 1988; 5: 533-536.
19. Chien YW. Rate-control drug delivery systems: controlled release vs. sustained release.Medical Progress through Technology 1989; 15: 21-46.
20. Chien YW. Oral drug delivery and delivery system in novel drug delivery Systems, Ed., 50, Marcel Dekker publication, New York, 1992.
21. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *European Journal*of*Pharmaceutical*Sciences 2001; 13:123–33.
22. Cain J. An alternative technique for determining ANSI/CEMA Standard 550 flow ability ratings for granular materials. Powder Handling and Processing 2002; 14: 218-220.
23. Chawla G, Gupta P, Koradia V, Bansal AK. Gastro retention: A Means to address regional variability in intestinal drug absorption. Pharmaceutical Technology 2003; 27: 250-268.
24. Chandrasekhara Rao Baru, Vidyadhara S, Raghavendra Rao KV, Vanitha Prakash K and Umashankar B. Formulation and evaluation of Ibuprofen floating tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(4): 472-481.
25. Chandra S and Kilimozhi D. Formulation and in-vitro evaluation studies on floating beads of cefaclor by emulsion gelation technique. Indo American Journal of Pharmaceutical Research, 2014; 4(8):3365-3377.
26. Desai S. A Novel Floating Controlled Release Drug Delivery System Based on a Dried Gel Matrix Network [master's thesis], Jamaica, NY: St John's University; 1984.
27. Davis SS, Stockwell AF, Taylor MJ. The effect of density on the gastric emptying of single- and multiple- unit dosage forms, Pharmaceutical Research 1986; 3: 208- 213.
28. Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. Journal of Pharmacology & Pharmacotherapeutics 1990; 42(7): 500-501.
29. Desai S and Bolton SA. Floating controlled-release drug delivery system: *in vitro-in vivo* evaluation. Pharmaceutical Research, 1993; 10(9): 1321-1325.
30. Deepika K, Alla Narayana Rao, Bhavana A, Ramana NV, Kalyani G**.** Formulation and evaluation of gastro retentive drug delivery of eprosartan mesylate using raft-forming approach. An International Journal of Advances in Pharmaceutical Sciences, 2014; 5(6):

2568-2574.

31. Groning R, Heun G. Dosage forms with controlled gastrointestinal transit. Drug Development and Industrial Pharmacy 1984; 10: 527- 539.
32. Gansbeke BV, Timmermans J, Schoutens A & Moes AJ. Intragastric positioning of two concurrently ingested pharmaceutical matrix dosage forms. Nuclear Medicine and Biology 1991; 18: 711-718.
33. Gergogiannis YS, Rekkas DM, Dallos PP, Chailis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Development and Industrial Pharmacy 1993; 19: 1061-1081.
34. Gupta P, Virmani K, and Garg S. Hydrogels: From controlled release to pH responsive drug delivery. Drug Discovery Today 2002; 7(10): 569-579.
35. Gadad AP, Patil MB, Naduvinamani SN, Mastiholimath VS, Dandagi PM, Kulkarni AR. Sodium alginate polymeric floating beads for the delivery of Cefpodoxime proxetil. Journal of Applied Polymer Science 2009;114:1921–6.
36. Gholap SB, Banarjee SK, Gaikwad DD, Jadhav SL. Thorat RM, Hollow microspheres: A Review. International Journal of Pharmaceutical Sciences and Research 2010; 1 (1): 74-79.
37. Gupta GD, Garg R. Gastroretentive floating microspheres of silymarin: Preparation and *in vitro* evaluation. Tropical Journal of Pharmaceutical Research 2010; 9 (1): 59-66.
38. Harries D, Sharma HL. GI transit of potential bioadhesive formulations in man: A scintigraphic study. Journal of Control Release 1990; 12: 45-53.
39. Hilton AK, Desai PB. *In vitro* and *in vivo* evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. International Journal of Pharmaceutics 1992; 86: 79-88.
40. Hetangi Rathod, Vishnu Patel, Moin Modasia. Floating drug delivery system: innovative approach of gastroretention. International Journal of Pharmaceutical sciences Review and Research 2010; 4(3): 183-192.