FORMULATION AND EVALUATION STUDIES OF FLOATING DRUG DELIVERY SYSTEM CONTAINING CEFACLOR ANTIBIOTIC

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LIST OF SYMBOLS AND ABBREVIATION

#	:	Number
%	:	Percentage
% EE	:	Percentage Entrapment Efficiency
^{0}C	:	Degree Celsius
AUC	:	Area under Curve
BP	:	British Pharmacopoeia
CMC	:	Carboxy Methyl Cellulose
CO_2	:	Carbon-di-oxide
Conc.	:	Concentration
Cp	:	Plasma drug concentration
CRDDS	:	Controlled-release drug delivery systems
EE	:	Entrapment Efficiency
F	:	Force
FDDS	:	Floating Drug Delivery System
FT-IR	:	Fourier Transform Infrared
g	:	Gram
GIT	:	Gastro Intestinal Tract
GRDF	:	Gastro-Retentive Dosage Form
GRT	:	Gastric Residence Time
h	:	Hour
HBS	:	*Hydro dynamically Balanced System*
HCl	:	Hydro Chloric Acid
HPLC	:	High Performance Liquid Chromatography
HPMC	:	Hydroxypropyl Methyl Cellulose
IP	:	Indian Pharmacopoeia
Kg	:	Kilogram
LHRH	:	Luteinising Hormone-Releasing Hormone
Log	:	Logarithm
M	:	Mole
M/L	:	Mole/liter
mg	:	Milligram

Min	:	Minutes
ml	:	Milliliter
MMC	:	Migrating Myoelectric Cycle
N	:	Normal
Nm	:	Nanometer
pH	:	Negative logarithm of hydrogen ion concentration
PK	:	Phamacokinetic
PVA	:	Polyvinyl Alcohol
PVA	:	Poly vinyl alcohol
PVP	:	Polyvinylpyrrolidone
rpm	:	Revolution per minute
SEM	:	Scanning Electron Microscope
SGF	:	Simulated Gastric Fluid
SR	:	Sustained Release
t ½	:	Time required by the reaction to reduce its half of theinitial concentration.
USP	:	United States Pharmacopoeia
UV	:	Ultra Violet
WU	:	Water Uptake
yrs	:	Years
λ	:	Lambda
µg	:	Micro gram

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1. INTRODUCTION

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, super porous hydrogels and magnetic systems. The current review addresses briefly about the FDDS that is one of the most leading methodologies in gastro retentive drug formulations. (S.Gopalakrishnan et al., 2011)

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) and characteristics of dosage forms (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.

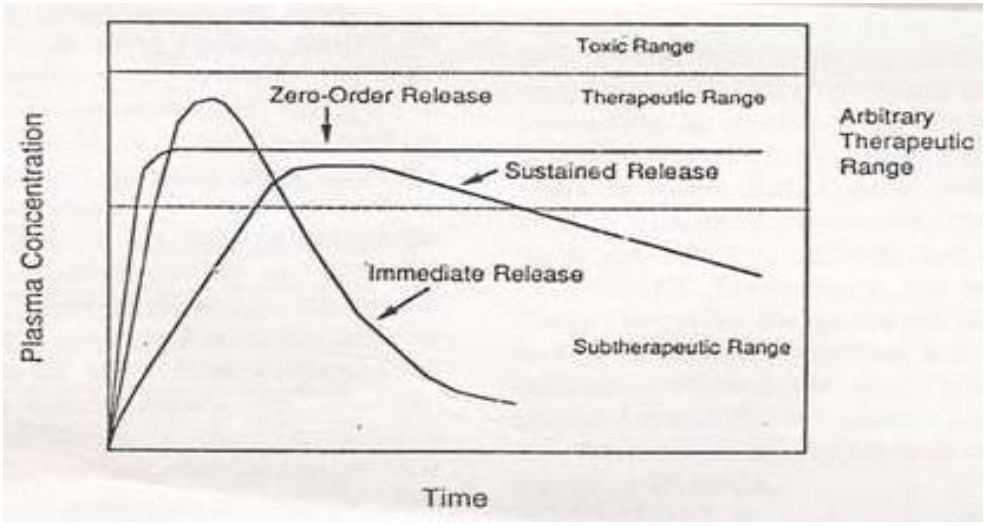


Figure 1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

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).

1.1 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).

1.2 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.

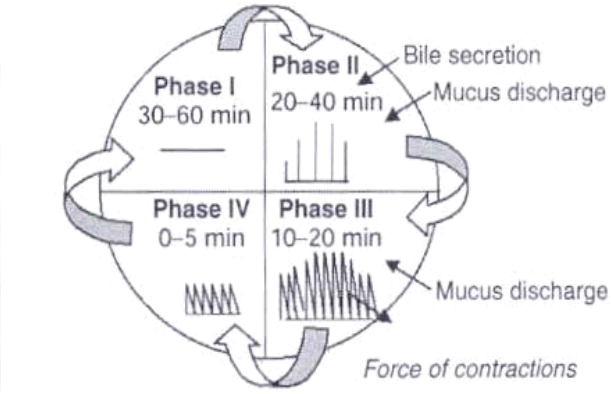


Figure 2: Motility pattern in GIT

1.3 Stomach Physiology:

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.

There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

- Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- Parietal cells: secrete hydrochloric acid.
- Chief cells: secrete pepsin, a proteolytic enzyme.
- G cells: secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions

- Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying. (Nikita Dixit., 2011)

1.4 Factors Affecting Gastric Retention

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and

in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down (Singh BN et al., 2000). The gastric retention time (GRT) of dosage form is controlled by several factors, that affect their efficacy as a gastroretentive system.

1.4.1 Density – Density of the dosage form should be less than the gastric contents (1.004gm/ml).

1.4.2 Size – Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.

1.4.3 Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

1.4.4 Single or multiple unit formulation – Multiple unit formulations show a more predictable due to failure of units, allow co- administration of units with

different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

1.4.5 Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

1.4.6 Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release (AJ.et al.1993).

1.4.7 Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

1.4.8 Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

1.4.9 Gender – Mean ambulatory GRT in males (3.4-0.6 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.

1.4.10 Age – Elderly people, especially those over 70, have a significantly longer GRT.

1.4.11 Posture – GRT can vary between supine and upright ambulatory states of the patient (Well LJ et al.,1998).

1.4.12 Concomitant drug administration– Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

1.5 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).

1.5.1 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).

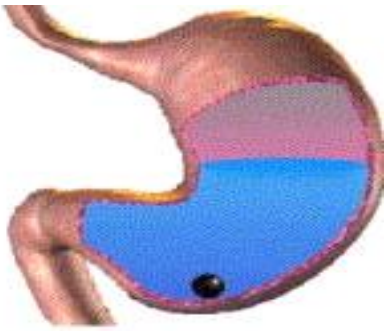


Figure 3: High density systems

1.5.2 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.

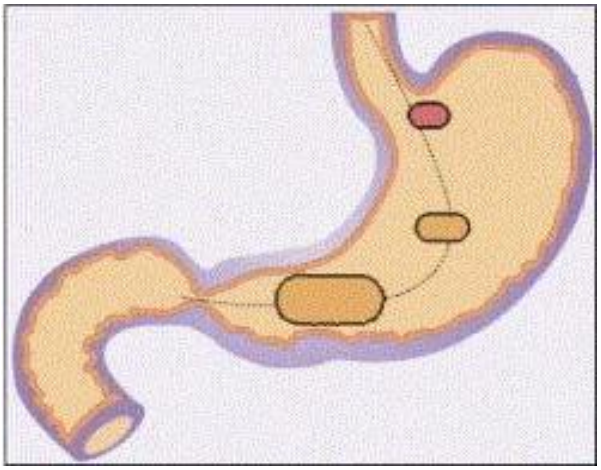


Figure 4: Swellable tablet in stomach

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).

1.5.3 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).

1.5.4 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).

1.5.5 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).

1.5.6 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.

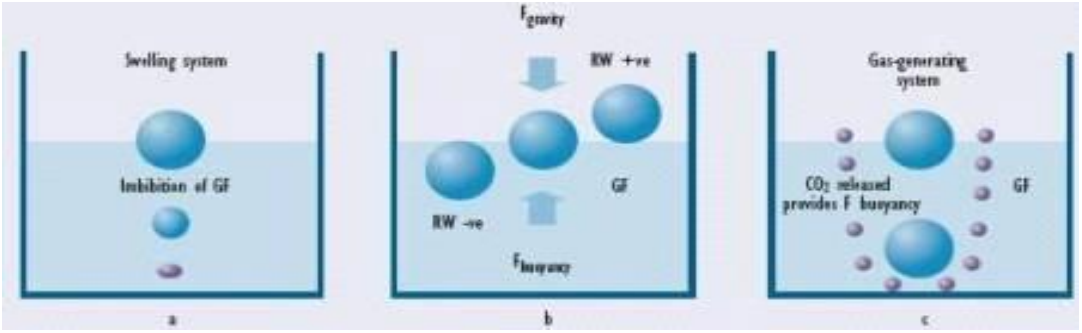


Figure 5: The mechanism of floating systems

1.6 TYPES OF FLOATING DRUG DELIVERY SYSTEMS

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

1.6.1 Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol. The various types of this system are as:

1.6.1.1Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

1.6.1.2 Bi-layer Floating Tablets:

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

Alginate Beads:

Multi-unit floating dosage forms were developed from freezedried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

1.6.1.4Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is

poured into an agitated aqueous solution of PVA that is thermally controlled at 40 ˚C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

1.6.2 Effervescent FDDS

1.6.2.1 Volatile liquid containing system:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

1.6.2.2Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

1.7DRUG CANDITATE SUITABLE FOR FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin)
- Drugs those are locally active in the stomach (e.g. misroprostol, antacids)

- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole)
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin)
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil)

1.8List of Drugs Explored For Various Floating Dosage Forms:

1.8.1 Microspheres Tablets /Pills:

Chlorpheniramine maleate, Aspirin, griseofulvin, Acetaminophen, p-nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxycillin trihydrate, Terfenadine, Ampicillin, Tranilast,Atenolol, Theophylline, Captopril, Isosorbide di nitrate, Sotalol, Isosorbide mononitrate.

1.8.2 Films: P-Aminobenzoic acid, Cinnarizine, Piretanide, Prednisolone, Quinidine gluconate.

1.8.3 Granules: Cinnarizine, Diclofenac sodium , Diltiazem, Indomethacin ,Fluorouracil, Prednisolone , Isosorbide mononitrate ,Isosorbide dinitrate.

1.8.4 Powders: Riboflavin,phosphate, Sotalol, Theophylline.

1.8.5 Capsules: Verapamil HCl, Chlordiazepoxide HCl, Diazepam, Furosemide, L- ,opa and benserazide Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine

1.9 Polymers and other ingredients used in preparations Of floating drugs:

1.9.1Polymers: The following polymers used in preparations of floating drugs - HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

1.9.2 Inert fatty materials (5%-75%) : Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

1.9.3 Effervescent agents : Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

1.9.4 Release rate accelerants (5%-60%): eg. lactose, mannitol.

1.9.5 Release rate retardants (5%-60%): eg. Dicalcium phosphate, talc, magnesium stearate.

1.9.6 Buoyancy increasing agents (upto80%): eg. Ethyl cellulose.

1.9.7 Low density material: Polypropylene foam powder (Accurel MP 1000)..

1.10 Advantages of FDDS

1. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.

3. The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.

4. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.

5. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

1.11 Limitations of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.

3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

1.12 APPLICATION OF FLOATING DRUG DELIEVERY SYSTEM:

1.12.1 Enhanced Bioavailability:

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.(Cook JD et al.1990)

1.12.2 Sustained drug delivery:

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited. (Moursy NM et al.2003)

1.12.3. Site specific drug delivery systems:

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin. (Menon A et al.1994).

1.12.4. Absorption enhancement:

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.(Rouge N et al.1998)

1.12.5. Minimized adverse activity at the colon:

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

1.12.6. Reduced fluctuations of drug concentration:

Continuous input of the drug following CRGRDF administration produces blood drug concentrations Within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. (Yie Chein et al.1992)

1.13 FUTURE PERSPECTIVES IN FLOATING DRUG DELIVERY SYSTEMS

Among the drugs currently in clinical use are several narrow absorption window drugs that may benefit from compounding into a FDDS. Replacing

parentarl administartion of drugs to oral pharmacotherapy would substantially improve treatment. It is anticipated that FDDS may enhance this possibility. Moreover, it is expected that the FDDS approach may be used for many patentially active agents with narrow absorption window, whose development has been halted due to lack of appropriate pharmaceutical FDDS technologies. Combination therapy to treat H.Pylori infection in a single FDDS need to be developed. Further investigation may concentarte on the following concept:

- Identification of a minimal cut-off size above that DFs retained in the human stomach for prolonged period of time. This would permit a more specific control to be achieved in gestroretentivity.
- Design of array of FDDS, each having a narrow GRT for use according to the clinical need e.g. dosage and state of disease. This may be achieved by compounding polymeric metrices with various boidegradation prpoerties.
- Study of the effect of various geometric shape, in a more excessive manner than previous studies, extended dimensions with high rigidity, on gestroretentivity.
- Design of novel polymers according to clinical and phamaceutical need.

2. LITERATURE REVIEW

Basak SC, Selvin CDS, sabapathy R. Formulation and in-vitro evaluation of amoxicillin dispersible tablets. The ind Pharma 2006;5(49): 71-73.

Bharathi, A *et al.*, (2011) investigated that hydrophilic polymers alone are not efficient in controlling the release of highly water soluble drugs. Waxes have been closely investigated for sustaining the release of drug. They provide several advantages include effectively retard the water soluble drug and good stability at varying pH ranges. In that study a novel approach where the water soluble drug is first incorporate in wax matrix prepared by melt granulation technique and this matrix is subsequently granulated with hydrophilic polymers. Hence it was considered that the combination of hydrophobic and hydrophilic polymers to prepare the matrix tablets would result in the desired slow release profile. Diclofenac sodium is preferred as a model drug since it is water soluble and having short half-life of 1-2 h. Sustained release matrix tablets were prepared by employing combination of hydrophilic polymers such as Sodium CMC, Sodium alginate, HPMC K4M and hydrophobic polymer stearic acid.

Chandrasekhara Rao Barru, *et al.*, (2012) formulated Ibuprofen floating tablets for optimizing the gastric floating drug delivery system by using various polymers like Carbopol 940 and HPMC K4M to enhance the bioavailability and therapeutic efficacy of ibuprofen by direct compression method.

Chowdary, KPR *et al.*, (2012) evaluated floating tablets of gliclazide, that is a poorly water soluble drug and it was formulated by employing (i) HPMC K100M (ii) Carbopol 934P and (iii) HPMC K4M as matrix formers, bees wax as floating

enhancer, sodium bicarbonate as gas generating agent and the tablets were analysed for floating and drug releases characteristics.

Desai, S *et al.*, (1993) prepared a novel floating controlled-release drug delivery system with the extension of gastric retention time of the dosage form and to control drug release. The buoyancy was attributed through the process of air and oil which got entrapped in the agar gel network. The *in vitro* drug release rate of the floating tablet was slower. The floating controlled-release theophylline tablet maintained constant of its release levels of about 2 mg/ml for 24 h that may be attributable to the release from agar gel matrix and the buoyancy of that tablet in the stomach.

Indian pharmacopeia.Ministry of Health and family welfare. Government of India, Delhi, vol -2, 1996:350.

Jain CP, Naruka PS .formulation and evaluation of fast dissolving tablets valsartan. Int J Pharm sci 2009; 1(1); 219-226.

Krunali, *et al.*, (2011) prepared a gastro retentive formulation of Mebendazole. Hydroxypropyl methyl cellulose and Chitosan of various viscosities were used. Sodium bicarbonate was incorporated in the formulation as a gas-generating agent. The effects of stearic acid and citric acid on drug release profile and floating properties were studied. The addition of stearic acid, which reduces the drug dissolution mainly because of its hydrophobic nature. The specific work was carried out to formulate such a dosage form that can neutralize the acidity locally in the stomach. Fluidized bed processor in which top spray technique was used for the preparation of the granules.

Lachman L, Liber HA. Pharmaceutical dosage forms of tablets. Marcel Dekker, Vol-2, 1981:241-243.

Manoj N. Gambhire, *et al.*, (2007) prepared a floating drug delivery system of diltiazem hydrochloride. These tablets were prepared using polymers such as hydroxypropylmethylcellulose, Compritol, alone or in combination and other standard excipients by direct compression technique. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of succinic acid and sodium bicarbonate on drug release profile and floating properties were investigated.

Moneghini M,bellich B, Baxa P, Principalle F. Microwave generated solid dispersions containing ibuproben .int J Pharma 2008;361:125-130.

Margret Chandira, R et al., (2009)*studied on the*formulation floating tablets of Diltiazem Hydrochloride using an effervescent approach for gastro retentive drug delivery system by direct compression technique using hydrophobic polymer and hydrophilic polymer in different quantities (%w/w), citric acid, magnesium stearate, sodium bicarbonate, talc and lactose in varying ratio to formulate the floating tablets.

Margret Chandira, R *et al*., (2010) formulated floating tablets containing itopride hydrochloride using effervescent approach for the gastro retentive drug delivery system. Floating tablets containing itopride hydrochloride, carbopol and polymers along with gas generating agent like sodium bi-carbonate and citric acid were fabricated using direct compression method.

Pillay, V and Fassihi, R *et al*., (1998) investigated the effect of delivery system positioning in accordance with the USP 23-recommended dissolution

methods and the proposed modification of the drug release from controlled release systems that having different operating release mechanisms namely, swellable sticking, swellable floatable and osmotic pump. The delivery systems were studied by placing each of the dosage form either in the dissolution vessel in accordance with the USP 23 methods or over/below a designed ring/mesh device so as to achieving full surface exposure to the dissolution medium for sticking or floatable systems respectively.

Patrick JS. Physical pharmacy and Pharmaceutical sciences.Lippncott Williams and Wilkins fifth edition, 2006:553-559

Patil, UK *et al.*, (2008) developed amlodipine besylate effervescent floating tablets by employing different grades of polymers and effervescent agents such as citric acid and sodium bicarbonate. The prepared tablets were evaluated for various buoyancy studies, dissolution parameters, physical parameters and drug released mechanisms.

Peterson Bhoi*, et al.*, (2010) prepared floating matrix drug delivery system of Diclofenac sodium. These tablets were prepared by melt granulation technique, using polymers such as ethyl cellulose, bees wax, Hydroxy propyl methyl cellulose alone or in combination with Cetyl alcohol and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on floating properties were studied.

Patel, DM *et al.*, (2011) describes an influence of ratio of Gelucire 43/01(hydrophobic) to hydroxypropyl methylcellulose K4M and different fillers on release of famotidine from gastro-retentive tablets using 3(2) full factorial design method. Gastro-retentive tablets that were prepared by a solvent free melt

granulation technique using Gelucire 43/01 as a hydrophobic meltable binder. Sodium bicarbonate and HPMC K4M were used as gas generating agent and matrixing agent respectively.

Ravi Kumar, *et al.*, (2009) developed and evaluated the floating tablets of famotidine which, after oral administration, are designed to extend the gastric residence time by increasing drug bioavailability and target the gastric ulcer. Floating drug delivery system was developed by using gas-forming agents, like citric acid, sodium bicarbonate and hydrocolloids, like carbopol and hydroxypropyl methylcellulose.

Ravi Kumar, *et al.*, (2009) prepared floating matrix drug delivery system of aceclofenac. This floating matrix tablets were developed to prolong gastric residence time and increase its bioavailability. It was prepared by melt granulation technique, using polymers such as ethyl cellulose, bees wax, hydroxyl propyl methylcellulose, cetyl alcohol, glycerin monostearate alone or in combination and other standard excipients which were added.

Rupavath Mahendar, *et al.*, (2012) developed Gastro retentive floating matrix tablets containing Stavudine without the gas generating agent of any type and was designed for the treatment of HIV and AIDS. The matrix tablets were prepared by using natural polymer such as pullulan gum. The drug release kinetics study reveals that the tablet formulations were follow the first order release with diffusion mechanism.

Simone S, Peter CS. Fast dispersible ibuproben tablets. Eur j Pharm Sci 2002; 15:295-305.

Shishu Gupta, N and Aggarwal, N *et al.*, (2007) developed and evaluated the single unit floating tablets of 5-Fluoro Uracil that, after oral administration, are designed to extend the gastric residence time by increasing the drug bioavailability and target the stomach cancer with citric acid, sodium bicarbonate and hydrocolloids, like Carbopol and hydroxypropyl methylcellulose.

Swatiu R, Sanjay KJ. Slublity enhancment of celecoxib using b-cyclodextrin inclusion complexes. Eur J pharm Biophgarm 2009; 57:263-27.

Swarna kamala, CH *et al.*, (2012) performed a study to formulate and evaluate gastroretentive floating drug delivery system using the drug gabapentin in the form of tablets using polymers like HPMC K100M, Polyox WSR 303 HPMC K15M, and sodium bicarbonate as gas generating agent by direct compression method.

Sybrahmanyam CVS. Text book of physical pharmaceutics. 2nd edition Delhi, Vallabh prakashan, 204; 210-228.

Tabasum, MD *et al.*, (2013) demonstrated on preparation and evaluation of diclofenac sodium prepared by wet granulation method of controlled release matrix tablets by using various quantities of natural polymer Abelmoschus esculentus mucilage powder as release controlling factor.

Yunxia B, Sunanda H. Preparation and evaluation of compressed tablets rapidly disintegration in the oral cavity.Chem Pharma Bull 1996;44(11):2121-2127.

Studies on Cefaclor

Anil Patel, et al., (2012) formulated cefaclor extended release tablets using hydrophilic swellable polymers HPMC E-15 & HPMC K-100M with lactose as

diluents. Talc, Magnesium stearate, LHPA, colloidal silicon dioxide and Croscarmellose sodium were used as excipients.

Rasool, Bk and Fahmy, SA et al.,(2013) developed and characterized the coated chitosan-alginate beads containing cefaclor as a controlled release delivery system. Cefaclor coated beads were prepared by solvent evaporation techniques and the beads were found to be intact and spherical in shape. The shellac coated chitosan-alginate beads would be considered as a successful controlled release oral cefaclor dosage form.

Bazigha K. Abdul Rasool, et al.,(2013) developed and characterized the coated chitosan-alginate beads containing cefaclor as a controlled release delivery system. By using solvent evaporation techniques the coated cefaclor beads were prepared.

BeataMedenecka, et al., (2009) studied the influence of temperature and relative air humidity on the stability of cefaclor in crystalline form and in its pharmaceutical preparations (slow release tablets and oral suspension) was investigated. The process of degradation was studied by using high-performance liquid chromatography using ultraviolet(UV) detector.

While gone through the review of floating tablet preparation the authors mainly focused on preparation by direct compression technique using hydrophilic polymer and hydrophobic polymer. Some instances it was also prepared by melt granulation technique. At the same time wet granulation method also used to prepare the tablets. One of the authors prepared the granules by fluidized bed processor in which top spray technique was adopted for forming the granules. This floating technique is mainly used for gastro retentive drug delivery using effervescent

approach. This is designed to increase drug bioavailability, prolong the gastric residence time and target the gastric ulcer. In the preparation of floating tablet the polymers used such as HPMC, ethyl cellulose, bees wax, carbopol, cetyl alcohol, glycerinmonostearate, Sodium CMC, Sodium alginate and hydrophobic polymer stearic acid alone or in combination and other standard excipients. Hydrophilic polymers are not quite efficient in controlling the release of highly water soluble drugs. Natural polymer, Abelmoschusesculentus mucilage powder and pullulan gum were used as release controlling factor in the formulation. Waxes have been extensively investigated for sustaining the release of drug and as floating enhancer. Gas forming agents such as sodium bicarbonate and citric acid were used.

Based on the review, different authors were prepared the beads or micro beads by various methods like drug –layered pellets which were coated with micronized polymer powders, Multiple unit floating beads, emulsion gelation method and ionotropic gelation method. In the micronized polymer powders ethylcellulose,(Eudragit) RS, and shellac by a dry powder were used. Macromolecular drugs also formulated in the form of beads from calcium-alginate gel beads. The bi-polymeric beads are used in the environment of varying pH to mimic transition of oral dosage from mouth to colon using behavior of ionically cross-linked sodium alginate/chitosan polymer. Polymers (Raymond C Rowe et al.,2009) such as carbopol, gelatin and sodium carboxy methyl cellulose, while sodium alginate being the commonly used polymer with a cross linking agents like calcium chloride and aluminium sulphate by the different authors. In these types of formulation as gas generating agent sodium bicarbonate and citric acid have been used.

Cefaclor is an antibiotic which possess low biological half-life and high stability in the acidic pH. With this drug, extended release tablets using hydrophilic swellable polymers and chitosan-alginate beads were prepared as a controlled release delivery system. No work has been carried out with cefaclor as floating tablet by direct compression technique and floating beads by emulsion gelation preparation method. Hence with these background the work was designed to "Formulation and evaluation of floating drug delivery system for selected antibiotic" with Cefaclor by preparing tablets and beads.

3. AIM AND OBJECTIVE OF THE WORK

Cefaclor was selected as a model drug.

- To carry out preformulation study of excipients and their compatibility with the API [Active Pharmaceutical Ingredient]
- To reduce the frequency of administration and to improve patient compliance
- Selection and optimization of the best formulation
- Comparitive study of optimize formulation and marketed product.
- To perform stability studies on the most satisfactory formulation

OBJECTIVE

The objective of the present study is to design and formulae a floating tablet comparable to the marketed formulation with better stability, high production feasibility and excellent patient acceptability.

PLAN OF WORK

To achieve the desired floating tablet formulation of Cefaclor and the experimental study was framed as follows.

Phase-1

- Preformulation study of the Active powder drug
- Preformulation study using FT-IR study
    - ✓ Drug and HPMC K15M
    - ✓ Drug and HPMC K100M
    - ✓ Drug and Carbopol 934P

- ✓ Drug and PVP K30
- ✓ Drug and microcrystalline cellulose

Phase-2

- To carry out the evaluation test of pre compression blend like
  - ✓ Angle of repose
  - ✓ Bulk density and Tapped density
  - ✓ Compressibility index
  - ✓ Hauser's ratio

Phase-3

- To evaluate the physical characteristics of prepared tablets like
  - ✓ Thickness
  - ✓ Friability
  - ✓ Hardness
  - ✓ Weight variation
  - ✓ Assay

Phase-4

- Dissolution kinetic study.
  - ✓ Investigation of drug release mechanism

Phase-5

- Stability study of the selected formulation as per ICH guideline.

4. MATERIALS AND METHODS

4.1 MATERIALS AND METHODS

4.1.1 Materials

All the chemicals used in the study are spectrograde. All the glass wares used in the studies were of Borosil grade. The chemicals and instruments were used for the present research study are summarized in Table 1 and 2 respectively.

Table 1: List of Chemicals

S. No.	Chemicals	Supplier
1.	Cefaclor	Yarrow chemicals , Mumbai, India
2.	Hydroxy propyl methyl Cellulose k15m, k100m.	Yarrow chemicals , Mumbai, India
3.	Carbopol 934 p	S.D. Fine Chemicals, Chennai, India
4.	Poly vinyl pyrollidine k 30	S.D. Fine Chemicals, Chennai, India
5.	Microcrystalline Cellulose	Thomas baker Pvt. Ltd., Mumbai, India.
6.	Sodium bicarbonate	Thomas baker Pvt. Ltd., Mumbai, India.
7.	Citric acid	Thomas baker Pvt. Ltd., Mumbai, India.
8.	Magnesium stearate	Thomas baker Pvt. Ltd., Mumbai, India.
9.	Talc	Thomas baker Pvt. Ltd., Mumbai, India.

Table 2: List of Instruments

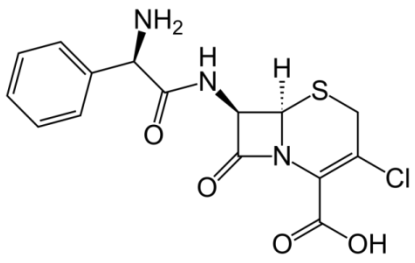
S.NO	INSTRUMENTS	MANUFACTURERS
1	Single pan electronic balance	Shimadzu-corporation, Japan.
2	Vernier calipers	Mitutoyo corpn, Japan.
3	Hardness tests	Monsanto
4	Friability test apparatus	Electro lab, India.
5	Tapped density tester	Electro lab, India.
6	Dissolution Apparatus	Electro lab, India.
7	HPLC with PDA/Binary System	Shimadzu-corporation, Japan.
8	FTIR spectrophotometer 83000	Shimadzu-corporation, Japan.
9	pH Meter	Mettler Toledo
10	Moisture balance	Sartorius

4.2 Drug Profile

Cefaclor is also known as cefachlor or cefaclorum (Brands: Biocef, Ceclor, Distaclor, Keflor, Raniclor etc.), which is a Second-generation cephalosporin antibiotic that is used to reduce the development of drug-resistant bacteria and treat certain infections caused by the bacteria such as pneumonia and infections of the throat, lung, ear, skin and urinary tract.

4.2.1 Properties of the drug

Structure of Cefaclor:



Molecular formula	:	$C_{15}H_{14}CIN_3O_4S.H_2O$
Molecular Weight	:	367.804 g/mol
Relative molecular mass	:	385.82
IUPAC Name	:	(6R,7R)-7-[(2R)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
Chemical name	:	3-Chloro-7-D-(2-Phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate

4.2.2 Physical properties:

Cefaclor is a slightly yellow or white in colour and poses slight characteristic odour. It is practically insoluble in methanol and in methylene chloride but slightly soluble in water. It should be stored at 20°- 25°C (68° to 77°F). It has the melting point of 327^{o}c

4.2.3 Half-life: 0.6-0.9hrs.

4.2.4 Mechanism of Action:

Cefaclor, like the penicillins, is a beta-lactam antibiotic. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins. It is possible that cefaclor interferes with an autolysin inhibitor.

4.2.5 Pharmacodynamics:

Cefaclor is a second generation cephalosporin antibiotic with a spectrum resembling first-generation cephalosporins. *In vitro* tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections: Gram positive aerobes - Staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains), *Streptococcus pneumoniae*, and *Streptococcus pyogenes* (group A ß-hemolytic streptococci). Gram-negative aerobes - *Escherichia coli*, *Haemophilus influenza* (including ß-lactamase-producing ampicillin-resistant strains), *Klebsiella sp*, and *Proteus mirabilis*.

4.2.6 Metabolism:

No appreciable biotransformation in liver (approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours).

4.2.7 Route of Elimination:

Approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours.

4.2.8 Clinical Pharmacology

Cefaclor is well absorbed after oral administration, whether taken with food or while fasting; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from 45 minutes to 1 hour later. The presence of food

in the gastrointestinal tract does not alter the total amount of cefaclor absorbed. Following administration of 250 mg,500 mg, and 1 g doses to fasting subjects average peak plasma levels of antibacterial activity (expressed as μg/mL of cefaclor) of 7, 13 and 23 μg/mL, respectively, were obtained at 30 to 60 minutes. The reduced peak serum levels resulting from the administration of cefaclor with food should be considered with reference to the sensitivity of the infecting organism, severity of illness, the dose being administered and the variability in the peak plasma levels which occur with cefaclor. The plasma half-life in healthy subjects is independent of dosage form and averages 40-60 minutes. In elderly subjects (over age 65) with normal serum creatinine values, a higher peak plasma concentration and AUC are effects resulting from mildly diminished renal function and are not expected to have clinical significance. Therefore, dosage changes are not necessary in elderly subjects with normal renal function. There is no evidence of metabolism of Cefaclor in humans.

4.2.9 Indications

Cefaclor is indicated for the treatment of the following types of infections caused by or likely to be caused by susceptible organisms: Lower respiratory infections, including pneumonia, bronchitis and exacerbations of chronic bronchitis. Upper respiratory infections, including pharyngitis, tonsillitis and otitis media. Skin and skin structure infections. Urinary tract infections, including pyelonephritis and cystitis.

4.2.10 Contraindications

Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics or who have previously experienced a major

allergy to penicillin. Cefaclor is also contraindicated in infants under the age of one month as safety and efficacy of this product has not been established in prematures and infants under one month of age.

4.2.11 Precautions

In penicillin-sensitive patients, cephalosporin antibiotics should be administered cautiously. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins and there are instances in which patients have had reactions, including anaphylaxis, to both drug classes. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients on penicillin/ cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/ cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with a penicillin/cephalosporin.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Prolonged use of Cefaclor may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of Cefaclor in anuria is 2.3 to 2.8 hours,

dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with Cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

Cefaclor should be used with caution in patients with liver disease, as documented clinical experience in this group of patients is lacking.

4.2.12 Drug Interactions

As with other ß-lactam antibiotics, the renal excretion of Cefaclor is inhibited by probenecid.

4.2.13 USES:

Use in Pregnancy - The oral administration of high dose Cefaclor (500 mg/kg) in pregnant rats and mice has resulted in a slight increase of minor skeletal malformations. Safety of this product for use during pregnancy has not been established. Cefaclor should not be used in women of child bearing potential unless, in the judgement of the treating clinician, its use is considered essential to the welfare of the patient and the expected benefits outweigh potential risks.

Use in Lactation -Small amounts of Cefaclor have been detected in mother's milk following administration of single 500 mg doses of Cefaclor. Average levels were 0.18, 0.20, 0.21 and 0.16 μg/mL at 2, 3, 4 and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when Cefaclor is administered to a nursing woman.

Use in Children - Safety and effectiveness of this product for use in infants less than one month of age have not been established. Serum sickness-like reactions

including arthritis and arthralgia have been reported more frequently in children than in adults.

4.2.14 Adverse Reactions

Gastrointestinal: The most frequent side effect has been diarrhoea. Nausea and vomiting have been reported rarely. Colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Cefaclor.

Hepatic -- Transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity -- Allergic reactions, such as urticaria and morbilliform eruptions, have been observed, as have pruritus and positive Coombs' tests. These reactions usually subsided upon discontinuation of the drug. Angioedema and fever have been reported rarely.

Blood -- Eosinophilia, transient lymphocytosis, leukopenia, and rarely, thrombocytopenia, thrombocytosis, haemolytic anaemia, aplastic anaemia, agranulocytosis, and reversible neutropenia of possible clinical significance. There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and warfarin concomitantly.

Kidney -- reversible interstitial nephritis.

Superinfection -- Genital pruritis, moniliasis or vaginitis.

Central Nervous System -- Rare: reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, headache or somnolence have been reported.

Other -- Transitory abnormalities in clinical laboratory test results have been reported, but their clinical significance is uncertain. These include slight elevations in AST, ALT, or alkaline phosphatase values; transient fluctuations in leukocyte count, predominantly lymphocytosis in infants and young children; and slight elevations in serum urea or serum creatinine or abnormalities of urinalysis (haematuria; pyuria).

4.2.15 DOSAGE AND ADMINISTRATION

Cefaclor is administered orally.

Directions for reconstitution of Cefaclor powder for oral liquid bottle 125 mg/5 mL - Add 60 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition. 250 mg/5 mL - Add 45 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition. Adults-The usual adult dosage is 250 mg every 8 to 12 hours. For bronchitis and pneumonia, the dosage is 250 mg administered 3 times daily. For more severe infections or those caused by less susceptible organisms, doses may be doubled (500 mg 8 hourly). Doses of 2 g/day should not be exceeded. For skin and skin structure infections the dosage is 250 mg 2-3 times a day. Children-The usual recommended daily dosage for children with mild to moderate infections is 20 mg/kg/day in divided doses every 8 hours (maximum 1 g/day). For streptococcal pharyngitis/tonsillitis and impetigo, 12 hourly administration appears equally effective. In more serious infections, otitis media, and infections caused by less susceptible organisms, the recommended dosage is 40 mg/kg/day in divided doses every 8 to 12 hours (maximum 2 g/day). For otitis media, 12 hourly administration appears equally effective. Cefaclor may be administered in the

presence of impaired renal function. Under such a condition, the dosage usually is unchanged). In the treatment of beta-haemolytic streptococcal infections, a therapeutic dosage of Cefaclor should be administered for at least 10 days.

4.2.16 Over dosage

Signs and Symptoms -- The toxic symptoms following an overdose of Cefaclor may include nausea, vomiting, epigastric distress and diarrhoea. The severity of the epigastric distress and the diarrhoea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

Treatment -- In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefaclor.

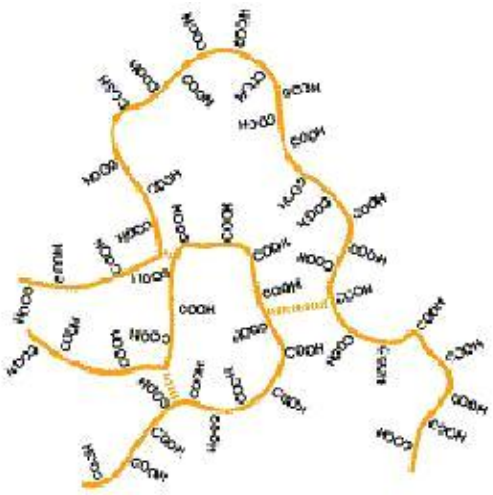
4.3 Carbopol

Synonyms: Acrypol; Acritamer; acrylic acid polymer; carboxyvinyl polymer; Pemulen; Tego Carbomer; carbomera; Carbopol; carboxy polymethylene; polyacrylic acid.

Chemical name: Sodium; prop-2-enoic acid.

Molecular weight: 94.04 g/M

Structure:



Description: Carbomers are white-colored, acidic and hygroscopic powders with a characteristic slight odor. Granular carbomers are also available. Decomposition occurs less than 30 min at 268^{o}C. It is swellable in glycerin and water, after neutralization, in ethanol (95%). Carbomers do not soluble, but merely swell to a remarkable extent, because they are three-dimensionally crosslinked microgels.

Functional category: Bioadhesive material, emulsifying agent, emulsion stabilizer, rheology modifier, stabilizing agent, controlled-release agent, suspending agent and tablet binder.

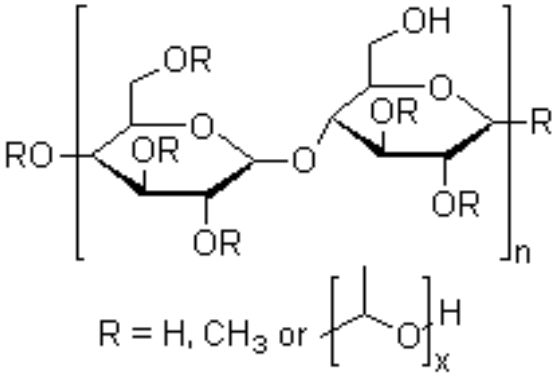
4.4 Hydroxy Propyl Methyl Cellulose

Synonym: Cellulose, Hypromellose, 2–Hydroxypropylmethyl ether, Methocel, Pharmacoat, Methyl hydroxy propyl cellulose, Metolose.

Chemical name: Cellulose-2-hydroxy propyl methyl ether

Molecular weight: 10,000 – 15, 00,000 g/M

Structure:



Description: It is a yellowish white, white or greyish white and practically odorless, fibrous powder or granules. It is practically insoluble in hot water, dehydrated alcohol, chloroform and ether but soluble in cold water, forming a colloidal solution. It will be browns at 190-200°C; chars at 225-230 °C.

Functional category: Tablet binder, suspending, thickening agent, film coating and in sustained release preparations, and emulsifier.

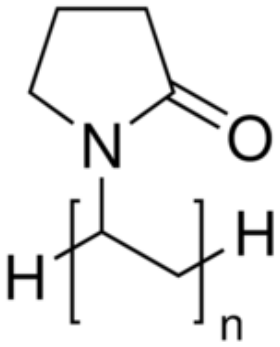
4.5 Polyvinylpyrrolidone (Grade used PVP K30)

Synonyms: Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; Polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

Chemical name: 1-Ethenyl-2- pyrrolidinone homopolymer.

Molecular weight: 2500-3,000,000 g/M

Structural formula:



Description: Povidone is a white to creamy-white colored, fine, odorless and hygroscopic powder. It softens at 150^0C. It is freely soluble in acids, ketones, methanol, water, chloroform and ethanol but practically insoluble in ether, mineral oil and hydrocarbons.

Functional Category: Tablet binder, suspending agent, stabilizing or viscosity-increasing agent and coating agent.

4.6 METHODS

4.6.1 Primary characterization of active ingredient and additives

4.6.1.1 Description of Cefaclor

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

4.6.1.2 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.

Table 4.3: Identification test

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.

4.6.2 Preformulation study of Cefaclor

Preformulation studies were carried out in order to find out of the drug excipients interactions. Compatibility study was 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).

4.6.2.1 FTIR studies of Cefaclor

Infrared spectrum obtained for pure Cefaclor. 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.

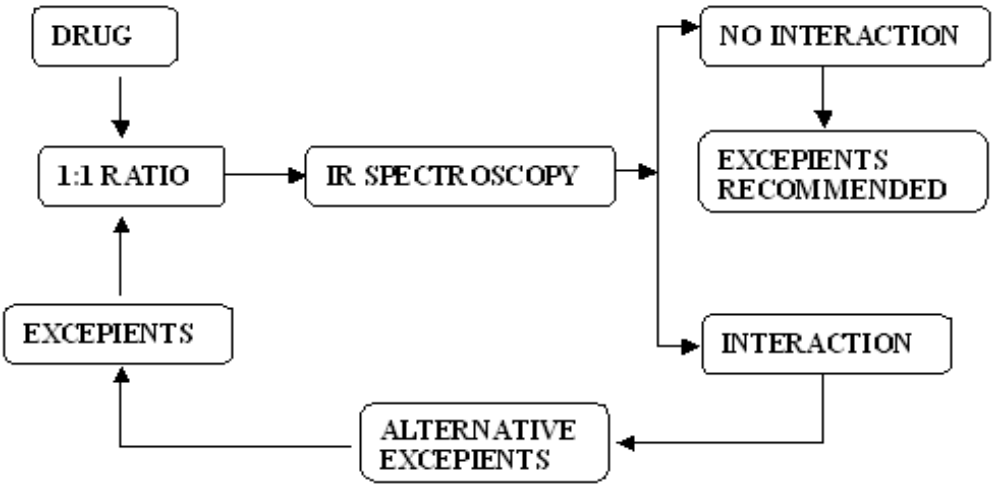


Figure 6: Schematic representation of compatibility studies

4.6.2.2 Differential Scanning Calorimetry studies of Cefaclor

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.

4.6.2.3 Melting Point determination

Melting point of Cefaclor was determined by capillary method (Akash Jain, 2004). Fine powder of cefaclor 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.

4.6.2.4 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.

Table 4: Limits of angle of repose

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

4.6.2.5 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

4.6.2.6 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

4.6.2.7 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,

$$C.I. = \{(Pt - P_{0)} / P_{t}\} \times 100$$

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

Table 5: Limits of Carr's Compressibility index

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

4.6.2.8 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.

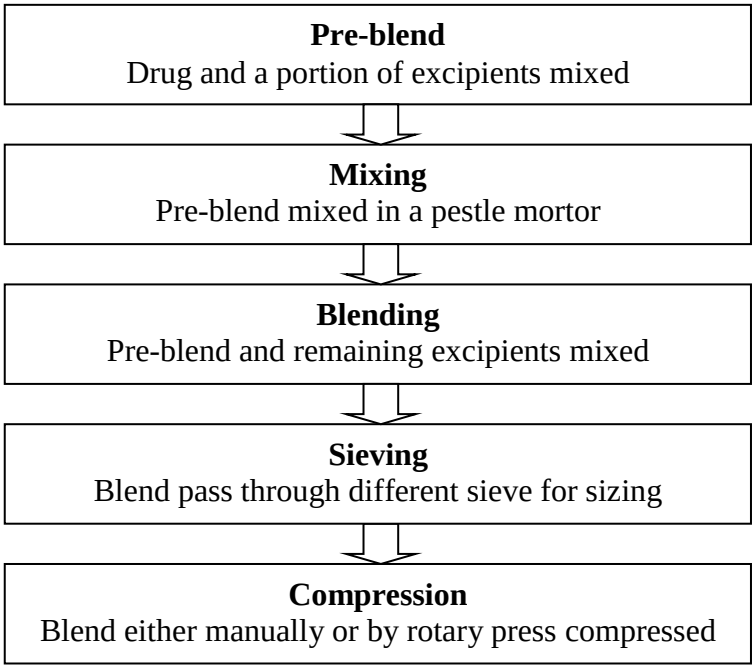


Figure 7: Formulation of Floating Tablets of Cefaclor

4.6.2.9 Determination of λ_{max} of Cefaclor

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}.

4.6.2.10 Preparation of Calibration Curve of Cefaclor in 0.1 N HCl

Cefaclor was quantitatively analyzed by various techniques. In the current study, Cefaclor was quantified by UV spectrophotometry method.

Stock solution was prepared by dissolving 100 mg of Cefaclor 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.

4.6.3 Formulation of floating tablets of Cefaclor by direct compression technique

Floating tablets of each containing 250 mg Cefaclor 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 Cefaclor 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 Cefaclor blend which was also passed through sieve # 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and blended for 2 minutes, further the talc was added and mixed for 2 minutes.

Table 6: Composition of Cefaclor floating tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Cefaclor	250	250	250	250	250	250	250	250	250	250	250
HPMC K15M (Hydrophilic Polymers)	100	100	-	-	100	100	-	50	50	40	40
HPMC K 100 M (Hydrophilic Polymers)	50	-	100	-	50	-	100	100	100	110	120
Carbopol 934 P (Hydrophilic Polymers)	40	-	-	100	-	50	50	-	50	50	40
Sodium bicarbonate (Effervescent agent)	-	60	60	60	60	60	60	60	60	60	60
Citric acid (Effervescent agent)	-	30	30	30	30	30	30	30	30	30	30
PVP K 30	10	10	10	10	10	10	10	10	10	10	10
Micro crystalline cellulose (Filler)	100	100	100	100	50	50	50	50	-	-	-
Aerosol	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate (Lubricant)	3	10	10	10	10	10	10	10	10	10	10
Talc (Antiadherant)	3	5	5	5	5	5	5	5	5	5	5

4.6.4 Post-compression parameters

4.6.4.1 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.

4.6.4.2 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).

4.6.4.3Hardness

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).

4.6.4.4 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).

$$\% \text{ friability} = \frac{\text{initial wt} - \text{final wt}}{\text{initial wt}} \text{x} 100$$

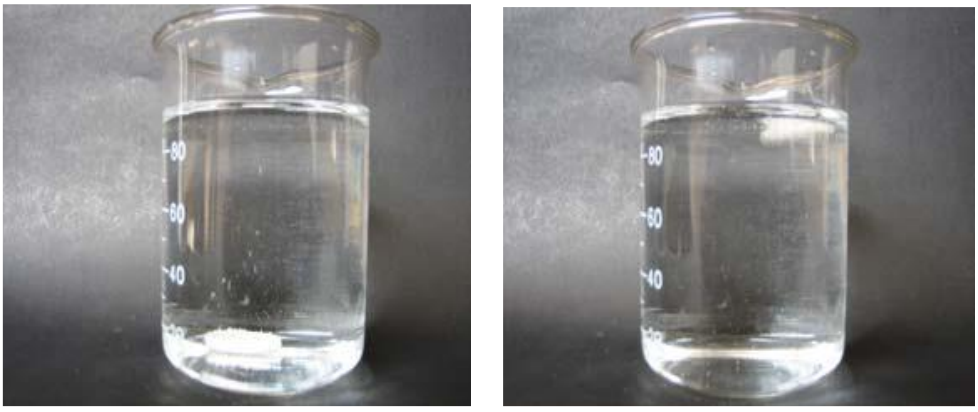
4.6.4.5 *In vitro* Buoyancy Study

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±2^{o}C. 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 Cefaclor tablet was presented in Figure 4.3.

4.6.4.6 *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±0.5°C. 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.



At initial time **After 4 min**

Figure 8: Floating behavior of Cefaclor optimized floating tablets (F11)

4.6.4.7 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. The swelling index (SI) of each formulation was calculated using the following equation:

$$\% \text{ SI} = \frac{W2-W1}{w1} \times 100$$

Where, W1 is the initial weight and W2 is the final weight.

4.6.4.8 Drug Release Kinetics

To study the release kinetics, data obtained form in vitro drug release studies were plotted in various kinetic models: zero order as the cumulative percentage of drug release vs time, first order as the log of the amount of drug remaining to be released vs time, Higuchi model as the cumulative percentage of drug release vs.square root of time, Korsmeyer - Peppas release model as the log time vs.log % drug release and Hixon- Crowell release model as the time vs. Cubic root of % drug remaining.

1. Zero order kinetics:

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

$$Q_t = Q_o + K_o t$$

Where, Q_t = amount of drug dissolved in time t,

Q_o = initial amount of drug in the solution

K_o = zero order release constant.

2. First order kinetics

To study the first order release rate kinetics the release rate data were fitted to the following equation.

$\text{Log } Q_t = \log Q_o + K_1 t/2.303$

Where Q_t is the amount of drug released in time t,

Q_o is the initial amount of drug in the solution,

K_1 is the first order release constant.

3. Higuchi model

Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is

$$Q_t = K_H.t^{1/2}$$

Where, Q_t = Amount of drug released in time t,

K_H = Higuchi dissolution constant.

4. Korsmeyer - Peppas release model

Korsmeyer et al. derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model.

$$Mt / M\infty = Ktn$$

Where, Mt / M∞ is a fraction of drug released at time t,

k is the release rate constant and

n is the release exponent.

The n value is used to characterize different release for cylindrical shaped matrices.

Table 7: Interpretation of diffusional release mechanisms

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.45<n=0.89	Non-Fickian diffusion	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

5. Hixson- Crowell model

To study the Hixson – Crowell model the release rate data are fitted to the following equation

$W_0^{1/3}-W_t^{1/3}=K_st$

Where, W_o is the amount of drug in the dosage form,

W_t is the remaining amount of drug in the pharmaceutical dosage form,

K_s is a constant incorporating the surface-volume relationship.

4.6.4.9 MOISTURE UPTAKE STUDIES

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic.

Moisture uptake studies were carried out by weight method.

Method

- Clean and dry petriplates were taken and their empty weights were recorded.
- 10 tablets were placed into each petriplates and the total weight of each petriplate with the test substance was recorded.
- Finally the petriplates were placed in desiccators saturated 75% relative humidity at 25□C using various standard salt solutions.
- The weights of all the petriplates were recorded at the end of 1, 2, 4, 6, 8, 24, 48, 72 hr.
- The petriplates were carefully wiped with tissue paper to remove any adhering moisture before the weight was recorded.
- The percentage of moisture absorption was determined using the formula

$$\% \text{ Moisture absorption} = \frac{\text{Observed weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

4.6.4.10 STABILITY STUDIES

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Design Plan

Accelerated study: The product is subjected to accelerated stability studies at 40°C±2°C/75% ±5% RH for 3 months.

Package type

The tablets were packed as 30's count in HDPE containers, induction sealed with adsorbent cotton and silica gel.

Stability studies

Table 8: Stability Sampling Withdrawl Schedule

S.NO	STORAGE CONDITION	TEST PERIOD
1.	40°C± 2°C/75±5% RH	1ST month 3 months

4.6.4.11 ASSAY (UV method):

From the tablet an amount equivalent to 5 mg of Cefaclor was weighed & dissolved in 50 ml of methanol & sonicated for 10 min. Then the solution was filtered through whatman filter paper no.41, final volume made upto 50 ml with methanol to get a stock solution of 100 µg/ml-1 of Cefaclor. The absorbance of resultant solution was measured at 239 nm. The concentration of drug present in sample solution calculated by using the equation generated from the calibration curve.

5. RESULTS AND DISCUSSION

5.1 Primary characterization of active ingredient and additives

5.1.1 Description of Cefaclor

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 Cefaclor was complies as per IP specifications (IP, 2006).

Table 9: Description of active ingredient

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

5.1.2 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.

Table 10: Identification test for additives

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.

5.2 Preformulation study of Cefaclor

5.2.1 FTIR studies of Cefaclor

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

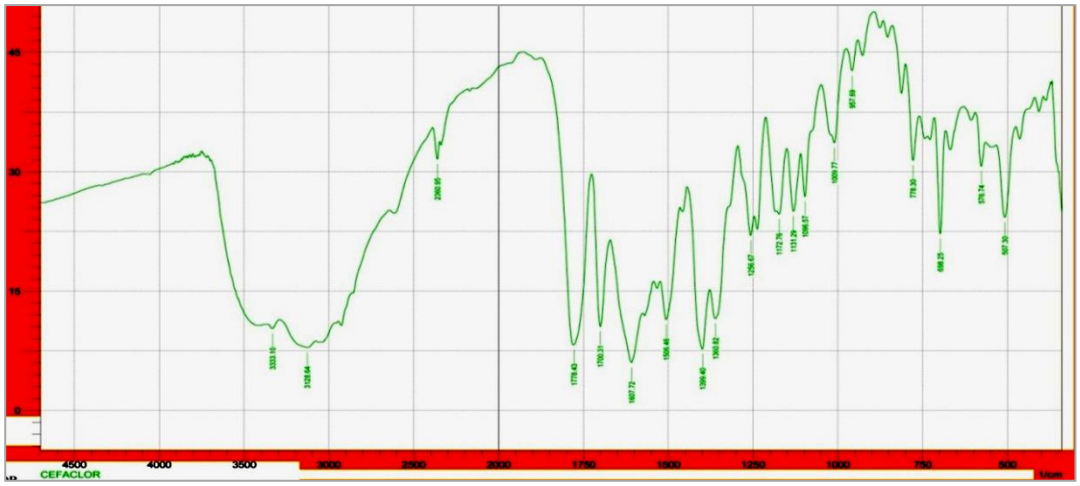


Figure 9: FTIR Spectrum of Cefaclor

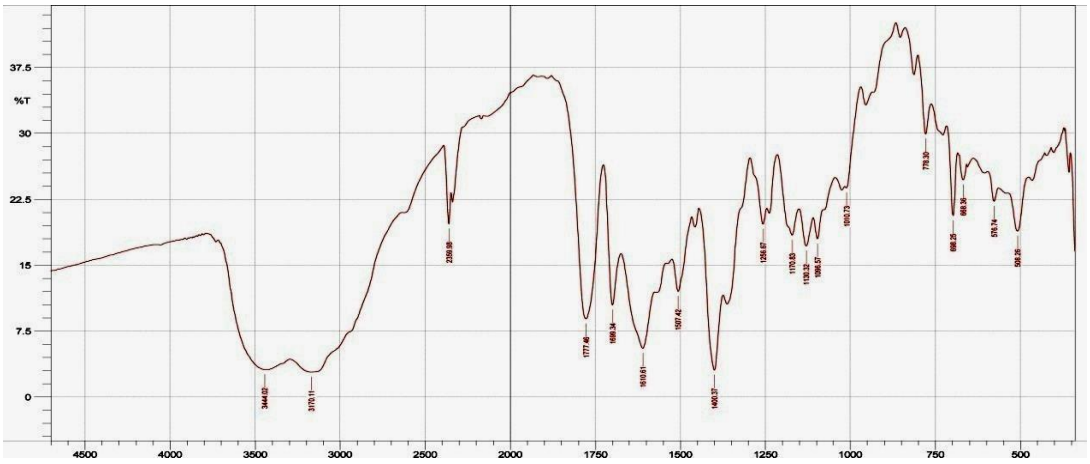


Figure 10: FTIR Spectrum of Cefaclor with HPMC K15M

Figure 11: FTIR Spectrum of Cefaclor with HPMC K100M

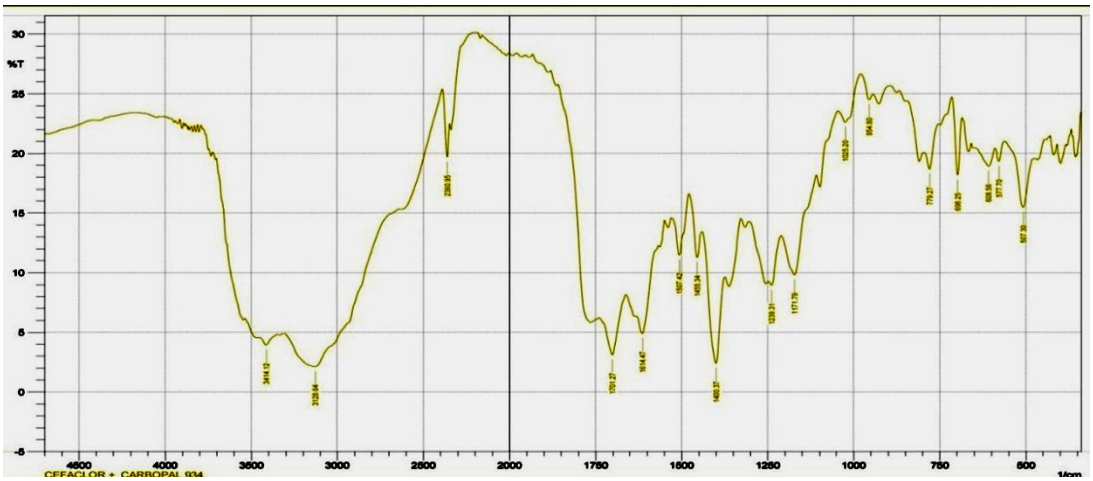


Figure 12: FTIR Spectrum of Cefaclor with Carbopol 934P

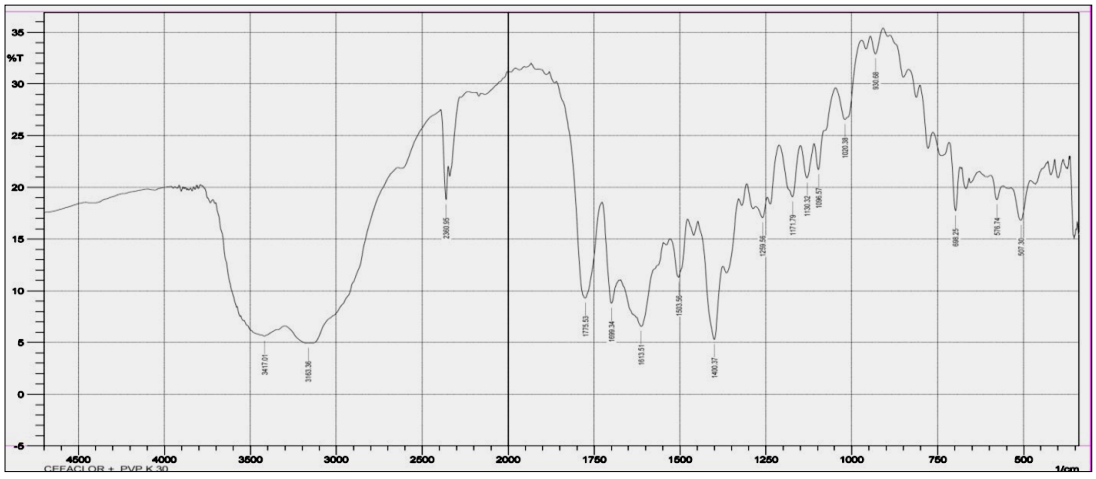


Figure 13: FTIR Spectrum of Cefaclor with PVP K30

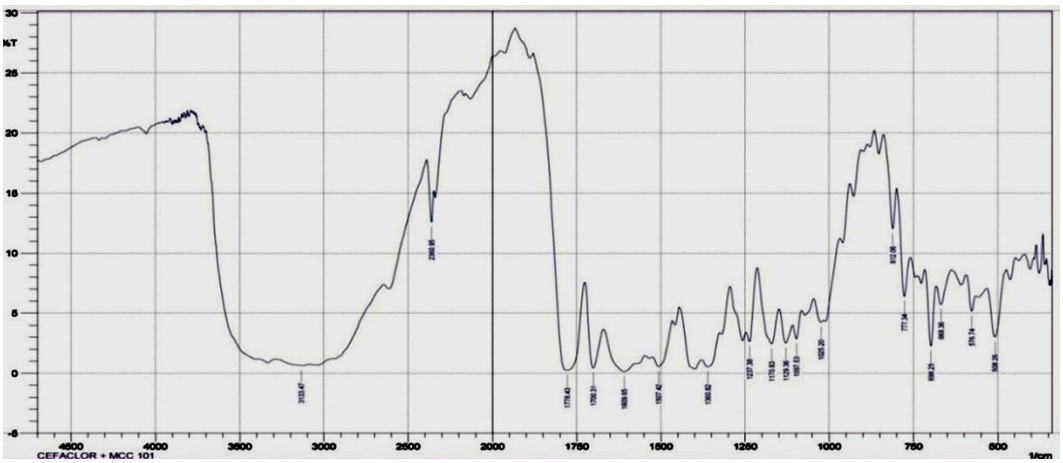


Figure 14: FTIR Spectrum of Cefaclor with Microcrystalline cellulose

In an effort to investigate the possible chemical interaction of drug with polymer, that have been analyzed (a) Cefaclor; (b) HPMC K15M; (c) HPMC K100M; (d) Carbopol 934P; and (e) PVP K30. Cefaclor 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.

Table 11: Characteristics of final blend of cefaclor 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'	0.365	0.386	13.53	1.156
F2	22^0.15′	0.345	0.412	13.79	1.165
F3	21^0.23′	0.343	0.417	13.98	1.135
F4	23^0.36′	0.351	0.387	13.45	1.146
F5	24^0.18′	0.344	0.415	12.31	1.546
F6	23^0.51′	0.356	0.418	13.98	1.154
F7	21^0.72′	0.343	0.378	13.26	1.168
F8	24^0.11′	0.356	0.405	13.60	1.158
F9	23^0.57′	0.358	0.418	17.33	1.112
F10	21^0.22′	0.365	0.415	16.32	1.184
F11	22^0.38′	0.356	0.416	11.25	1.175

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

5.2.2. Differential Scanning Calorimetry studies of Cefaclor

Differential Scanning Calorimetry (DSC) study of Cefaclor was performed as described in 4.6.2.2. Thermograms were obtained for pure Cefaclor and mixed matrix floating tablet containing Cefaclor with other excipients. Pure powdered Cefaclor 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.

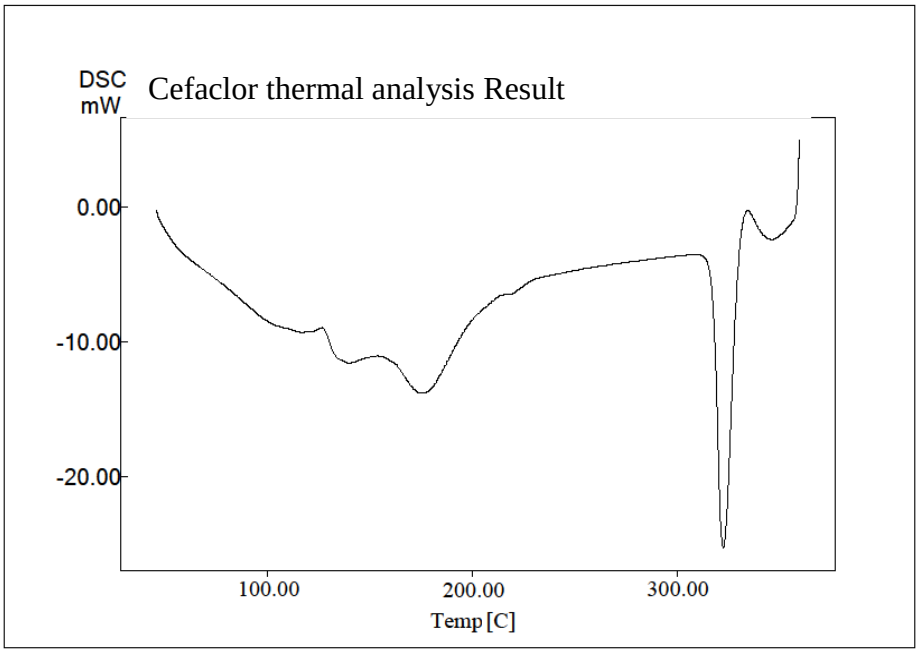


Figure 15: DSC thermogram of Cefaclor

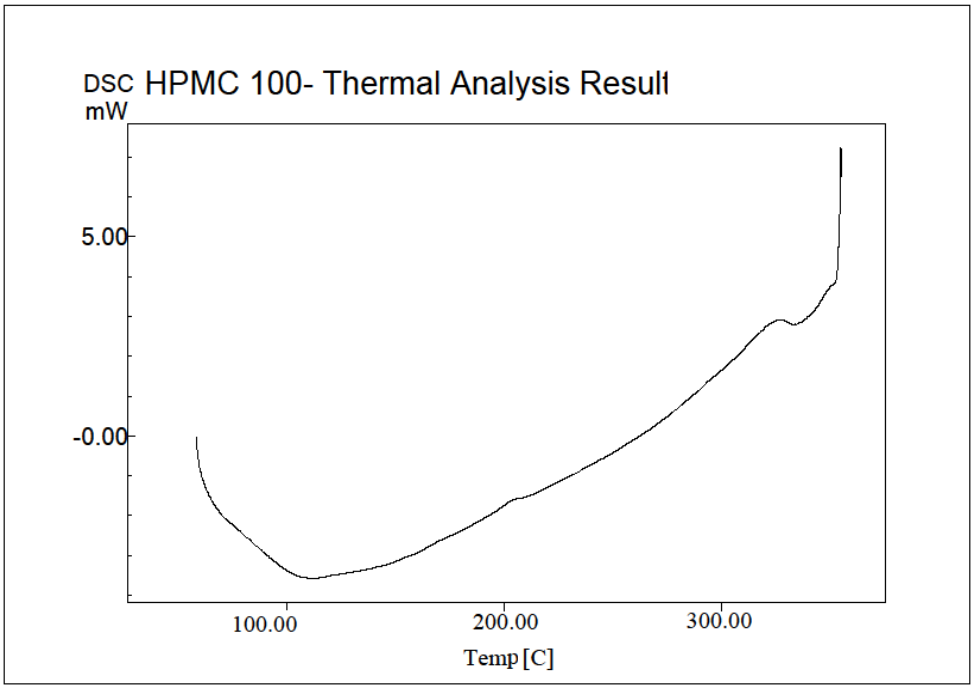


Figure 16: DSC thermogram of HPMC 100

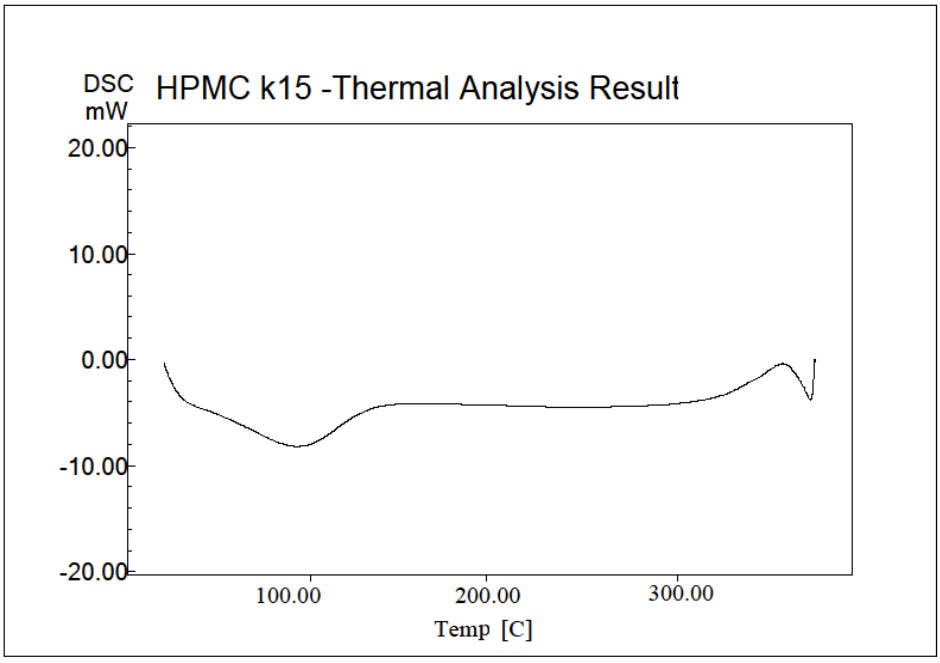


Figure 17: DSC thermogram of HPMC K15

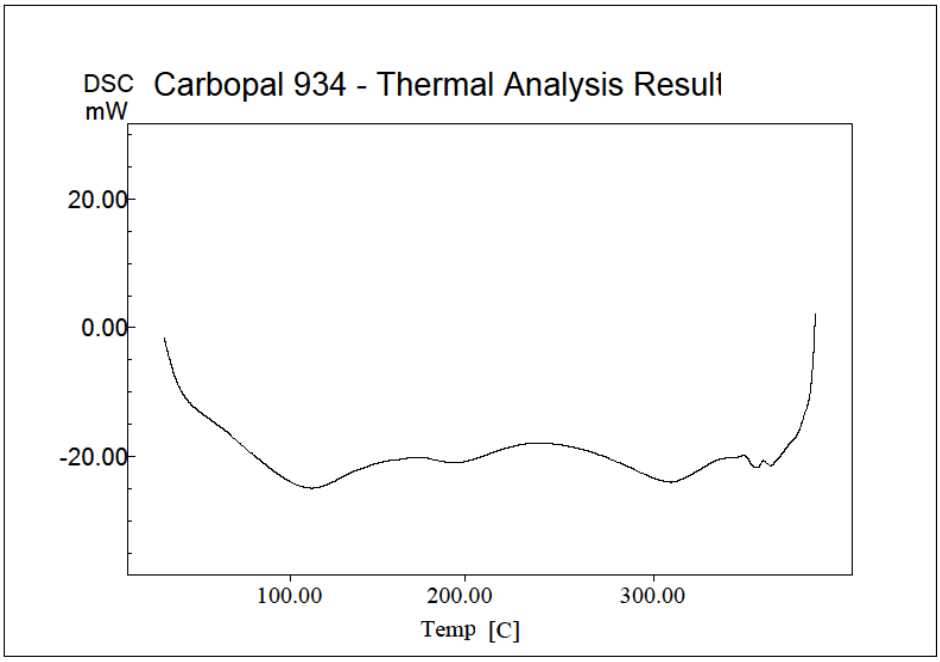


Figure 18: DSC thermogram of carbopol

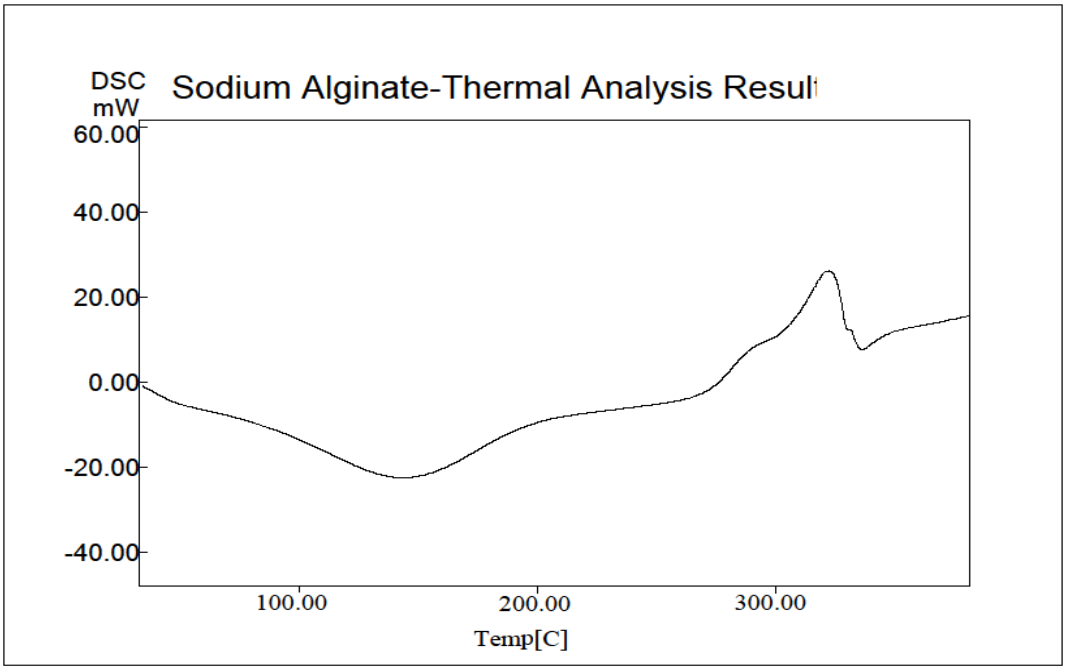


Figure 19: DSC thermogram of Sodium alginate

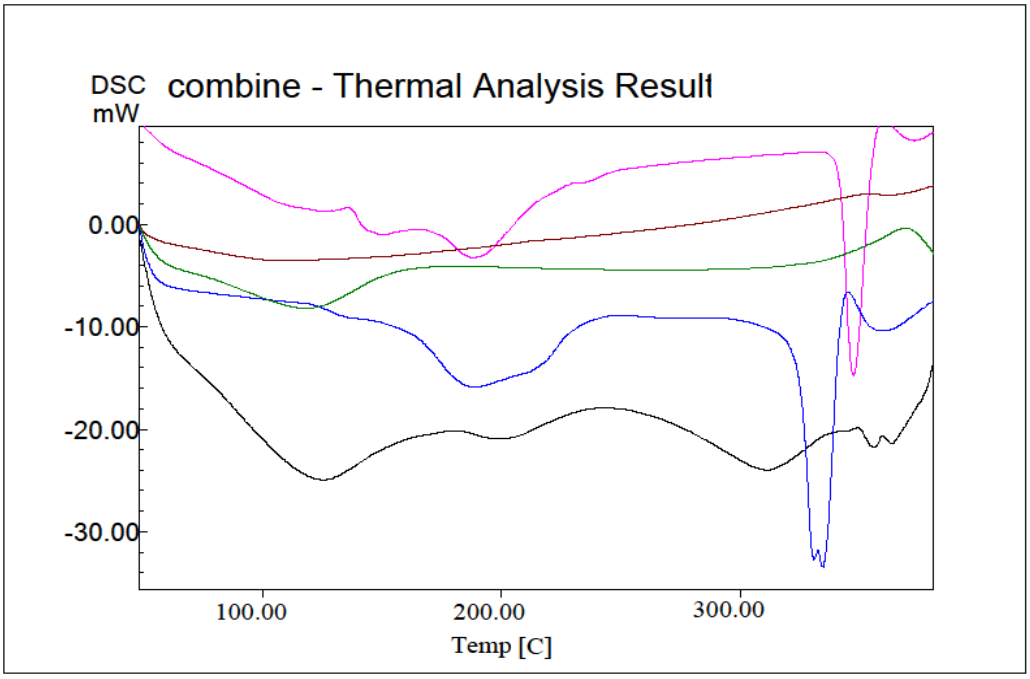


Figure 20: DSC thermogram of Cefaclor and polymers

5.2.2 Melting point determination

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

5.2.3 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.

5.2.4 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 0.337 and 0.372 g/ml, which is ideal. The observed values are presented in the Table 11.

5.2.5 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 0.384 and 0.423 g/ml, which is ideal. The observed values are presented in the Table 11.

5.2.6 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 17.33, which is ideal (5 – 16). The observed values are presented in the Table 11.

5.2.7 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 1.109 and 1.195, which is ideal (< 1.25). The observed values are presented in the Table 11.

5.2.8 Determination of λ_{max} of Cefaclor

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 Cefaclor was presented in Figure 21.

5.2.9 Preparation of calibration curve of Cefaclor

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

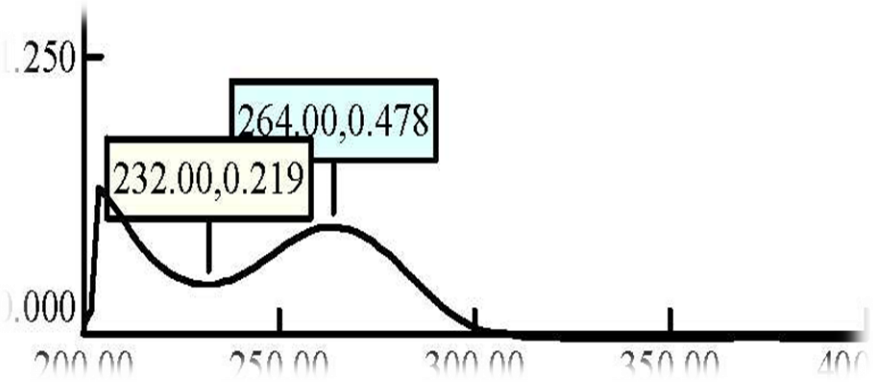


Figure 21: Absorption spectrum of Cefaclor

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.

Table 12: Linearity profile of Cefaclor

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

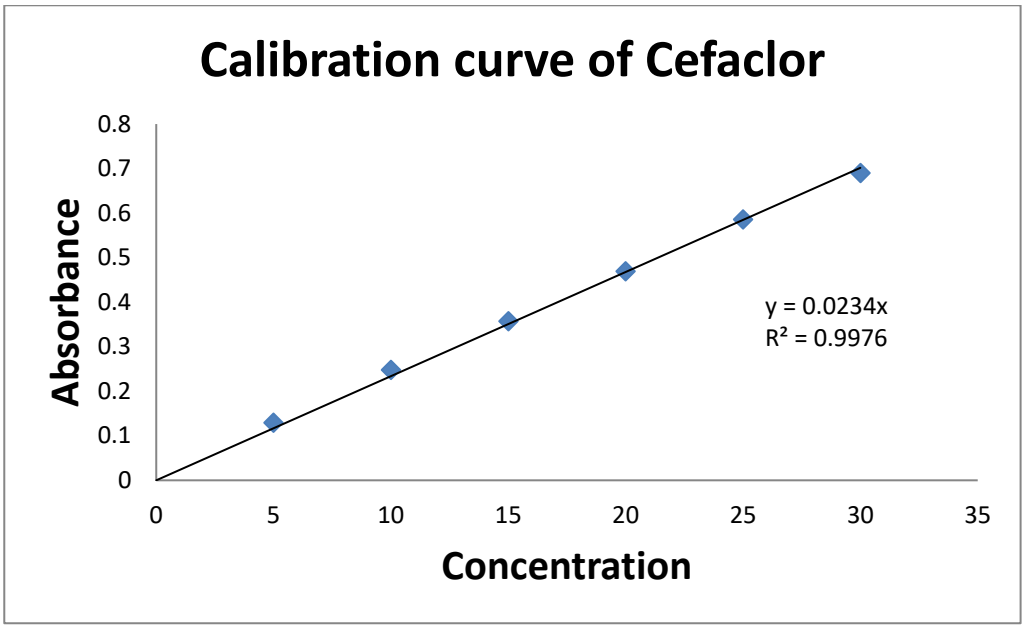


Figure 22: Calibration curve of Cefaclor in 0.1 N HCl

5.3 Post-Compression Parameters (Evaluation of Tablets):

5.3.1 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%.

5.3.2 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).

5.3.3 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).

5.3.4 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).

Table 13: Evaluation of Cefaclor floating tablets

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug uniformity (%)
F1	567±5	10.4	0.214	93.52
F2	568±5	10.7	0.282	96.09
F3	569±5	10.3	0.320	94.12
F4	568±5	10.8	0.275	97.24
F5	567±5	11.3	0.314	98.85
F6	570±5	11.2	0.203	96.92
F7	569±5	10.2	0.317	96.42
F8	569±2	10.5	0.252	99.94
F9	568±5	10.7	0.218	100.02
F10	571±5	10.3	0.314	96.72
F11	570±5	10.5	0.312	99.95

5.3.5 *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.

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

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	9	>10
F7	5	>12
F8	5	>12
F9	5	>12
F10	4	>12
F11	4	>12

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 CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, 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 F10 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.

5.3.6 *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.

Table 15: *In vitro* dissolution test of cefaclor floating tablet

S.NO	Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	1	22.67	23.12	23.04	23.14	23.90	23.48	23.45	23.61	23.78	25.11	25.92
2	2	31.44	30.65	31.32	34.95	36.73	36.89	36.82	37.10	37.21	39.23	39.71
3	4	45.63	47.43	48.96	40.93	42.98	41.67	41.71	41.82	41.90	43.72	43.89
4	6	58.24	59.74	57.86	59.65	59.10	60.20	60.23	60.35	60.42	62.39	62.93
5	8	75.41	77.32	80.32	68.78	68.83	69.16	69.25	69.41	69.53	71.23	71.74
6	10	87.84	90.31	91.27	78.46	79.02	79.18	78.41	78.50	78.59	82.14	82.92
7	12	90.25	92.42	92.52	92.93	93.56	93.68	93.70	93.81	93.99	94.10	94.91

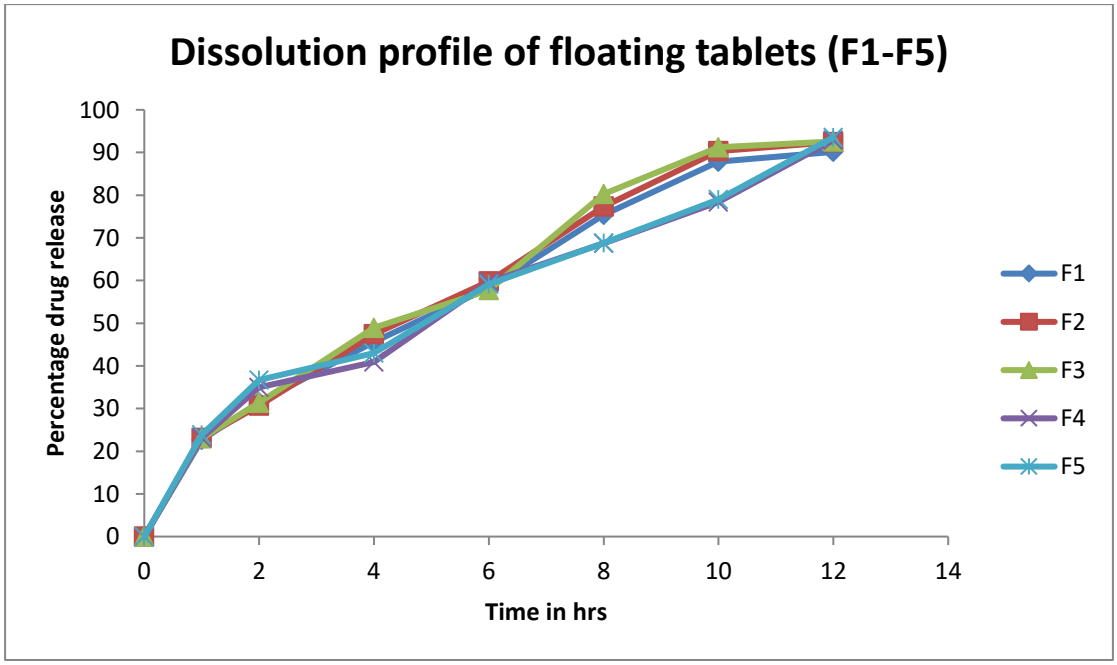


Figure 23: *In vitro* dissolution profile of Cefaclor floating tablets (F1-F5)

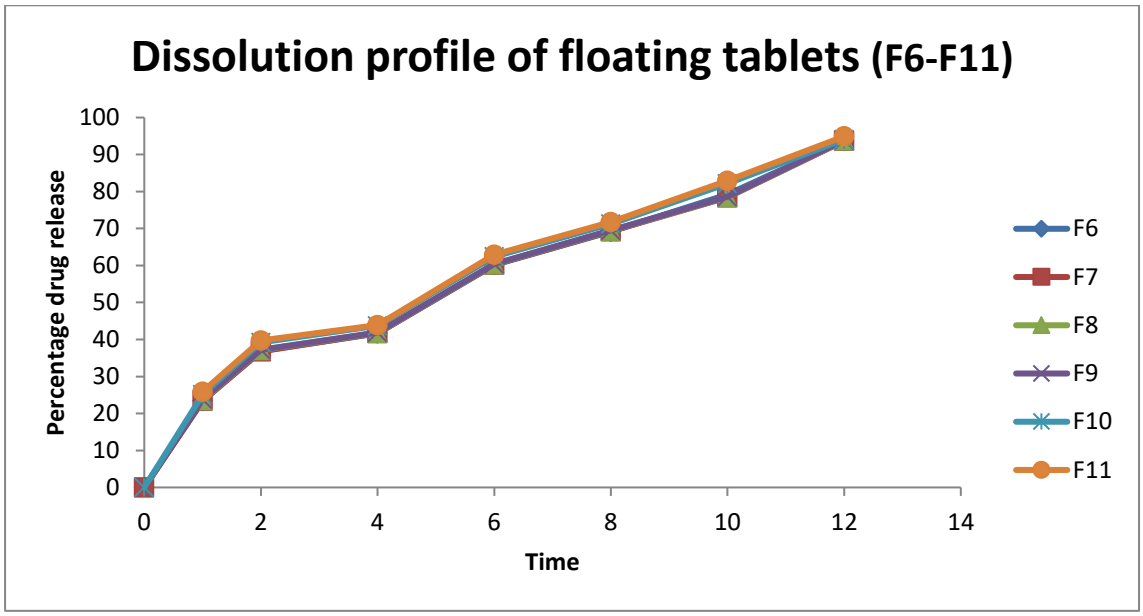


Figure 24: *In vitro* dissolution profile of Cefaclor floating tablets (F6-F11)

The percentage drug release from batch F1 to F11 vary from 90.15 to 94.91%. In formulation F1 without sodium bicarbonate the *in vitro* result shows 90.15% and from formulations F2 –F4 with only one polymer were showed 92.45, 92.59 and 92.90% at the end 12th h, formulations from F5 to F8 keeping one polymer as constant and different proportions of other polymer showed the results as 93.56, 93.68, 93.70 and 93.81 and formulations F9 to F11 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, F11 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.

5.3.7 Study of swelling behavior

The floating tablets were formulated as described in 4.6.3, was evaluated for swelling characteristics as described in 4.6.4.7. The outcome of the results was presented in Table 16.

Table 16: Study of swelling characteristics of effervescent floating tablets of Cefaclor

Batch Code	Time in h (% Swelling)			
	2	**4**	**6**	**8**
F1	99.81	99.95	110.16	91.95
F2	66.74	82.35	91.56	87.76
F3	69.56	75.12	99.34	95.61
F4	65.58	78.15	101.56	99.58
F5	66.18	86.51	115.61	106.15
F6	75.51	99.56	105.52	97.15
F7	71.15	86.61	110.59	105.61
F8	82.59	99.68	104.18	95.74
F9	105.59	110.78	115.61	107.58
F10	100.18	110.98	120.59	115.19
F11	110.28	118.21	125.72	121.38

The order of swelling observed in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymers were achieved after 2-8 h. The swelling index was calculated with respect to time. As the time increases, the swelling index was increased, because weight gain by the tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. Formulation, F11 is selected as optimized formulation among all the formulations, which swelled to 121.38 % at the end of 8 h as shown in Table 16.

5.4 Comparative study of tablets and marketed product

The optimized formulations of floating tablets (F11) and marketed product were selected and evaluated. The dissolution profile of the formulated tablets and marketed product were noted and the results were presented in Table 17 and Figure 25. From the comparative study, it was found to be that the floating tablets containing Cefaclor present the fast and sustained drug release.

Table 17: *In vitro* dissolution study of floating tablets and marketed product

Sl. No	Time (h)	Floating tablets F11 (%)	marketed product (%)
1	1	25.92	44.50
2	2	39.71	53.78
3	4	43.89	64.62
4	6	62.93	72.11
5	8	71.74	80.30
6	10	86.92	87.13
7	12	94.91	94.56

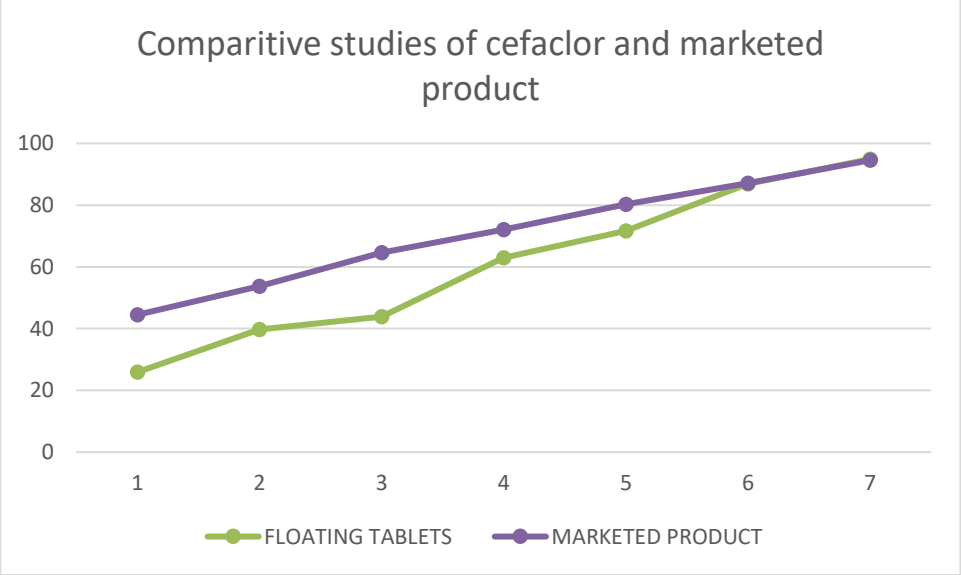


Figure 25: comparative studies of cefaclor and marketed product

Hence from the results the selected floating tablets of cefaclor (F11) shows best results when compared to the marketed product.

5.5. DRUG RELEASE KINETIC DATA

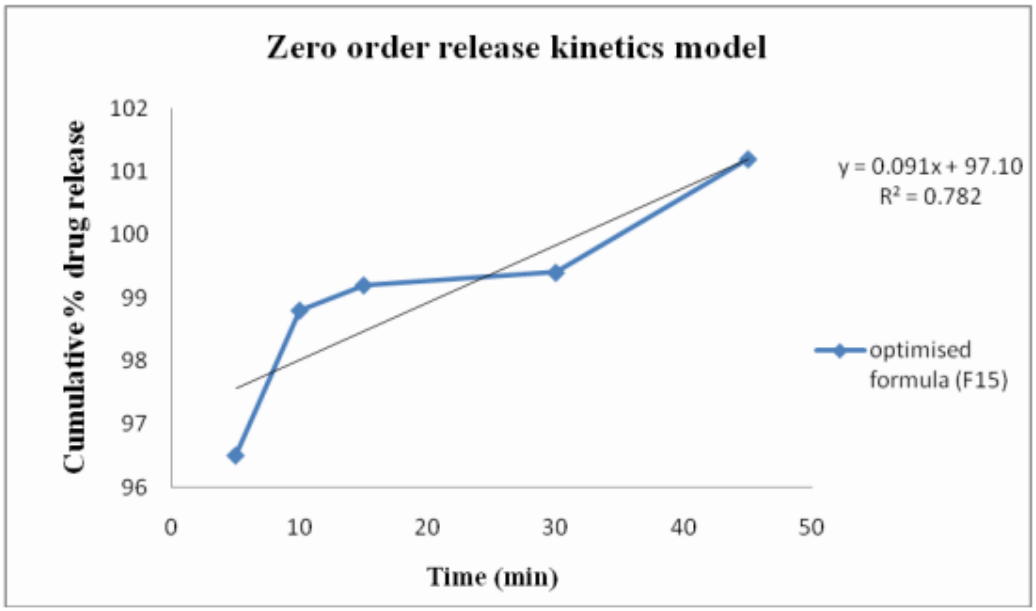


Figure 26: Zero order release kinetics model

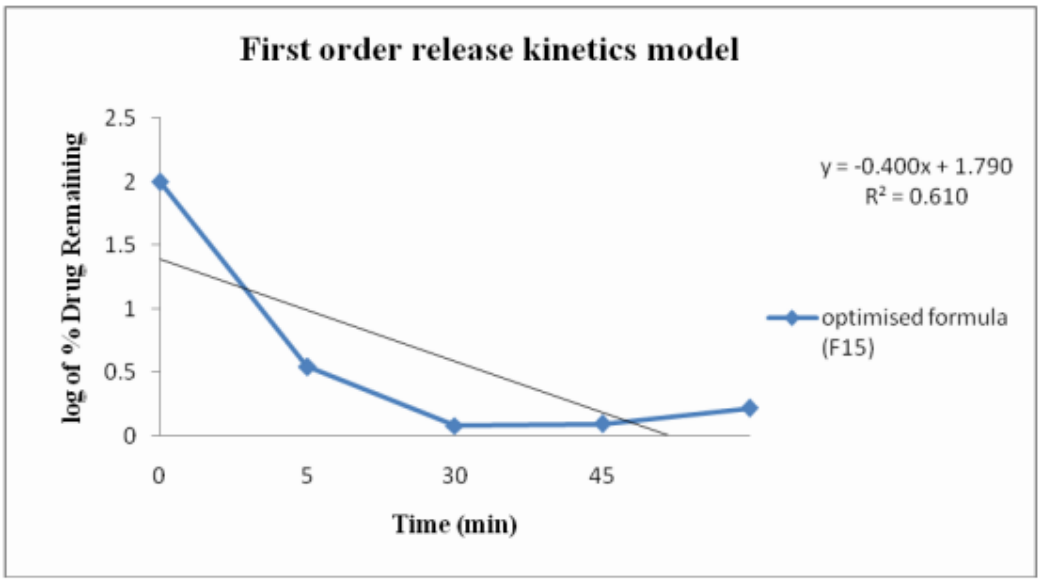


Figure 27: First order release kinetics model

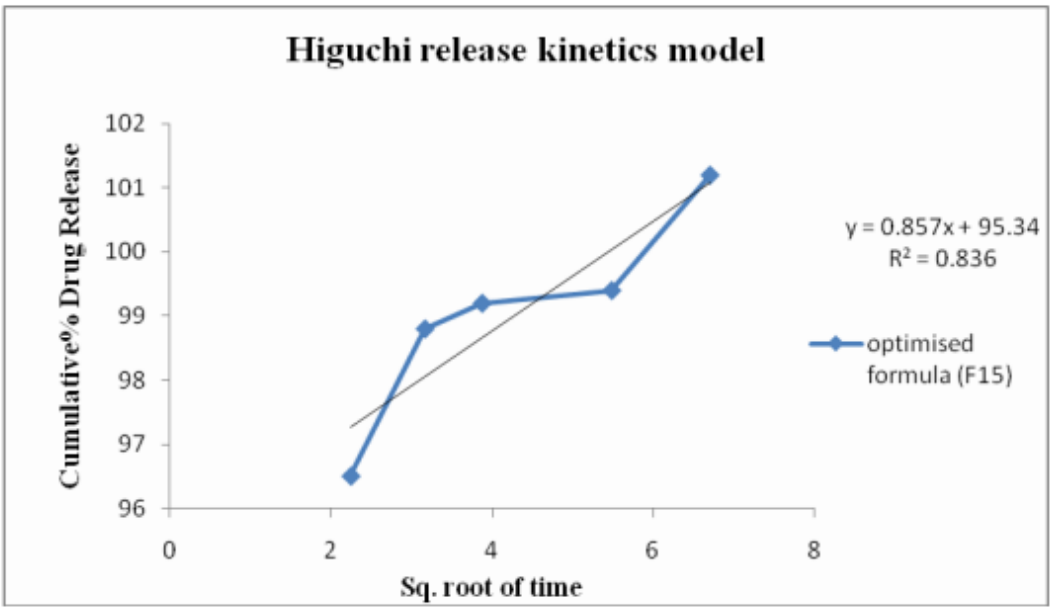


Figure 28: Higuchi release kinetics model

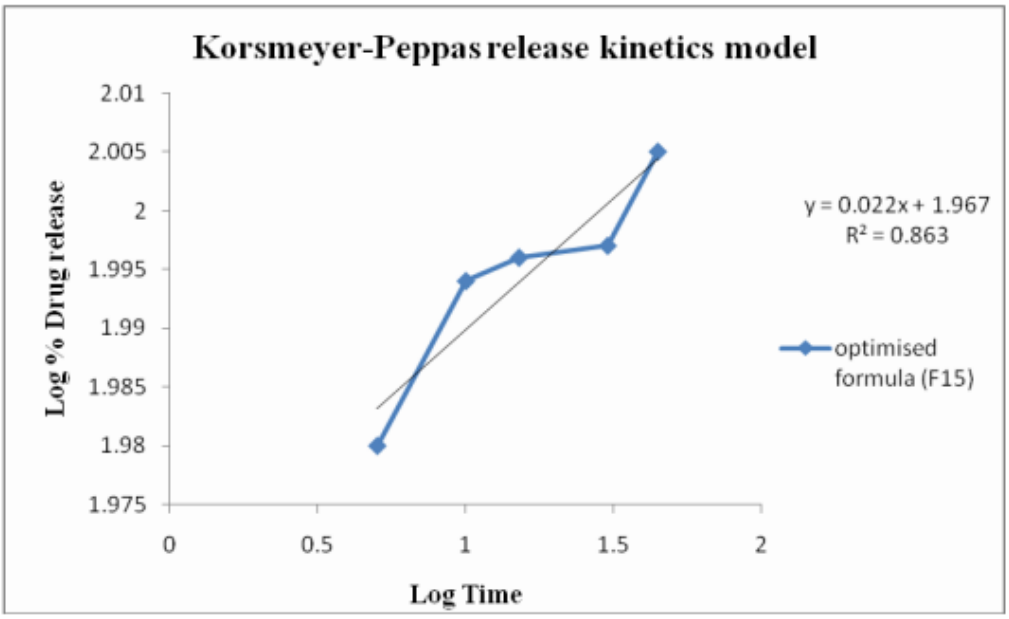


Figure 29: Korsmeyer-Peppas release kinetics model

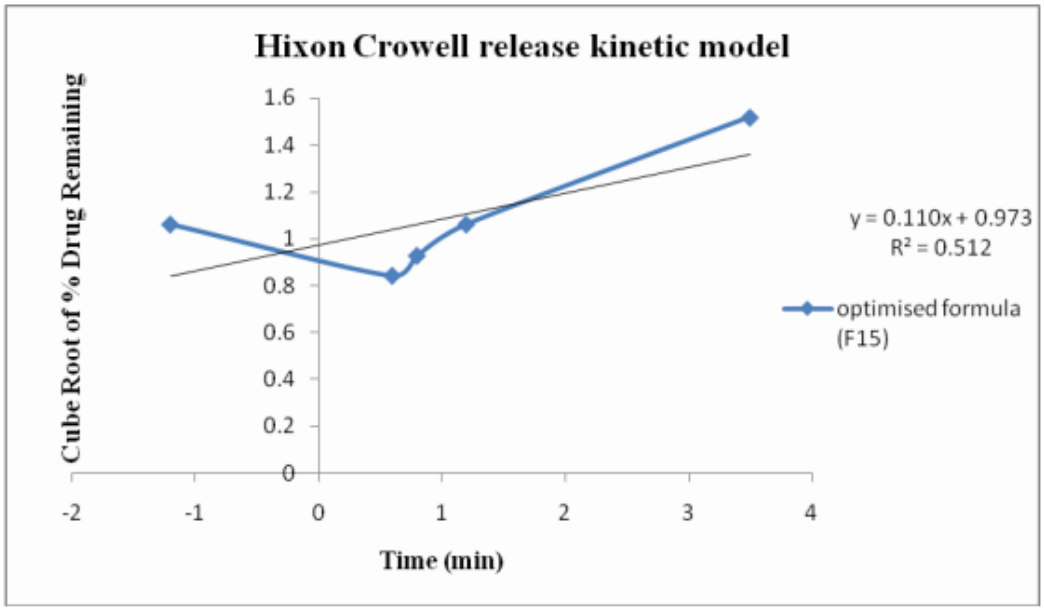


Figure 30: Hixon Crowell release kinetic model

5.5.1. Fit of different kinetic models for release of drug from ODTs (F11)

Table 18: Release parameters of Cefaclor FDDS (F11)

ZERO ORDER		FIRST ORDER		HIGUCHI MODEL	
R^2	$K_0(h^{-1})$	R^2	$K_1(h^{-1})$	R^2	$K_H(h^{-1/2})$
0.782	0.091	0.610	0.921	0.836	1.817

KORSEMEYER-PEPPAS			HIXON-CROWELL	
R^2	n	$K_{kp}(h^{-n})$	R^2	$K_{HC}(h^{-1/3})$
0.863	0.022	1.82	0.512	0.11

5.6. ASSAY RESULTS OF CEFACLOR

Table 19: Assay results of Cefaclor

Formulation code	F-1	F-2	F-3	F-4
Cefaclor(%)	98.8	98.4	97.3	96.5

F-5	F-6	F-7	F-8	F-9	F-10	F-11
98.7	98.5	99.7	98.4	98.6	97.3	99.2

5.7. RESULTS OF MOISTURE UPTAKE STUDIES

Moisture uptake studies (by weight gain method),

Condition: 75%RH

Weight of petridish: 41.789 gm, Weight of 10 tablets: 2.421 g (each tablet weight 240mg)

Gross weight (weight of tablets + petridish): 44.21 g

Table 20: Moisture uptake observations at 75% RH

Time	Initial	1hr	2hr	4hr	6hr	8hr	24hr	48hr	72hr
Observed RH	75%	75%	75%	75%	75%	75%	75%	75%	75%
Observed Temperature(°C)	30°C	30° C	31°C	30°C	30°C	30°C	29°C	30°C	29°C
Physical observation	No Change	No change	No Change	No Change	No Change	No Change	Light Black spots	Light Black spots	Light Black spots
Observed Weight(g)	2.421	3.708	3.720	3.745	3.758	3.766	3.779	3.765	3.735
Percentage Moisture uptake	0%	1.28 %	1.299 %	1.324 %	1.337 %	1.345 %	1.35%	1.34%	1.31%

5.8. DRUG RELEASE KINETICS STUDY OF OPTIMIZE BATCH

In-vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 5 rpm. The percentage drug release at the end of 45minutes was found in the range 98 – 100 %.

From the in-vitro data it was found that Formulation F-11 shows the better release among other formulations.

The in-vitro drug dissolution result of batch F11 was used for in various mathematical models (zero, first, Higuchi's square root, Hixson-Crowell cube root law and Peppas equation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data.

It was found that the in vitro drug release of optimize batch F11 was best explained by Korsemeyer-Peppas model as the plots showed the highest linearity ($r^2 = 0.863$) compared to Higuchi's model ($r^2 = 0.836$), zero order ($r^2 = 0.782$) and first order ($r^2 = 0.61$).

Mechanism of drug release:

By incorporating release data, mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. The n value was 0.022 which was indicative of Fickian diffusion release. Fickian diffusion release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient.

5.9. RESULTS OF STABILITY STUDIES

Table 21: Results of Cefaclor stability studies for F11

Parameter	Initial value	After 3 months
Weight variation (mg)	570±5	570±7
Hardness (kg/cm^2)	10.5	10.9
Friability (%)	0.310	0.314
Drug uniformity (%)	99.94	99.96

6. 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.

Cefaclor is an effective simple antibiotic drug. Therefore the objective of this thesis was to develop a new floating drug delivery system of Cefaclor, 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 Cefaclor remained unaffected by excipients.

- This project of final blend of Cefaclor 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 (< 25^{o}) indicates good flow properties of drug.
- The absorption maximum of Cefaclor 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.

- Eleven batches of floating tablet were formulated using Cefaclor 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 (0.337-0.372), tapped density (0.384-0.423), Carr's index (11.25-17.33) and Hausner's ratio (1.109-1.195) 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 Cefaclor floating tablets F7 to F11 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 F11 is selected as optimized formulation among all the formulations, which shows 94.91 % sustained release at the end of 12 h. Formulation F11 is selected as optimized formulation among all the formulations, which swelled to 121.38 % at the end of 8 hours.
- The selected formulation were packed in wide mouth bottle. They were then stored at 25 ºC ± 2 ºC/60% RH, 40 ºC ± 2 ºC/75% RH for 3 months chamber and also evaluated for their physical appearance, drug content, drug dissolution and other studies at specified intervals of time. Long term testing 25 ºC + -2 ºC/60%

RH + -5% accelerated testing 40 ºC + -20 ºC/75% RH + -5% for months registered conditions 5 ºC + -3 ºC. Stability studies for the present work carried out at 25 ºC + -2 ºC/60% RH, 40 ºC + -2 ºC/75%. RH for the selected formulation for three months and 5 ºC + -3 ºC refrigerated conditions for 14 days.

In the present study the floating tablets of Cefaclor 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 Cefaclor has been an equivalent dose of Cefaclor and the target concentration achieved more rapidly and with less variability in plasma concentrations compared with eternal formulations.

7. BIBLIOGRAPHY

1. AJ. Gastroretentive dosage forms.Crit Rev Ther Drug Carrier Syst 1993; 10(2) :193-95.
2. 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.
3. Arora S, Ali A, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS PharmSciTech 2005; 6(3): E372- E390.
4. Asane GS. Mucoadhesive gastrointestinal drug delivery system: An overview. 2007; www.pharmainfo.net.
5. 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.
6. 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.
7. 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.
8. 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.

9. 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; 1984.
10. Bolton S and Desai S, Floating sustained release therapeutic compositions, US Patent, 1989, 4,814,179.
11. 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.
12. 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.
13. Bell TA. Flowability measurement and interpretation in industry. Handbook of Conveying and Handling of Particulate Solids, 10th (Ed.), 2001, p. 3-13.
14. Bhise SB and Rajkumar M. Controlled Nasal Drug Delivery of Ondansetron hydrochloride. Indian Journal of Pharmaceutical Education and Research 2006; 2(7): 229-235.
15. Bodhmage A. Correlation between physical properties and flowability indicators for fine powders. Department of Chemical Engineering, University of Saskatchewan, 2006.
16. 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.
17. 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.

18. Carr RL. Evaluating flow properties of solids. Chemical Engineering 1965; 18: 163-168.
19. 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.
20. Chien YW. Rate-control drug delivery systems: controlled release vs. sustained release. Medical Progress through Technology 1989; 15: 21-46.
21. Chien YW. Oral drug delivery and delivery system in novel drug delivery Systems, Ed., 50, Marcel Dekker publication, New York, 1992.
22. Cook JD, Carriaga M, Kahn SG, Schalch W.Gastric delivery system for iron supplementation. Lancet.1990;335:11361139.PubMed DOI: 10.1016/0140-6736(90)91135W
23. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *European Journal*of*Pharmaceutical*Sciences 2001; 13:123–33.
24. 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.
25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. Desai S and Bolton SA. Floating controlled-release drug delivery system: *in vitro-in vivo* evaluation. Pharmaceutical Research, 1993; 10(9): 1321-1325.

32. 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.

33. Groning R, Heun G. Dosage forms with controlled gastrointestinal transit. Drug Development and Industrial Pharmacy 1984; 10: 527- 539.

34. 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.

35. 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.

36. Gupta P, Virmani K, and Garg S. Hydrogels: From controlled release to pH responsive drug delivery. Drug Discovery Today 2002; 7(10): 569-579.

37. 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.

38. 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.

39. S.Gopalakrishnan ,Floating Drug Delivery Systems: A Review Journal of Pharmaceutical Science and Technology Vol. 3 (2), 2011,548-554.

40. Gupta GD, Garg R. Gastroretentive floating microspheres of silymarin: Preparation and *in vitro* evaluation. Tropical Journal of Pharmaceutical Research 2010; 9 (1): 59-66.

41. Harries D, Sharma HL. GI transit of potential bioadhesive formulations in man: A scintigraphic study. Journal of Control Release 1990; 12: 45-53.

42. 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.

43. 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.

44. Hassan Kawsar MD, Jakir Ahmed Chowdhury, Sheikh Tasnim Jahan, Masud Morshed MD, Jewel Mallick, Aninda Kumar Nath, Zia Uddin MD, Mycal Dutta, Kaisarul Islam M. Development and evaluation of Diclofenac Sodium loaded alginate cross-linking beads. Bangladesh Pharmaceutical Journal, 2011; 14(1): 41-48.

45. Iannuccelli V, Coppi G, Cameroin R. Air compartment multiple unit system for prolonged gastric residence. II. *In vivo* evaluation. International Journal of Pharmaceutics 1998; 174: 55-62.

46. Indian Pharmacopoeia, The Indian Pharmacopoeial Commission, Ghaziabad, 2006.

47. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and in vitro characterization. Journal of Control Release2005; 107(2): 300-309.

48. Jaber Emami, *In vitro - In vivo* Correlation: From Theory to Applications, Journal of *Pharmacy* and *Pharmaceutical* Sciences 2006; 9(2): 169-189.

49. Jasmin Shah, Rasul Jan M, Sultan Shah, and Naeem Khan M. Development and Validation of HPLC Method for Simultaneous Determination of Ceftriaxone and Cefaclor in Commercial Formulations and Biological Samples. Journal of the Mexican Chemical Society **2013;**57(4): 314-320

50. Kawashima Y, Nima T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. Journal of Pharmaceutical Sciences 1998; 81: 135-140.

51. Kedzierewicz F, Thaivenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation for peroral silicon dosage forms in human by gamma-scintigraphy. Journal of Control Release 1999; 58: 195-205.

52. Klausner EA, Lavy E, Stepensky D, Cserepes E, Batra M, Freidman M & Hoffman A. Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers. Journal of Clinical Pharmacology 2003; 43: 711-720.

53. Koner P, Saudagar RB, Dharwal J. Gastro-retentive drugs a novel approach towards floating therapy in http://www.pharmainfo.net/exlusive/reviews /gastro- retentive drugs a novel approach towards floating therapy/, 2007

54. Krunal Patel M, Biswajit Biswal, Nabin Karna, Janki Patel. Preparation and evaluation of gastro retentive floating tablets of Mebendazole. International Journal of Current Pharmaceutical Research, 2011; 3(1): 63-65.

55. Lachman L, Lieberman H, Kanig J. The theory and practice of industrial pharmacy. Varghese publication house, 3rd (Ed.), 1991.

56. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. International Journal of Pharmaceutics 2003; 253: 13-22.

57. Muller Lissner SA, Blum AL. The effect of specific gravity and eating on gastric emptying of slow-release capsules. New England Journal of Medicine 1981; 304: 1365-1366.

58. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Effects of gender, posture, and age on gastric residence time of indigestible solid: pharmaceutical considerations. Pharmaceutical Research 1988; 10; 639- 664.

59. Mishra B, Rajnikanth S. Preparation and in vitro characterization of gellan based floating beads of acetohydroxamic acid for eradication of *H. Pylori* Acta Pharmaceutica 2007; 57: 413.

60. Mastiholimath VS, Dandagi PM, Gadad AP, Mathews R, Kulkarni AR. *In vitro* and *in vivo* evaluation of ranitidine hydrochloride ethyl cellulose floating microparticles. Journal of Microencapsulation 2008; 25(5):307-314.

61. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Journal of Pharmaceutical Technology 2008; 1(14): 345-348.

62. Margret Chandira, Chandra Mohan, Debjit. Design and characterization of sustained release gastro retentive floating tablets of Diltiazem hydrochloride. Der Pharmacia Lettre, 2009; 1(2): 25-38.

63. Margret Chandira R, Debjit Bhowmik and Chiranjib BJ. Formulation and evaluation of gastroretentive drug delivery system of gastroprokinetic drug Itopride hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(1): 53-65.

64. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994;83:239-245.PubMed

65. Moursy NM, Afifi NN, Ghorab DM, ElSaharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie. 2003;58:38-43.PubMed

66. Mowafaq MG, Anmar AI and Ahmed AH. Preparation and characterization of Cinnarizine floating oil entrapped calcium alginate beads. International Journal of Pharmaceutical Sciences and Research, 2012; 3(2): 501-508.

67. Mihir Patel, Patel KR, Patel MR, Patel NM. A review on floating drug delivery system. International Journal of Universal Pharmacy and Bio Sciences, 2013; 2(1): 8-19.

68. Nattee S, Natalie DE. *In vitro-In vivo* Correlation Definitions and Regulatory Guidance, International Journal of Generic Drugs, Available online at http://www.locumusa.com [Accessed on: 07/06/2009].

69. Neha Narang, An Updated Review on: Floating Drug Delivery System, International Journal of Applied Pharmaceutics 2010; 3(1): 1-7.

70. Nikita Dixit, sFloating Drug Delivery System Journal of Current Pharmaceutical Research 2011 ;7 (1): 6-20.

71. Oth M, Franze M, Timmermans J, Moes A. The bilayer-floating capsule: a stomach directed drug delivery system for misoprostol. Pharmaceutical Research 1992; 9: 298-302.

72. Pillay V and Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. Journal of Controlled Release, 1998; 55:45–55.

73. Pearnchob N and Bodmeier R. Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit) RS, ethylcellulose and shellac. *European* Journal of Pharmaceutics and Biopharmaceutics, 2003; 56(3): 363-369.

74. Pornsak S, Nartaya T, Satit P. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. European Journal of Pharmaceutical Sciences 2005; 24:363–373.

75. Patel YL. The effect of drug concentration and curing time on processing and properties of calcium alginate beads containing Metronidazole by response surface methodology. AAPS Pharm Sci Tech 2006; 7(4): 86.

76. Patel R. Recent development in floating drug delivery system for gastric retention of drugs: an overview. 2007; http://www.swatijaininst.com/etechno /feb2007/roma.rtf

77. Paterson RS, O'mahony B, Eccleston GM, Stevens HNE, Foster J & Murray JG. An assessment of floating raft formation in a man using magnetic resonance imaging. Journal of Pharmacology & Pharmacotherapeutics 2008; 8: S2.

78. Patil UK, Pare A, and Yadav SK. Formulation and evaluation of effervescent floating tablet of Amlodipine besylate. *Research Journal* of *Pharmacy and Technology, 2008; 1(4):* 526-530.

79. Peterson Bhoi, Dash RK and Dalai MK. Formulation and *in vitro* evaluation of oral floating matrix tablets of Diclofenac Sodium. International Journal of PharmTech Research, 2010; 2(4): 2420-2428.

80. Pradeep KN and Vidyasagar G. Preparation and evaluation of floating calsium alginate beads of clarithromycin. Pelagia Research Library Der Pharmacia Sinica 2010; 1(1): 29-35

81. Patel DM, Patel MJ, Patel AN and Patel CN. Formulation and evaluation of mixed matrix gastro-retentive drug delivery for Famotidine. International Journal of Pharmaceutical Investigation, 2011; 1(4): 247-254.

82. Parveen Kumar, Nirmala, and Hari Kumar SL. Approaches for gastroretentive drug delivery systems-A review. Journal of Drug Delivery & Therapeutics, 2014; 4(3): 14-24.

83. Rosa M, Zia H, Rhodes T. Dosing and testing in vitro of a bioadhesive and floating drug delivery system for oral application. International Journal of Pharmaceutics 1994; 105: 65-70.

84. Ravi Kumar, Patil MB, Sachin RP, Mahesh SP. Formulation and evaluation of effervescent floating tablet of Famotidine. International Journal of PharmTech Research, 2009; 1(3): 754-763.

85. Ravi Kumar, Swati Patil MB, Patil, Sachin RP, Mahesh SP. Design and *in vitro* Evaluation of oral floating matrix tablets of Aceclofenac. International Journal of Chem.Tech Research, 2009a; 1 (4): 815-825.

86. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, Hand book of Pharmaceutical Expients, 6th (Ed.), 2009.

87. 81.Ramana BV, Parameswari CS, Triveni C, Arundathi T, Venkateswara Reddy, Nagarajan G. Formulation And evaluation of sodium alginate microbeads of Simvastatin. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(3): 410-416.

88. Rasool Bazigha KA and Sahar AF. Development of coated beads for oral controlled delivery of Cefaclor: *In vitro* evaluation. Acta Pharmaceutica, 2013; 63: 31-44.

89. Richa Joshi and Sayantan Mukhopadhyay. Review on floating drug delivery system. International Journal of Pharmaceutical Archive, 2014; 3(5): 424-438.

90. Rouge N, Allémann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple unit capsule, a high density multiple unit capsule and an immediate release tablet containing 25 mg atenolol. Pharm Acta Helv. 1998;73:8187.PubMed DOI: 10.1016/S0031-6865(97)00050-2

91. Sheth PR, Tossounian JL. Sustained release pharmaceutical capsules, US Patent, 1978, 4,126,672.

92. Smolen VF. Bioavailability and Pharmacokinetic Analysis of Drug Responding Systems. Annual Review of Pharmacology and Toxicology 1978; 18: 495-522.

93. Sezer AD, Akbuğa J. Release characteristics of chitosan treated alginate beads: II. Sustained release of a low molecular drug from chitosan treated alginate beads. Journal of Microencapsulation,1999; 16(6): 687-96.

94. Singh BN, Kim KH. Floating drug delivery system: An approach to the controlled drug delivery via gastric retention. Journal of Controlled Release 2000; 63: 235-259.

95. Seham AE, AlaaEldeen BY, Saleh Alsuwayeh, Fayza AA. *In vitro* and *In vivo* evaluation of Floating controlled release dosage forms of verapamil hydrochloride. Pharmaceutical Ind., 66, Nr. 11, 2004, 1064-1372.

96. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of cimetidine: formulation, Characterization and *in vitro* evaluation. Acta Pharmaceutica 2005; 55: 277–285.

97. Sajid Bashir, Mohammad Jamshaid, Bashir Ahmad, JaveidIqbal. Pharmacokinetics of ciprofloxacin in normal rabbits and changes observed in induced dehydrated state. *Pakistan*Journal of*Pharmaceutical*Sciences 2008; 21(3): 225-229.

98. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. International Journal of Pharmaceutical Research 2009; 1(3): 623-633.

99. Sherina VM, Santhi K and Sajeeth CI. Formulation and evaluation of sodium alginate microbeads as a carrier for the controlled release of Nifedipine. International Journal of Pharmaceutical and Chemical Sciences, 2012; 1(2): 699-710.

100. Swarna Kamala Chinthala CH, Srinivas Reddy Kota K, Hadassah M, Hepsibha Metilda E, Sridevi S. Formulation and evaluation of gastroretentive floating tablets of Gabapentin using effervescent technology. International Journal of Pharmaceutical and Biomedical Research, 2012; 3(4): 202-208.

101. Sarang UK, Ravikiran MS, Mahendra JR, Pratap BB, Barhate SD, Patil PP. Floating drug delivery system: A review. Pharma Science Monitor, 2013; 4(4):403-413.

102. Sisode NR, Shaikh TJ, Wagh RD. Floating drug delivery system: A review. World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(2): 1165-1178.

103. Timmermans J, Gansbeke VB, Moes AJ. Assessing by gamma scintigraphy the *In vivo* buoyancy of dosage forms having known size and floating force profiles as a function of time. Vol I. Proceedings of the 5th International Conference on Pharmacy Technology. Paris, France: APGI, 1989: 42-51.

104. Timmermans J, Gasnsbeka BV, Moes A. Accessing by gamma- scintigraphy the *in vivo* buoyancy of dosage form having known size and floating force profiles as a function of time. Pharmaceutical Technology 1989; 1: 42-51.

105. Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. Journal of Pharmaceutical Sciences 1994; 83; 18-24.

106. Tardos GI. Ingress of atmospheric moisture into bulk powders: II. Application to caking of fine crystalline powders. Powder Processing & Handling 1996; 8:215-220

107. Tanwar YS, Naruka PS, Ojha GR. Development and evaluation of floating microspheres of verapamil hydrochloride. Brazilian Journal of Pharmaceutical Sciences 2007; 43: 529-534.

108. The official compendium of standards, The United States Pharmacopoeial Convention, 2007, USP30-NF25

109. Sanikommu Baji Reddy. Formulation and evaluation of Diclofenac Sodium matrix tablets using *Abelmoschus esculentus* mucilage as a polymer. International Journal of Pharmaceutical Chemical and Biological Sciences, 2013; 3(2): 418-423.

110. Thulasi VM, Sajeeth CI. Formulation and evaluation of sustained release sodium alginate microbeads of Carvedilol. International Journal of PharmTech Research, 2013; 5(2): 746-753.

111. United States of Pharmacopoeia, 124, The United States Pharmacopeial Convention, Rockville, M.D, 2000, 1942.

112. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Advanced Drug Delivery Reviews 2005; 57: 1640-1665.

113. Vishal Bhardwaj, Nirmala, Harikumar SL. Floating drug delivery system: A review. Pharmacophore, 2013; 4(1): 26-38.

114. Well LJ, Gardner RC, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 1998; 30th August: 4,767,627.

115. Wilson CG, Washington N. The Stomach: its role in oral drug delivery.In: Rubinstein, M.H., (Ed.). Physiological pharmaceutics: biological barriers to drug absorption. Ellis Harwood, Chechester, 1989: 47-70.

116. Whitehead L, Collet JH, Fell JT, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. Journal of Control Release 1998; 55: 3-12.

117. Whitehead L, Collet JH, Fell JT, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. Journal of Control Release 1998; 55: 3-12.

118. Ylitalo P, Hinkka H, Neuvonen PJ. Effect of exercise on the serum level and urinary excretion of tetracycline, doxycycline and sulphamethizole. *EuropeanJournal*of *Clinical Pharmacology*, 1997; 12(5): 367-373.