FORMULATION AND IN – VITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF CEFADROXIL MATRIX SUSTAINED RELEASE TABLET

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DECLARATION

I here by declare that the dissertation work entitled **FORMULATION AND INVITRO EVALUATION OF GASTRIC FLOATING DRUG DELIVERY SYSTEMS OF CEFADROXIL MATRIX SUSTAINED RELEASE TABLETS** is based on the original work carried out by me in Annaivelankannis Pharmacy College Chennai -600015 and Bright labs at Hyderabad under the guidance of G.Anilkumar for the submission toThe Tamilnadu Dr.MGR Medical university,Chennai in the partial fulfilment of the requirement for the award of degree Master of pharmacy in Pharmaceutics.The work is original and has not submitted any where.

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LIST OF ABBREVIATIONS

DDS	Drug Delivery System
GIT	Gastro Intestinal Tract
FDDS	Floating Drug delivery System
GRDF	Gastro- Refractive Dosage form
GRT	Ggastro Refractive Time
NSAIDS	Non Steroidal Anti-inflammatory drugs
HBS	Hydro dynamically Balanced System
PVA	Poly Vinyl Alcohol
HPMC	Hydroxy Methyl Cellulose
HCL	Hydro Chloric Acid
UV	Ultra violet
HPLC	High Performance liquid Chromatography
NaHco3	Sodium Bi Carbonate
Fig	Figure
SD	Standard deviation
SDs	Solid dispersions
SEM	Scanning electron microscope
XRD	X-ray diffraction
UV	Ultra violet
w/w	Weight by weight
λ max	Wavelength maximum
vs	Verses
µg	Microgram

INTRODUCTION

1. INTRODUCTION

1.1 NOVEL DRUG DELIVERY SYSTEM:

Historically, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations. However, it is a well accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hours is possible for many drugs that are absorbed uniformly from GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e. stomach and small intestine.

The design of oral controlled drug delivery systems (DDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug. Depending upon the manner of drug

1.1.1. Classification

A. Continuous release system: These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form. The various systems under this category are:

- Dissolution controlled release systems
- Diffusion controlled release systems

- Dissolution and diffusion controlled release systems
- Ion-Exchange resins – drug complexes
- slow dissolving salts and complexes
- pH –dependent formulations
- Osmotic pressure controlled systems
- Hydrodynanic pressure controlled systems

B. Delayed transit and continuous release system: These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage is fabricated to retain in the stomach and hence the drug present therein should be stable at gastric P^H.

Systems included in this category are:

- Altered density systems
- Mucoadhesive systems
- Size-based systems

C. Delayed release systems: The design of such systems involve release of drug only at a specific site in the GIT.

The drugs contained in such system have following category:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site, or
- Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:

- Intestinal release systems

- Colonic release systems

Oral controlled release dosage forms have been developed for the past three decades due to their various benefit characteristics which includes.

Table No.1: Advantages

Benefit of oral controlled-release drug delivery systems	
Benefit	**Reason**
Therapeutic advantage	Reduction in drug plasma level fluctuations; maintenance of a steady plasma level of the drug over a prolonged period, ideally simulating an intravenous infusion of a drug
Reduction in adverse side effects and improvement in tolerability	Drug plasma levels are maintained within a narrow therapeutic window with no sharp peaks and with AUC of plasma concentration versus time comparable with total AUC from multiple dosing with immediate release dosage form.
Patient comfort and compliance	Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.
Reduction in health care cost	The total cost of the controlled release product could be lower than the immediate release product. With reduction in side effects the overall expense in disease management also would be reduced.

Despite several advantages associated with controlled drug delivery system, there are number of disadvantages present with this type of drug delivery system.

Advantages of Sustained drug delivery

As mentioned earlier, drug absorption from oral controlled release (CR) dosage forms is often limited by the short GRT available for absorption.

However, HBS type dosage forms can retain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs. .

These special dosage forms are light, relatively large in size, and do not easily pass through pylorus, which has an opening of approx. 0.1– 1.9 cms.

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper 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.

The eradication of *Helicobacter pylori* requires the administration of various medicaments several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDDS. Floating alginate beads have been used for the sustained release of Amoxycillin trihydrate. Thus, it can be expected that the topical delivery of antibiotic through a FDDS may result in complete removal of the organisms in the fundal area due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer.

Pharmacokinetic advantages

As sustained release systems, floating dosage forms offer various potential advantages. Drugs that have poor bioavailability because their absorption is limited to upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavalabilities.

Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance. In addition, it might provide a beneficial strategy for gastric and duodenal cancer treatment.

The concept of FDDS has also been utilized in the development of various anti-reflux formulations. Floating systems are particularly useful for acid soluble drugs, drugs poorly soluble or unstable in intestinal fluids, and those which may undergo abrupt changes in their pH dependent solubility due to food, age and disease states.

Limitations

- They require a sufficiently high level of fluids in the stomach for the drug delivery buoyancy, to float therein and to work efficiently.
- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluid.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first- pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability.
- Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

Table No.2: Disadvantages

Disadvantage of oral controlled-release drug delivery systems

Disadvantage	Reason
Over dose	There is always possibility of sudden release of the total dose administered i.e. dose dumping, which may result in toxic manifestations.
Less flexibility in dose adjustments	The adjustment of dosage for controlled release dosage form is very difficult. The physician has less flexibility in adjusting the dosage regimens.
Side effects	Along with longer duration of action controlled release preparations shows long duration of side effects, especially if the patient is hypersensitive to the given medication.
Cost	The cost of unit dose of controlled therapeutic system is higher than the conventional dosage forms.

To overcome these problems and improve the efficacy of oral administration, some recent studies have reported that controlled oral drug delivery system with prolonged gastric residence time, such as floating dosage system have been proved to be advantages.

A gastrointestinal drug delivery system can be made to float in the stomach by a gelling process of hydrocolloid materials or by incorporating a floatation chamber with vaccum or gas. In this way bulk density less than that of gastric fluid is produced. However, most of the devices generating gas or gelling need time to be floated and this parameter must be checked carefully in order to prevent the dosage form from transiting in to the small intestine along with food before floating in stomach. The floating system, more predictable drug release kinetics, less chances of localized mucosal damage, insignificant impairing of performance due to failure of a few units, co

administration of units with different release profile or obtaining incompatible substances, larger margin of safety against dosage form failure.

1.2 GASTRO-RETENTIVE DOSAGE FORMS (GRDF):[8-13]

These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

The gastric emptying time mainly depends upon the design of the dosage form and physiological state of the subject, which last from a few minutes to 12hrs. The average gastric emptying time in human is 2-3hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose. So drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.

GRDF will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time.

Finally, GRDF will be used as carriers for drugs with so called absorption windows: these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. Need of gastro retention arises because of two reasons, viz.

- To improve bioavailability of drugs such as cyclosporin, ciprofloxacin, ranitidine, metoprolol tartarate, cefuroxime axetil etc. which are mainly absorbed from upper part of GIT or get degraded in alkaline P^H.
- For local action in case of pathologies of stomach.

1.2.0 Anatomy and Physiology of Stomach:[14]

1.2.1a) Anatomy

The stomach is j- shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach.

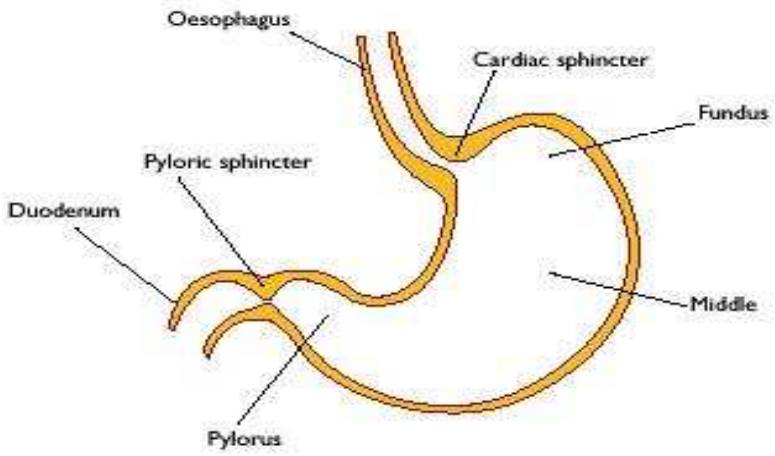


Figure No. 1: Anatomy of the stomach.

The stomach has four main regions:

1. Cardia
2. Fundus
3. Body and
4. Pylorus

The main function of the fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region, to pass through the pyloric sphincter into the small intestine.

1.2.1.b) Physiology

Various factors like absorption ability, presystemic clearance, gastric motility; gastrointestinal transit time and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form.

Absorption ability

The absorption capability of various segments of gastrointestinal tract differs from each other. i.e. most of the absorption takes place in small intestine and lesser extent in colon and stomach. Unless drugs are absorbed equally in both the colon and in small intestine, the duration for most of the drugs is 3-8 hours. This will be the major limiting factor for sustained release and controlled release drug delivery systems.

Presystemic clearance

Even if the drugs that can be absorbed equally well throughout the gastrointestinal tract, bioavailability is significantly reduced by the site-specific changes in presystemic clearance. Degradation of the drug is also carried out by hydrolysis in the stomach, enzymatic digestion, and metabolism in the brush border of the gut wall and by the microorganisms.

Such degradation may leads to high variation in plasma drug concentration and poor absorption of drug in to the systemic circulation.

Gastric motility

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action and potential contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complication, that of short gastric residence time and unpredictable gastric emptying rate.

Gastrointestinal Transit Time

Food content remains in each segment of the gastrointestinal tract for different periods of

time. The resident time for both liquid and solid foods in each segment of the gastrointestinal tract is as reported by park.

Table No.3: Transit time of food in each segment of the gastrointestinal tract

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

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So one has to take most of the drugs 3-6 times a day.

1.2.1 c) Various factors affecting the gastric emptying time:[15]

I. State of the stomach: gastric emptying time depends upon the fed state of the stomach, which increases the gastric emptying time as compared to unfed state.

II. Circadian rhythms: which are increased in daytime and less during night, also affects the gastric retention time (GRT).

III. Size of the dosage form: greater the energy content of the meal (carbohydrate and high fat content), longer the duration of emptying.

IV. Density of the oral dosage form: The density of the gastric fluid is reported to be 1.2g/cm. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for longer period of time.

V. Diseased state: State of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.

VI. Drug therapy: Plays an impotent role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase the gastric emptying time.

VII. Age: Increase in age decreases the gastric motility thereby increasing the gastric emptying time.

VIII. Posture: It was seen that the supine posture on the right side showed better results than on the left side.

1.2.1 d) Criteria for selection of drug candidate for GRDF:[15]

The gastric retentive drug delivery systems are suitable for following types of drug therapy:

- Absorption from upper GIT: Drugs have a particular site for maximum absorption e.g. ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may be poorly bioavailable since absorption appears to diminish when the dosage form pass in to large intestine.
- Drugs having low P^{Ka}, which remains unionized in stomach for better absorption.
- Drugs having reduced solubility at higher P^{H} e.g. captopril and chlordiazepoxide and the bioavailability of drugs that get degraded in alkaline P^{H} can be increased by formulating gastro-retentive dosage forms. e.g. doxifluridine, which degrades in small intestine.
- Local action as it is seen in the treatment of H. Pylori by amoxicillin and misoprostol for ulcers.
- To minimize gastric irritation which may be caused by sudden increase of drug concentration in the stomach. e.g. NSAIDs.
- Improve effectiveness of particular drugs. E.g. antibiotics in the colon tend to disturb the microflora causing overgrowth of microorganisms like Clostridium difficile causing colitis.

1.3 GASTRO RETENTIVE DRUG DELIVERY SYSTEM:[1(b),15,16]

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Oral medication is generally considered as the first

avenue investigated in the development of pharmaceutical formulations because of patient acceptance, convenience in administration and cost effective manufacturing processes. Oral route offers an attractive approach of drug targeting at the specific site within GI tract for certain types of drug.

Requirements for gastro retention

From the discussion of the physiological factors in stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease

Approaches to gastric retention

Over the last 3 decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Bioadhesive systems, swelling and expanding systems, High density systems, Floating systems, Modified systems [1] .

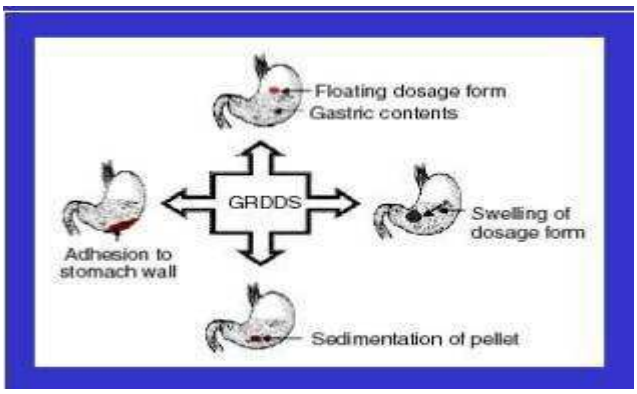


Figure No. 2 Approaches to gastric retention

Floating Drug Delivery Systems

The concept of FDDS was described in the literature as early as 1962. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration [6] .

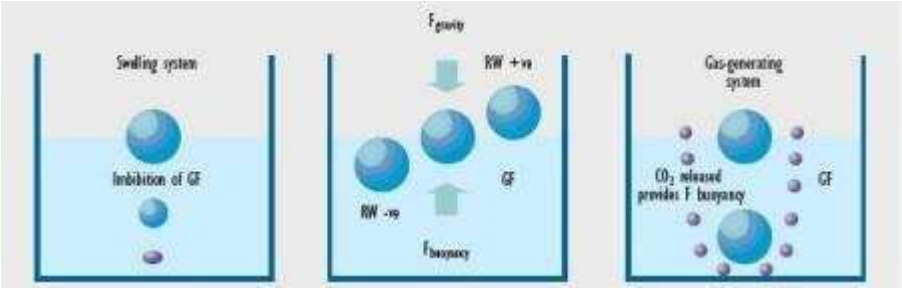


Figure No. 3 The mechanism of floating systems

Formulation of this device must comply with the following criteria

1. It must have sufficient structure to form a cohesive gel barrier.
2. It must maintain an overall specific gravity lower than that of gastric contents (1.004 – 1.010).
3. It should dissolve slowly enough to serve as a drug reservoir.

A list of drugs used in the development of FDDS thus far is given in Table-4:

Table. No.4 List of drugs explored for various floating dosage forms [6]

Dosage Forms	Drugs
Microspheres	Aspirin, Ibuprofen, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Capsules	Diazepam, Furosemide, L-Dopa and Benserazide
Tablets / pills	Amoxycillin Trihydrate, Ampicillin, Diltiazem, *p* -Aminobenzoic acid, Riboflavin-**5'**-phosphate, Theophylline, Verapamil HCl

Based on the mechanism of buoyancy, two distinctly different technologies, i.e. noneffervescent and effervescent systems, have been utilized in the development of FDDS.

1.3.1 Approaches to Gastric Retention[:]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:

a) Floating Systems:[17]

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

b) Bio/Muco-adhesive Systems:[18]

Bio/Muco-adhesive systems are those which bind to the gastric epithelial surface or

mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

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

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

c) Swelling and Expanding Systems:

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as “plug type system” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

d) High Density Systems

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

e) Incorporation of Passage Delaying Food Agents

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

f) Ion Exchange Resins:[19]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The nflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug

reservoir compartment and osmotically active compartment.

1.3.2 Types of Floating Drug Delivery Systems (FDDS):[20-21]

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

A. Effervescent System

B. Non- Effervescent System A. Effervescent System:

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate) and other organic acid (citric acid and tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

I. Gas Generating Systems

1. Intra Gastric Single Layer Floating Tablet or Hydrodynamically Balanced System (HBS)

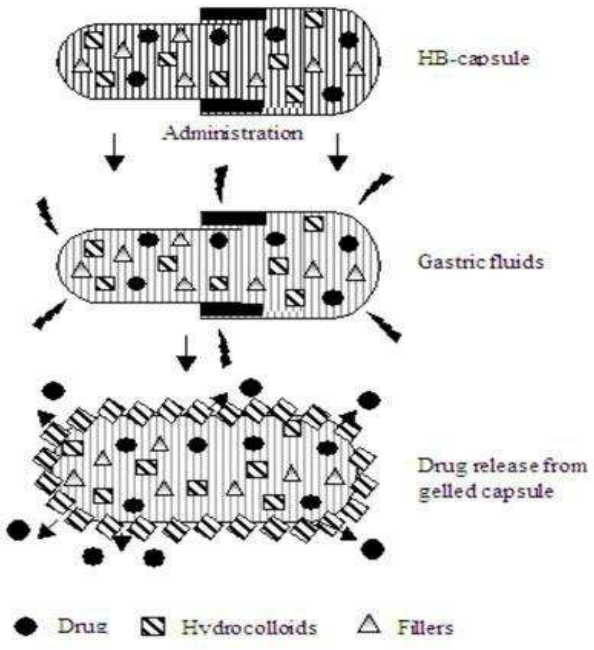


Figure No. 4: hydrodynamically balanced system

These are formulated by mixing the CO_2 generating agents and the drug within the matrix tablet (Fig. 4). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayered Floating Tablets

These are also compressed tablet and contains two layers for:

i) Immediate release layer and ii) Sustained release layer (Fig. 5).

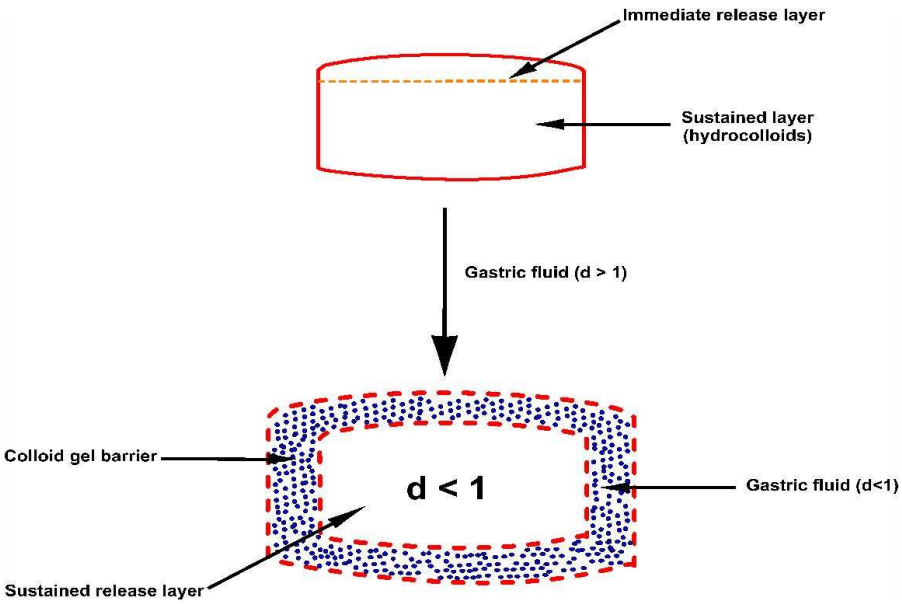


Figure No. 5: Intra Gastric Bilayer Floating Tablet. 3. Multiple Unit type floating pills:

These systems consist of sustained release pills as „seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swollen pill like balloon and float as the density decreases (Fig. 6&7).

Figure No. 6
A multi-unit type oral floating dosage system

Figure No. 7
Stages of floating mechanism

A. Penetration of water

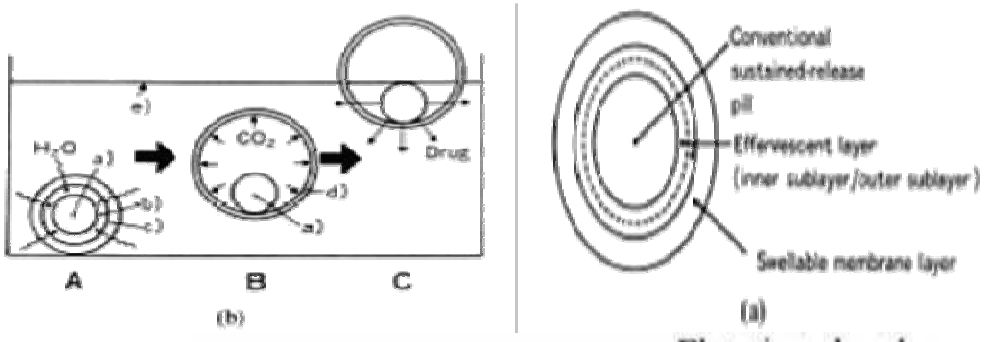
B. Generation of CO_2 and floating

C. Dissolution of drug

II. Volatile Liquid / Vacuum Containing Systems

1. Intragastric Floating Gastrointestinal Drug Delivery System:[23]

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment (Fig. 8).



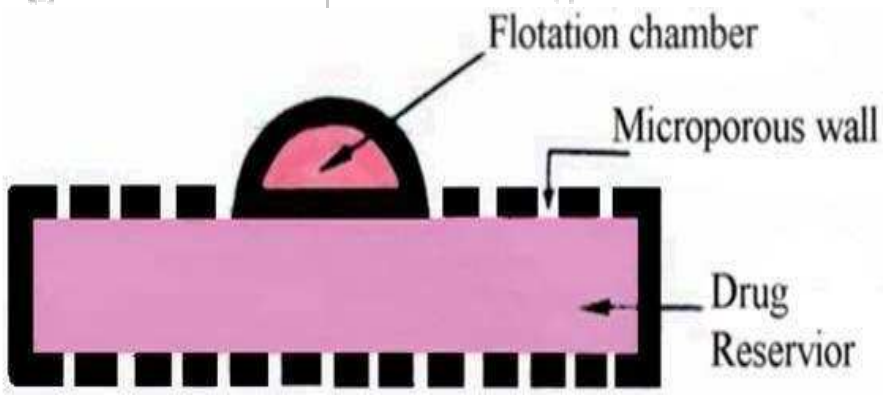


Figure No. 8: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable

chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid (Fig. 9).

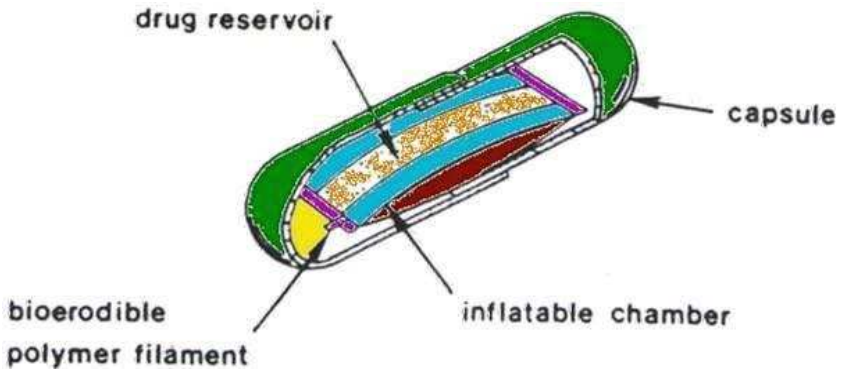


Figure No. 9: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Fig. 10).

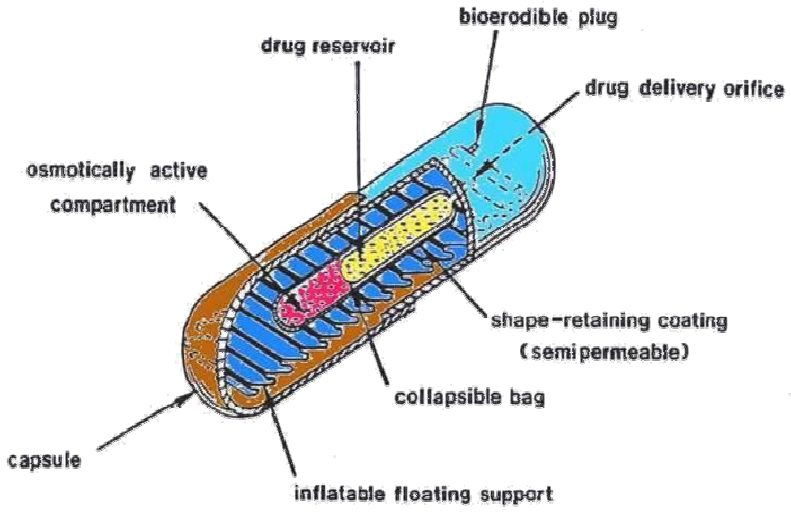


Figure No. 10: Intragastric Osmotically Controlled Drug Delivery System

B. Non Effervescent Systems:

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 non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethacrylates, polystyrenes etc. and bioadhesive polymer such as chitosan and carbopol.

The various types of these systems are:

1. Single Layer Floating Tablets:[24-25]

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Alginate Beads:[26]

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a 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. These floating beads gave a prolonged residence time of more than 5.5 hour.

3. Hollow Microspheres:

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with Drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microballoons were floatable in vitro for 12 hours when immersed in aqueous media. Radiographical studies proved that microballoons orally administered to humans were dispersed in

the upper part of stomach and retained there for 3 hours against peristaltic movements.

1.4.1 Advantages of FDDS:[15]

1. Drugs that act locally in the stomach e.g., Antacids, Antibiotics for microbial based ulcers, etc.
2. Drugs that are absorbed primarily in the stomach e.g., Albuterol.
3. Drugs that are poorly soluble in alkaline pH.
4. Drugs that have a narrow window for absorption. i.e., Drugs that are absorbed mainly from the proximal part of small intestine. e.g., Riboflavin, Levodopa, p-amino benzoic acid.
5. Drugs that are absorbed rapidly from the GI tract. e.g., Amoxicillin.
6. Drugs that degrade in the colon. e.g., Captopril, Metoprolol.

1.4.2 Disadvantages of FDDS:[15]

1. High Variability in gastric emptying time due to variations in emptying process.
2. Drugs that cause irritation and lesions to gastric mucosa and unstable in gastric fluid cannot be formulated as FDDS.
3. Drug with unpredictable bioavailability, minimum effective concentration is achieved slowly.
4. Gastric retention is influenced by many factors such as gastric motility, pH, and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

1.4.3 Application of FDDS:[15]

1. For treating local inflammation and stomach ulcers.
2. For treating H. Pylori associated ulcers.

3. In chronic diseases associated with frequent medication and prolonged medication, FDDS can be promising drug delivery system.

1.5 MATRIX SYSTEMS:[1,27-30]

A matrix is a uniform mixture of drug and excipients. e.g. polymer that is homogeneously fixed in solid dosage form.

The drug substance, which has a solubility S gm /cm3 in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium. The concentration of drug in the matrix is „A' gm / cm^3. The matrix is porous, with a porosity of 'Є' and diffusion coefficient of „D_m'. The drug release from such system can be described by $dQ/dt = 2SD_mAt$. Liquid will intrude from the bulk liquid. The rate and extent of intrusion will follow the following equation:

$$\frac{dL}{dt} = \frac{-Qr2}{8\eta L} = -\frac{q}{L} \quad \text{..... (1)}$$

Where, L is the length of the intrusion at time t, r is the average radius of the pores, is the viscosity of the liquid and Q is a constant[21].

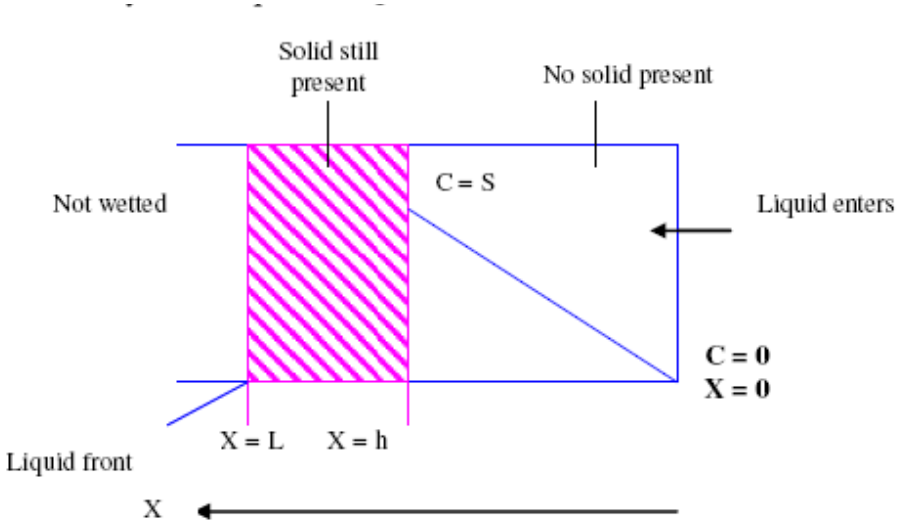


Figure No. 11: Dissolution of drug from a solid matrix

1.5.1 Hydrophillic Matrix System

A hydrophilic matrix controlled release system is a dynamic system composed of polymer wetting, polymer hydration and polymer dissolution. At the same time other soluble excipients or drug will also wet, dissolve and diffuse out of the matrix while insoluble materials will be hold in place until the surrounding polymer/ excipients / drug complex erodes or dissolves away.

The main principle is that a water-soluble binder, present throughout the tablet, **partially hydrates on the outer tablet "sink"** to form a gel layer. Throughout the life of ingested tablet the rate of drug diffusion (if soluble) out of the wet gel and the rate of tablet erosion control the overall dissolution rate and drug availability.

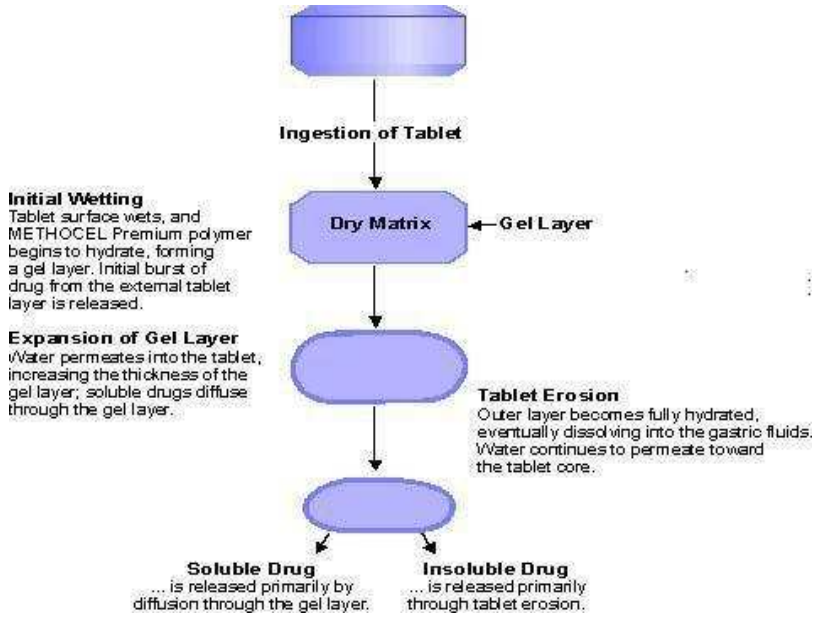


Figure No. 12 : Matrix System

1.5.2 Matrix Type[31]

The most common controlled delivery system has been the matrix type such as tablets and granules, where the drug is uniformly dissolved or dispersed through out the polymer, because

of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period.

Hydrophilic polymers are becoming more popular in formulating oral controlled release tablets, it is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile. The release of a dissolved drug inherently follows near first order diffusion either an initially high release rate, due to the dissolution of the drug present at the surface of the matrix followed by a rapidly declining drug release rate. The enhanced release rate observed at the beginning for the short time of release process is known as "burst effect" and is many a time undesirable since it may, have negative therapeutic consequences. After this burst effect, hydration and consequent swelling and/o**r** erosion of related polymer occur. These phenomenon's control the release process but with time, the diffusion path length increases and saturation effect is attained, resulting in a progressively slow release rate during the end of dissolution span.

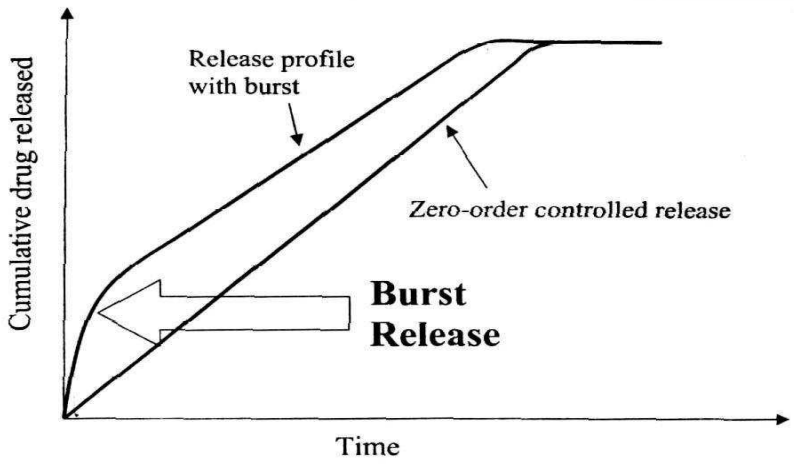


Figure No. 13 : Schematic showing the burst effect in a zero-order

Drug delivery system

In many controlled release formulations immediately upon placement in release medium, an initial large bolus of drug is release medium; an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is referred to as

burst release

1.5.3. Cause of burst release

1) Processing conditions
2) Surface characteristics of host material
3) Sample geometry
4) Host and drug interaction (surface adsorption)
5) Morphology and porous structure of dry material.

1.5.4. Prevention of burst release

Several advanced technologies to avoid burst include;

a) Surface extraction of active agent

Approaches have been taken to reduce the initial burst, such as extracting the drug formulation for a short period of time in vitro before using them in-vivo application. Burst effect is reduced because drug is removed from the outer layers of controlled release devices. E.g. Lee showed the effectiveness of surface extraction in reducing burst release of Oxprenolol HCl from P-HEMA hydrogen.

b) Coated surface

It is another method which prevents burst release is surface modification by additional coating steps to provide an outer layer with no drug. Colombo and co-workers have done extensive work in understanding the influence of exposed surface area on drug release. They defined a dimensionless parameter so, the swelling area number as

$$S_d = \frac{1}{D}.\frac{dA}{dt} \text{.....(2)}$$

Where, dA/dt = rate of releasing area charge

D = drug diffusion coefficient

c) Drug loading distribution

Non uniform drug loading, i.e. the increasing concentrations away from surface overcome the growing rubbery gel layer. This gel layer typically leads to diminishing release rates with time in uniformly loaded gels.

d) Polymer morphology and composition

The polymer microstructure and hydrophilic/hydrophobic interaction also play an important role in determining drug distribution profiles and release characteristics.

e) Surface modification

To prevent burst release from porous polymer structures caused by solvent evaporation during processing many methods have been attempted which are based on changing the surface characteristics of the devices.

1.6 SWELLING CHARACTERISTICS OF POLYMER:[2(a)]

The Peppa's plot is useful to determine whether the drug release from the matrix is controlled by swelling of the polymer or not. The Peppa's equation is

$$\log Q = \log (kt^{½}) \text{ ----------} \quad (3)$$

$$\log Q = \log k + 0.5 \log t \text{ ----------} \quad (4)$$

Where, Q = amount of drug release in time t per unit area

k = release constant.

If the slope of a plot of log Q Vs log t is exactly 0.5, then the drug release occurs by perfect diffusion obeying Higuchi's and Fick's law. If it is in the range of 0.5 – 1, then the mechanism of release is diffusion and rate of diffusion is controlled by swelling of polymer. If it is bellow 0.5, then there is no swelling of matrix occur.

1.7 DRUG RELEASE MECHANISM FROM MATRICES:[32]

From time to time, various authors have proposed different types of drug release mechanisms from matrices. It has been proposed that drug release from the matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and / or the erosion of the gelatinous layer. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, and nature of the drug and of course, the polymer used.[11]

a. Zero order kinetics: [31,33]

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

$$W_0 - W_t = Kt \text{ ---------} \textbf{(5)}$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form,

W_t = amount of drug in the pharmaceutical dosage form,

t = time,

K = Proportionality constant.

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

$$Q_t = Q_0 + K_0 t \text{ ----------} \textbf{(6)}$$

Where, Q_t = Drug dissolved in time t,

Q_0 = Initial amount of drug in solution,

K_0 = Zero order rate constant.

OR,

$$W = K.t \quad \text{(Xu and Sunada, 1995) ---------} \textbf{(7)}$$

Where W is percentage drug release at time t,

K is the release rate constant.

b. First order kinetics: [31,33]

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

$$\frac{dc}{dt} = K(C_s - C).....(8)$$

Where, C = Concentration of solute in time t,

C_S = Solubility in equilibrium at experience temperature.

k = First order proportionality constant

Hixson and Crowell adapted the above equation as

$$\frac{Dw}{dt} = KS(C_s - C).....(9)$$

Where, w = amount of solute in solution at time t,

S = Solid area accessible to dissolution.

$\log Q_t = \log Q_0 + K_1.t / 2.303$ --------- (10)

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

Q_0 = initial amount of drug in solution,

K_1 = First order release constant.

Above equation also represents this model.

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

OR, In (100 – W) = In 100 – k t (Singla and Medrata, 1988; and

Sunada 1995) ---------- (**11)**

c. Hixson Crowell Model or Hixson Crowell's cube Root equation:[31,34]

(Erosion Model) (Singla and Medirata, 1988)

Hixson Crowell recognizing that the particles regular area is proportional to the cubic root of its volume, derived an equation that can be described as

$W_0^{1/3} - W_t^{1/3} = K_S t$ ---------- **(12)**

Where, W_0 = initial amount of drug,

W_t = remaining amount of drug,

K_S = constant incorporating the surface volume relation,

This can also be expressed as

$(100 - w)^{1/3} = 100^{1/3} - Kt$ ---------- **(13)**

Where, w = Percentage drug release at time t,

K = Release rate constant.

d. Higuchi Model / Higuchi's square Root of time Equation (Diffusion model):[31]

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

$ft \quad Q(2C - C_S)C_S t$ ---------- **(14)**

Where, Q = Amount of drug released in time t per unit area.

C = Drug initial concentration

C_S = drug solubility in matrix media

D = Diffusivity of drug molecules in matrix substance.

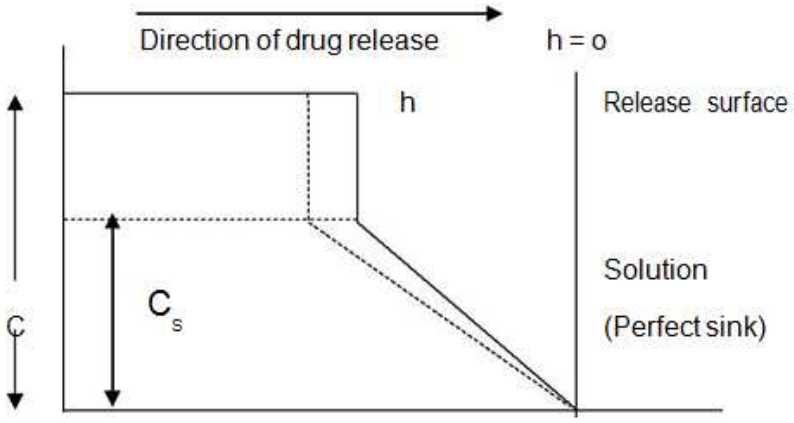


Figure No. 14: Drug theoretical concentration profile of a matrix system in Direct contact with a perfect sink release media

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

$$Q = \sqrt{tDC_s(2C - C_s)} \text{.....(15)}$$

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

$$ft = Q = \sqrt{\frac{DE}{T}(2C - \varepsilon C_s)\, C_s^t} \text{.....(16)}$$

Where, Є = matrix porosity.

Or,

$W = K t^{1/2}$ ---------- (17)

W = Percentage drug release at time t,

K = release constant.

e. Korsmeyer And Peppas Model:[35-37]

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

$$\frac{M_t}{M\infty} = Kt^n \text{.....(18)}$$

Where, $\frac{M_t}{M\infty}$ = fraction of drug release in time t,

K = constant incorporating structural and geometric characteristics of controlled release device.

n = diffusion release exponent indicative of release mechanism.

For release from swellable cylinders Ritger and Peppas have indicated,

n = 0.45 for Fickian diffusion,

n > 0 .45 and < 0.89 for anomalous diffusion or non Fickian diffusion (0.5 < n < 1)

n = 0.89 for zero order release

n = 1 or > 1 for super case

f. Baker – Lonsdale Model:[27,36,38]

Baker developed model which described the drug controlled release from a spherical matrix, being represented by the following expression

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right]-\frac{M_t}{M_\infty}=\frac{3D_mC_{ms}t}{r_0^2C_0} \quad .....(19)$$

M_t = drug release amount at time t, Є = Porosity of matrix

$M\infty$ = Drug released at ∞ Time, D_f = Diffusion coefficient.

Cms= Drug solubility in matrix

This model is used to linearization of release data from microcapsules or microspheres

g. Hopfenberg Model:[39]

Mechanism of release from erodable matrix has been described by Hopfenberg. A simple expression describing release from erodable is:

$$\left[1-\frac{M_t}{M}\right]^{1/3}=1-kt.....(20)$$

Where, Mt = Mass of drug release at time t,

k = erosion constant,

t = time

Thus a plot of $[M_t / M]^{1/3}]$ versus the time will be linear, if the release of drug from the matrix is erosion controlled.

This model assumes that rate limiting step of drug release is the erosion of matrix itself and that dependent diffusional resistance internal or external to eroding matrix do not influence it.

1.8 MECHANISM OF DRUG RELEASE FROM MATRIX SYSTEM:[38,39]

When a hydrophilic matrix system containing a swellable glassy polymer comes in contact with an aqueous medium, the fall in glass transition temperature leads to an abrupt change from a glassy to a rubbery state, causing swelling of the polymer on the surface and formation of a hydrated gel. Drug release is controlled by this gel diffusional barrier and/or by surface erosion of the gel. Surface leaching of the drug can lead to an initial burst, especially with highly soluble drugs.

Hydration of individual polymer chains leads to expansion in their end to end distance and radius of gyration to a new solvated state due to lowering of the polymer transition temperature, a sharp distinction between glassy and rubbery region is observed and the matrix increases in volume because of swelling.

As water infiltrates deep in to the core, the thickness of the gel layer increases with simultaneous dissolution and erosion occurring at the outer layer due to complete hydration.

When the system is hydrated to the core, the drug concentration falls below its solubility value and the release rate of the drug begins to decline. A concurrent increase in the thickness of the barrier layer with time increases the diffusion path length, further reducing the release rate. Drug release kinetic associated with this gel layer dynamics, range initially from Fickian to anomalous (Non-Fickian) and subsequently from quasi-constant (near zero order) to constant. Matrices of highly molecular weight polymers rarely shows all three regimens (Fickian, Non-Fickian and quasi-constant) of drug release because of a low chain disentanglement rate and insufficient external polymeric mass transfer.

Soluble drugs are primarily released by diffusion through aqueous filled porous network formed in the inert matrix former due to dissolution and erosion of the polymer from the surface. Far poorly soluble drugs dispersed in inert polymer systems erosion is the primarily release

mechanisms.

There are two major processes that control the drug release from swelling controlled matrix systems, these include:

1. Ingress of aqueous medium into the matrix followed by a hydration, gelation or swelling and
2. Matrix erosion.

Simultaneous occurrence of these processes leads to the formation of two fronts within the hydrating matrix, this are- **a swelling front**, at the junction of the unhydrated glassy matrix and the hydrated matrix and **an eroding front** where the polymer is completely hydrated. Thickness of the diffusion layer, i.e. the distance between the two fronts, depends on the relative rates at which the swelling and erosion occurs.

If the polymer gels slowly, solvent can penetrate deep into the glassy matrix, thus dissolving the drug; therefore, gel layer thickness and its stability are crucial in controlling drug release. Numbers of techniques have been used to study the swelling of matrix tablets and to characterize the gel layer and front movement such as, optical imaging, ^{1}H- NMR, pulsed –filled gradient spin echo NMR, confocal laser scanning microscopy, cryogenic scanning electron microscopy and texture analysis. The gel layer thickness is determined by the relative position of the swelling and erosion front.

1.9. ADVANTAGES OF HYDROPHILIC MATRIX SYSTEM:[39]-

A hydrophilic matrix system essentially consists of a drug dispersed in a water swelling viscous polymer. These systems offer a number of advantages over other sustained release technologies namely.

1. Simplicity of formulation.
2. High drug loading as high as 80 % is possible in many cases.
3. The system is usually inexpensive as the rate-controlling agent is usually a GRAS (generally accepted as safe) food polysaccharides.

4. Number of matrix former is available allowing development of formulations that meet special needs and avoid patent infringement.
5. The systems are eroded as they pass the GIT thus there are no accu**mulation of "Ghosts"** or empty shells.
6. As system depends on both diffusion and erosion for drug release, release is not totally dependent on GI motility.
7. No specialized equipment is required which substantially reduces manufacturing costs.
8. Offer easy scalability and process validation due to simple manufacturing processes.

The above listed advantages overshadow the undesirable property of reducing release rates with time.

1.10. FACTORS INFLUENCING DRUG RELEASE FROM MATRIX SYSTEMS:412,16,35

A number of formulation variables and properties of the rate controlling polymer and the drug itself can be altered to attain a desired release rate from a matrix system. The mechanism by which drug release is controlled in matrix tablets are dependent on many variables, these variables are summarized in figure.

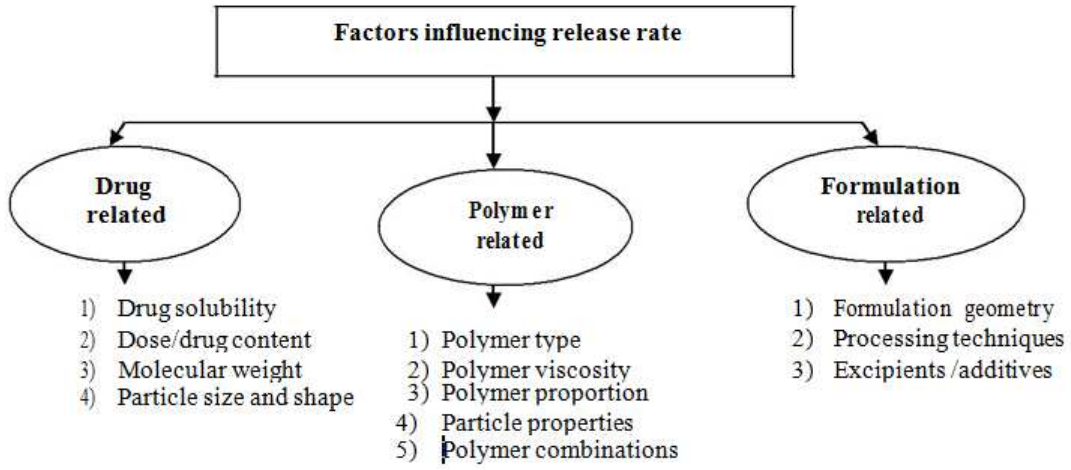


Figure No. 15 : Summary of factors influencing release rate from Matrix systems

There are several commercial products available based on the research activity of floating drug delivery (table-5).

Table.No. 5 Marketed Preparations of Floating Drug Delivery Systems[59]

S. No	Product	Active Ingredient	Reference No.
1	Madopar	Levodopa and benserzide	63
2	Valrelease	Diazepam	64
3	Topalkan	Aluminum magnesium antacid	65
4	Almagate flatcoat	Antacid	66

Table. No. 6. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

DOSAGE FORM	DRUG
• Tablets	Chlorpheniraminemaleate[4] Theophylline[23] Furosemide[31] Ciprofolxacin[37] Pentoxyfillin[40] Captopril[44] Acetylsalicylicacid[52] Nimodipine[59] Amoxycillintrihydrate[71] VerapamilHCl[75] Isosorbidedinitrate[76] Sotalol[77] Atenolol[89] Isosorbidemononitrate[100] Acetaminophen[102,103] Ampicillin[104] Cinnarazine[105] Diltiazem[106] Florouracil[107] Piretanide[108] Prednisolone[109] Riboflavin- 5′ Phosphate[110]
• Capsules	Nicardipine[41] L-Dopaandbenserazide[63] hlordiazepoxideHCl[64] Furosemide[84] Misoprostal[86] Diazepam[111]
	Propranlol[112] Urodeoxycholic acid[113]
• Microspheres	Verapamil[27] Aspirin,griseofulvin,andp-nitroaniline[43] Ketoprofen[49] Tranilast[55] Iboprufen[80] Terfenadine[114]
• Granules	Indomathacin[71] Diclofenacsodium[88] Prednisolone[115]
• Films	Drugdeliverydevice[62] Cinnarizine[106]
• Powders	Several basic drugs[56]

1.11. Antibiotics

The word "antibiotics" comes from the Greek anti ("against") and bios ("life"). Antibiotics are drugs that either destroy bacteria or prevent their reproduction. Antibiotics that kill bacteria are called "bactericidal" and the ones that stop the growth of bacteria are called "bacteriostatic".

Since penicillin's introduction during the 1940s, scientists developed numerous other antibiotics. Today, over 100 different antibiotics are available. About 90% of antibiotics are made from living organisms such as bacteria, others are produced synthetically, either in whole or in part.

Table No.7 Classification Of Antibiotics

Class (chemical structure)	Mechanism of action	Examples
B-lactam antibiotics Penicillins Cephalosporins Carbapenems	Inhibit bacterial cell wall synthesis	Penicillins Penicillin G Amoxicillin Flucloxacillin Cephalosporins Cefoxitin Cefotaxime Ceftriaxone Carbapenem Imipenem
Macrolides	Inhibit bacterial protein synthesis	Erythromycin Azithromycin Clarithromycin
Tetracyclines	Inhibit bacterial protein synthesis	Tetracycline Minocycline Doxycycline Lymecycline
Fluoroquinolones	Inhibit bacterial DNA synthesis	Norfloxacin Ciprofloxacin Enoxacin Ofloxacin

Sulphonamides	Blocks bacterial cell metabolism by inhibiting enzymes	Co-trimoxazole Trimethoprim
Aminoglycosides	Inhibit bacterial protein synthesis	Gentamicin Amikacin
Imidazoles	Inhibit bacterial DNA synthesis	Metronidazole
Peptides	Inhibit bacterial cell wall synthesis	Bacitracin
Lincosamides	Inhibit bacterial protein synthesis	Clindamycin Lincomycin
Other	Inhibit bacterial protein synthesis	Fusidic acid Mupirocin

1.11.1 Cephalosporins

Cephalosporin compounds were first isolated from cultures of Cephalosporium acremonium from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu. The first agent cephalothin (cefalotin) was launched by Eli Lilly in 1964.

Cephalosporins are used to treat a wide variety of bacterial infections, such as respiratory tract infections (pneumonia, strep throat, tonsillitis, and bronchitis), skin infections and urinary tract infections. They are sometimes given with other antibiotics. Cephalosporins are also commonly used for surgical prophylaxis - prevention of bacterial infection before, during, and after surgery.

A) Classification of Cephalosporins

Cephalosporins are grouped into "generations" based on their spectrum of antimicrobial activity. The first cephalosporins were designated first generation while later, more extended spectrum cephalosporins were classified as second generation cephalosporins. Each newer generation has significantly greater gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against gram-positive organisms. Fourth generation cephalosporins, however, have true broad spectrum activity.

a. First generation

First generation cephalosporins are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections and therefore are alternatives for skin and soft-tissue infections, as well as for streptococcal pharyngitis.

The first generation cephalosporins are Cefadroxil, Cephalexin, Cephaloridine, Cephalothin, Cephapirin, Cefazolin, and Cephradine. Cefazolin is the most commonly used first generation cephalosporin. The others have similar efficacy to Cephalexin, but must be dosed more often, and are therefore not as commonly prescribed.

b. Second generation

The second generation cephalosporins have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria. They are useful agents for treating upper and lower respiratory tract infections, sinusitis and otitis media. These agents are also active against E. coli, Klebsiella and Proteus, which makes them potential alternatives for treating urinary tract infections caused by these organisms.

The second generation cephalosporins are Cefaclor, Cefoxitin, Cefprozil, Cefuroxime.

c. Third generation

Third generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. Some members of this group (particularly those available in an oral formulation) have decreased activity against gram-positive organisms. The parenteral third generation cephalosporins (ceftriaxone and cefotaxime) have excellent activity against most strains of Streptococcus pneumoniae, including the vast majority of those with intermediate and high level resistance to penicillin. These agents also have activity against N. gonorrhoeae. Ceftazidime has useful antipseudomonal activity.

The third generation cephalosporins are Cefdinir, Cefixime, Cefpodoxime, Ceftibuten, Ceftriaxone, Cefotaxime.

d. Fourth generation

Fourth generation cephalosporins are extended spectrum agents with similar activity against gram-positive organisms as first generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis.

The fourth generation cephalosporins are Cefepime, Cefluprenam, Cefozopran, Cefpirome, Cefquinome.

1.12. RATIONALE BEHIND THE SELECTION OF CEFADROXIL AS FLOATING MATRIX SUSTAINED RELEASE TABLET

- cefadroxil is acid stable and its half life is 1.5 hrs
- Absorbed completed and rapidly from Gastro intestinal tract.
- Density is less than one.
- cefadroxil have pka. 9.69 which is unionized in acidic medium.
- GRDFs can be used as carrier for drugs with so-called absorption window. Example:
- Antifungal,
- Antiviral,
- Antibiotic agents.

Sulphonamides, quinolones, cephalosporin's, aminoglycosides and tetracycline are taken up only from very specific sites of the GI mucosa

LITERATURE REVIEW

2. LITERATURE REIVEW

Manoj N. Gambhire et al[31] Floating matrix tablets of DTZ were developed to prolong gastric residence time and increase its bioavailability.. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO, Sodium bicarbonate.. A 32 factorial design was applied to systematically optimize the drug release profile.The amounts of Methocel K100M CR (X1) and Compritol 888 ATO (X2) were selected as independent variables. The time required for 50% (t50) and 85% (t85) drug dissolution were selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR (X1) and Compritol 888 ATO (X2) favors the preparation of floating controlled release of DTZ tablets.

AV Mayavanshi* and SS Gajjar[21] Floating drug delivery systems to increase gastric retention of drugs Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The floating or hydrodynamically controlled drug delivery systems are useful in such application. The present review addresses briefly about the floating drug delivery systems.

Ramesh.R.Putheti1 Mahesh.C.Patil[22] Pharmaceutical Formulation and development of Floating and Swellable sustained drug delivery systems: .The purpose of this review on floating and swellable drug delivery systems is tocompile the recent literature with special focus on the principal mechanism offloatation to achieve gastric retention. The review also aims to discuss variousparameters affecting the behavior of floating and swelling multiparticulate in oraldosage form summarizes the in vitro techniques, in vivo studies to evaluate theperformance and application of floating and swellable systems, andapplications ofthese systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. From the formulation andtechnological point of

view, the floating and swellable drug delivery systems areconsiderably easy and logical approach. An attempt has been made in this reviewarticleto introduce the scientists to the current technological developments in floating and swellable drug delivery system.

Samyuktha rani b.1, vedha hari b.n.*1, brahma reddy.a.1, punitha. S.2, Parimala devi1, victor rajamanickam1 The recent developments on gastric floating Drug delivery systems. The purpose of this review on Floating Drug Delivery Systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recentdevelopments of FDDS including the physiological and formulation ariables which affect the gastric retention and approaches to design single-unit and multiple unit floating systems, their classification and formulation aspects are covered in detail. This review also summarizes various sophisticated and modern *in-vitro* techniques to evaluate the performance, advantages and applications of floating systems. These systems are useful to avoid all the problems that are encountered during the development of a pharmaceutical dosage forms. Thus floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

Shailesh T. Prajapati et al.,[23] Studied to develop an optimized gastric floating drug delivery system (GFDDS) containing domperidone. Box-Behnken design was employed in formulating the GFDDS with three polymers: hydroxypropyl methylcellulose K4M (HPMC K4M) (X1), Carbopol 934P (X2) and sodium alginate (X3), as independent variables. Floating lag time (FLT), total floating time (TFT), time required to release 50% of the drug (t50) and diffusion exponent (n) were selected as dependent variables, dissolution data obtained was fitted to the power law and floating profiles were analyzed. HPMC loading was found to be significant for floating propertiesand desired release.

D R Chisholm, R G DeRegis, and D A Behr[24] Therapeutic efficacy of cefadroxil and cephalexin for pneumonia in a rat test model. The therapeutic efficacies of cefadroxil and cephalexin were compared in a Streptococcus pyogenes-induced lung infection in rats. Although MICs, rates of in vitro killing in rat serum, and antibiotic serum levels after oral administration were similar for both drugs, cefadroxil was about eight times more effective than cephalexin in reducing the number of viable streptococci at the site of infection. This excellent in vivo bactericidal activity of cefadroxil in lung tissue and bronchial secretions was reflected in the 50% protective dose (PD50) after single or multiple oral treatments. A single treatment given 24 h after infection resulted in a PD50 of 2.8 mg of cefadroxil per kg, compared with 21 mg of cephalexin per kg. When treatment was administered three times, at 24, 27, and 30 h postinfection, the PD50s of cefadroxil and cephalexin were 0.7 and 8.0 mg/kg, respectively. In infected animals, treated 24 h postinfection, the area under the lung tissue concentration versus time curve for cefadroxil was significantly greater than that of cephalexin. This difference in pharmacokinetic behavior may account, at least in part, for the superior therapeutic results obtained with cefadroxil in this experimental pulmonary infection.

Shawky Tous S. et al.,[25] Developed Nitrofurantoin floating matrix tablets, Hydroxypropyl methylcellulose (HPMC) of different viscosity grades together with a gas generating agent (sodium bicarbonate) and other optional additives were examined to optimize the floating characters of the prepared tablets. The in vitro study of the floating behavior in simulated gastric fluid (pH 1.2, enzyme free) at 37°C showed that tablets eroded upon contact with the release medium. The results also showed that tablet composition had profound effect on the floating behavior and drug release. All formulations showed suitable floating lag time (20 s), with duration of floating more than 8 h. The drug release from those tablets was sustained over 8 h.

Leopoldo Villafuerte-Robles et al.,[26] Developed a controlled release formulation of Captopril, floating tablets, and studied the in vitro sustained release of captoprill varying the proportions of Metolose SH400 and bicarbonate, Floating behavior studying at two different compaction pressures at (155Mpa&165Mpa).

Other studied variables include the kinetics of the hydration volume, the matrices floating time and the matrix density. The results show that matrices compacted at 55 MPa float in the dissolution medium for more than 8 h while those compacted at 165 MPa. The matrix density is lower when compacted at 155 MPa. The drug release constant (k) decreases and the exponent indicative of the release mechanism (n) increases with increasing polymer contents.

Subhabrata Ray et al.,[36] Formulated Metformin hydrochloride floating microspheres. by non-aqueous emulsification solvent evaporation technique using Ethyl cellulose as the rate controlling polymer and Evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of floatation and drug release pattern to match target release profile was investigated in vitro floatation and release studies. floating time (> 8 hr) and the best results were obtained at the ratio of drug: polymer: solvent (250:750:12 and 250:146.45:9 [mg : mg : ml]), when both the batches were mixed in equal proportions.

Javed Ali et al.,[27] Formulated hydro dynamically balanced system for celecoxib as single-unit floating capsules. Various grades of low-density polymers were used. The capsules were prepared by physical blending of celecoxib and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). Capsules prepared with polyethylene oxide 60K and Eudragit RL100 gave the best in vitro percentage release and were used as the optimized formulation. By fitting the data into zero-order, first-order, and Higuchi models, we concluded that the release followed zero-order kinetics.

V.s Belgamwar[28] Floating bioadhesive drug delivery system using effervescent agents 2009 Asian journal of pharmaceutics The results also showed that tablet composition had profound effect on the floating behavior and drug release. All formulations showed suitable floating lag time (20 s), with duration of floating more than 8 h. The drug release from those tablets was sustained over 8 h.

Arvind Kumar Bansal et al., [49]Studied, regional variability in different segments of the gastrointestinal tra vis-a-vis solubility and metabolism were investigated, and the results indicated potential for a gastro retentive (GR) dosage form. Suitability of a GR dosage from for CP and finally in vivo efficacy were investigated. Thereafter, an effervescent floating GR dosage form was developed for CP and evaluated in rats. The GR dosage form improved the oral bioavailability of CP significantly by about 75%, hence providing a proof-of-concept. The T_{max} value increased to 1.43±0.24 h from 0.91 ±0.23 h of pure drug, while C_{max} values of 4735x802 ng ml and 3094 + 567 ng ml were obtained for the GR dosage form and pure drug respectively.

D.M. Patel et al.,[30] Developed carbamazepine Floating tablets using melt granulation technique. Bees wax, Hydroxy propyl Methyl cellulose, sodium bicarbonate and ethyl cellulose were used as matrixing agent, gas-generating agent and floating enhancer, respectively. A simplex lattice design was applied to investigate the formulation variables i.e. amount of hydroxypropyl methylcellulose (X_1), ethyl cellulose (X_2) and sodium bicarbonate (X_3). The floating lag time (F_{lag}), time required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were taken as responses. Results of multiple regression analysis indicated that, low level of X_1, and X_2 and high level of X_3 should be used to manufacture the tablet formulation with desired in-vitro floating time and dissolution.

Mukesh C. Gohel et al.,[31] Gastroretentive tablets of rifampicin (150 mg) were prepared by the wet granulation method using hydroxypropyl methylcellulose, calcium carbonate, and polyethylene glycol 4000. to minimize degradation of rilampicin in acidic medium and to modulate the release of rifampicin in the stomach and isoniazid in the intestine.. The in vitro drug release and in vitro drug degradation studies were performed. Rifampicin was released over 4 hours by zero-order kinetics from the novel dosage form. More than 90% of isoniazid was released in alkaline medium in 30 minutes

Anand Kumar Srivastava et al.,[32] Prepared and Evaluated Cimetidine floating microspheres. were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method . Microsphere float up to 8 h and buoyant up to10 h.

Shashi Kiran Mishra et al.,[33] Formulated gastro retentive controlled release system of loratadine was to increase the residence time in stomach and to modulate the release behaviour of the drug. Oil entrapped floating microbeads prepared by the emulsion gelation method were optimized by 23 factorial design and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (*m*/*V*) of oil (mineral oil or castor oil) and 0.45 mol L–1 calcium chloride solution as the optimized processing conditions for the desired buoyancy and physical stability. *In vitro* drug release in the fed state conditions demonstrated sustained release of loratadine for 8 h, which best fitted the Peppas model with $n < 0.45$. The ethyl cellulose coating on microbeads optimized by22 factorial design resulted in a controlled release formulation of loratadine that provided zero-order release for 8 h.

C. Narendra et al.,[34] Studied A^{23} factorial design was employed in formulating the GFDDS Of Metoprolol succinate with total polymer content-to drug ratio (X1), polymer-to-polymer ratio (X2), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) (X3) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, T50%, diffusion coefficient, and floating time. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that X1 and X2 significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was non significant. Regression analysis and numerical optimization were performed to identify the best formulation.

D. More et al.,[35] Prepared a Gastroretentive drug delivery system (bilayer tablets and capsules) of Rosiglitazone Maleate, because its maximum solubility was

in 0.1 N HCL i.e. (pH 1.2: 11.8035 mg/ml) and in differentbuffer it was (pH 5.8: 3.7025 mg/ml, pH 7.3: 3.5137 mg/ml, pH 10: 3.250 mg/ml). studied the effect of sodium bicarbonate, HPMC K 100 M, microcrystalline cellulose (MCC) and Dicalcium phosphate (DCP) on drug release profile, matrix integrity and floatingproperties of bilayer tablets were investigated.

Y. S. Tanwar et al.,[36] Floating tablets of famotidine were prepared employing two different grades of methocel K100 and methocel K15M by effervescent technique; these grades of methocel were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas generating agent. The floating tablets were evaluated *in vitro* buoyancy and dissolution studies. The effect of citric acid on drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. It was observed that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration.

Brijesh S. Dave,1 Avani F. Amin,1 and Madhabhai M. Patel1 [37] The purpose of this research was to prepare a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gumxanthan gum, and hydroxypropyl methylcellulose were eval-uated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 32 full factorial design was applied to systemically optimize the drug release profile. The amounts of citric acid anhydrous (X1) and stearic acid (X2) were selected as independent vari-ables. The times required for 50% (t50) and 80% drug disso-lution (t80), and the similarity factor f2 were selected as dependent variables. The results of the full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation. A theoret- ical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. These studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dis- solution profile similar to a theoretical dissolution profile.

3. AIM & OBJECTIVE

3.1 AIM

- Cefadroxil is acid stable and it is used in the treatment of bacterial infections, some dose related side effects (nausea, abdominal pain, head ache, diarrhoea, chest pain, depression, burning sensation, mental disorders dizziness) are associated with conventional dosage form.
- Normally conventional dosage form of Cefadroxil need twice or thrice daily which may lead to Non-compliance.
- The aim is to minimize the above side effects and to reduce the frequency of dose. This can be achieved through Gastro retentive drug delivery system.

3.2 OBJECTIVES

- To prepare a Gastro retentive Drug Delivery System for cefadroxil in two different strength (125& 250 mg) by using different concentrations HPMC K100M.
- To Evaluate the Physicochemical parameters, In-vitro drug release for 24 hours, swelling studies, Buoyancy studies (Buoyancy lag time and Floating duration time), Kinetics drug release and to find out the best formulation.

PLAN OF WORK

4. PLAN OF WORK

Preformulation Studies

- Description and solubility of drug.
- Predicting the max and identification of pure drug.
- FTIR studies (compatibility studies)

Preparation of Standard curve

- In Distilled water
- In 0.1 HCL.

Precompression parameters

- Determination of angle of repose.
- Determination of bulk and tapped density
- Carr's index.
- Hauser ratio

Formulation

- To formulate floating tablets in Two different strength (125 & 250 mg) by using different concentrations HPMC k 100M (effervescent method)

Evaluation of floating tablets

- Finding hardness,
- Weight variation
- Friability.
- Thickness.
- Assay (UV spectrophotometric method & HPLC method)
- Dissolution Studies (0.1N HCL)
- Swelling index.
    - Buoyancy studies.
    - Buoyancy lag time
- Floating duration time
- Kinetics Release Of Durg
- Accelerated stability studies

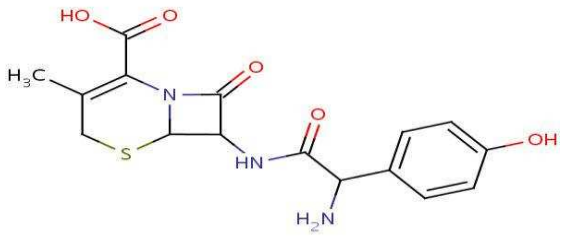
  (Environmental test chamber)

DRUG AND EXCIPIENT PROFILE

5. DRUG PROFILE

➢ Drug Name	:	Cefadroxil.
➢ Generation	:	First generation
➢ Category	:	Antibacterial.
➢ IUPAC Name	:	7 – (D – 2 - amino – 2 – (4 hydroxy pheny1) amino acetyl 13 – Methy 1 – 3 – Cephom – 4 – Carboxylic acid Monohydrate.
➢ Colour	:	White to off white
➢ Molecular formula	:	C16 H17 N3 05 S
➢ Molecular Weight	:	363.389 gl mol
➢ Solubility	:	Slightly soluble in Water and freely soluble in methanol
➢ Bioavailability	:	80%
➢ Protein binding	:	28%
➢ Half life	:	1.5hrs.
➢ dose	:	125 & 250 mg.

STRUCTURE OF CEFADROXIL



A) CHEMISTRY

CEFADROXIL is a first generation oral Cephalosporin. CEFADROXIL is water soluble and acid stable.

Ambroxol is a mucolytic agent which has an action on reducing the viscosity of the mucous in the respiratory tract. Chemically CEFADROXIL is 7-(D-2-amino-2-(4-hydroxy phenyl) amino acetyl 3-methyl-3-cepham-4-carboxylic acid monohydrate.

B) STRUCTURE ACTIVITY RELATIONSHIP

For Oral Cephalosporin

For oral cephalosporins a short C3 side chain and phenyl acetylamino side chain at C7 appear to be relevant.

In the CEFADROXIL structure apart from C3 and C7 substituents another attachment in the CEFADROXIL molecule plays an important role.

Structure Activity

Beta-lactam ring fused with Cepham ring Essential for antibacterial activity Beta - lactamase stability

C3 methyl group

Terminal hydroxy group Unique in CEFADROXIL and confers the longer plasma and tissue half-life

C) SPECTRUM

CEFADROXIL, like the other first generation Cephalosporins is active against a wide variety of gram +ve and gram -ve organisms.

Among the gram +ve organisms, CEFADROXIL is effective against most gram +ve pathogens including most penicillinase-producing staphylococci.

Among the gram -ve organisms, only E.coli, Klebsiella pneumoniae and Proteus mirabills are commonly susceptible.

Against H. influenzae, CEFADROXIL is immediately active.

CEFADROXIL is not active against most isolates of Proteus vulgaris, Proteus rettgeri, Enterobacter species, Pseudomonas aeruginosa, Citrobacter species, Acinetobacter species and Serratia marcescens.

D) MIC OF CEFADROXIL AGAINST VARIOUS ORGANISMS

Organisms MIC (mcg/ml)

Gram-Positive Bacteria

Staph. pyogenes (non-penicillinase producer) 2.0

Staph. pyogenes (penicillinase producer) 8.0

Strep. pyogenes (Group A) 0.63

Strep. faecalis (Enterococcus group) 57.0

Gram-Negative Bacteria

Escherichia coli 16.0 > 125.0

Klebsiella 4.0 - 125.0

Enterobacter spp. > 125.0

Proteus mirabilis 4.0 - 63.0

Proteus (other than mirabilis) > 125.0

Providencia spp. > 125.0

Serratia spp. > 125.0

Haemophilus influenzae 8.0 - 63.0

Pseudomonas aeruginosa > 125.0

E) MODE OF ACTION

CEFADROXIL acts by inhibiting the synthesis of PEPTIDOGLYCAN, a major component of the cell wall in multiplying bacteria.

F) STRUCTURE OF BACTERIAL CELL

The cell wall in bacteria is complex and relatively inelastic. Its main function is to confer shape to the organism and protect it from the external environment. The cell wall of the gram-positive bacteria differs from and is simpler than that of gram-negative bacteria. Peptidoglycan in both Gram-positive and Gram-negative bacterial cell wall maintains rigidity of the cell and is therefore responsible for the essence of the cell.

The beta-lactams act by inhibiting peptidoglycan synthesis but only in multiplying cells. They do not affect the pre-formed peptidoglycan.

Cell multiplication involves:

1. Breaking of peptidoglycan lattice to allow entry of new cell material (CELL ELONGATION).
2. Formation of a cross wall or septum which splits the parent cell (now elongated) into identical daughter cells.

Both theses processes involve secretion of endogenous lytic enzymes known as AUTOLYSINS. As soon as cell multiplication is complete, the autolysin secretion stops. If for some reason the autolysins go out of gear and cannot be stopped, the cells will undergo self destruction.

Beta-lactam compounds bind to Penicillin Binding Proteins and thereby inactivate endogenous inhibitors of autolysins. Autolysins then go haywire and disrupt the covalent bonds in the bacterial cell wall and cause bacterial lysis.

G) PHARMACOKINETICS

A unique feature of Cefadroxyl

The choice of an oral Cephalosporin depends on pharmacokinetic factors, such as long half-life and duration of action which may influence patient compliance.

The pharmacokinetic profile of CEFADROXIL differs from those of Cephalexin and Cephradine in its more prolonged duration of activity and significantly slower rate of excretion. This provides a broadening of the area under the plasma concentration-time curve (AUC), and results in higher plasma and urine concentrations over an extended period of time. Further the absorption of CEFADROXIL is virtually unaffected by food. These characteristics permit the administration of CEFADROXIL by a once - or twice-daily dosage regimen.

CEFADROXIL is well absorbed from the gastrointestinal tract. Almost 85% of the drug is absorbed. The peak serum concentrations of CEFADROXIL in healthy subjects after 0.5 and 1g doses were 16 and 28 mcg/ml, respectively, 2 hours after administration. Predictably, serum levels obtained after administration of 500mg CEFADROXIL are approximately twice as those obtained with lower dose. Unlike Cephalexin, food doesn't interfere with absorption.

The area under the curve (of CEFADROXIL) was 82.94 + 19.98 mcg/ml. The area under serum concentration versus time curve is larger and bioavailability greater for CEFADROXIL. High peak concentration and a large AUC necessary for effective antibiotic therapy are achieved with cefadroxil. In a five day multiple dose study CEFADROXIL pharmacokinetics were virtually unaltered and no drug accumulation was seen as 95% of the dose administered was excreted within 24 hours.

It has been shown that CEFADROXIL is water soluble and has a fair degree of lipid solubility. Volume of distribution is 20.65 + 3.9 lit/1.73 m2. The

volume of distribution of a drug is an indicator of penetration to tissues. CEFADROXIL is widely distributed to body tissues and fluids under normal and certain pathological conditions. Concentrations of CEFADROXIL are detectable in the tonsils, lungs, liver, gall bladder, bone, muscle, synovial capsule, prostate and gynecological tissues and in most body fluids, bile, sputum, amniotic fluid, breast milk, skin blisters and aqueous humour. CEFADROXIL is 20 percent serum protein bound. As CEFADROXIL is eliminated more slowly, it remains in body tissues for longer, after single doses.

The concentration of CEFADROXIL in the tonsillar tissue of adults undergoing tonsillectomies was approximately three times that of Cephalexin after 1 gm dose. After 4 hours, the concentration of CEFADROXIL in tissue was found to be 10 times the MIC for beta-hemolytic streptococci.

In three subjects without infection, concentrations of CEFADROXIL in saliva 3-4 hours after drug administration were 3.5 - 3.8 mcg/ml with a mean value of 3.6 mcg/ml and represented 40 to 112% of those found in serum.

Concentrations of CEFADROXIL in sputum collected from patients with exacerbations of chronic bronchitis ranged from 0.1 - 3.8 mcg/ml, with a mean value of 1.6 mcg/ml, when measured 2-4 hours after a 1g dose.

In 7 patients given a single dose of CEFADROXIL 500mg, peak concentrations of about 3.5 mcg/ml were attained in pleural fluid 6 to 8 hours later. After a single 500mg dose, CEFADROXIL was detectable in the pleural fluid for more than 12 hours.

Levels of antibiotic in lung tissue, which represented 54-69% of serum values, ranged from 3.8 to 11.5 mcg/ml (mean 8.2 mcg/ml). These levels appeared to decrease proportionately with serum levels. Substantial concentrations of CEFADROXIL are still detectable in lung tissue at 5 hours following administration. Concentrations of CEFADROXIL in the plasma and prostatic tissue measured at intervals from 1-5 hours after drug administration exceeded 10 ug/g.

CEFADROXIL reaches significant concentrations in the hepatobiliary system. The peak concentrations of CEFADROXIL in skin blister fluid was 20mcg/ml after 3 hours and the peak concentration of Cephalexin was 13.7mcg/ml after 2 hours. CEFADROXIL penetrates well into intraocular fluid. CEFADROXIL is not metabolized in the body. It is excreted unchanged in the urine by a double process of glomerular filtration and tubular secretion.

93% of a 0.5g oral dose is excreted in the urine during the first 24 hours, most of this occurs during the first 6 hours. When range of 400 - 2400 mg per ml. This explains its efficacy against gram negative rods like proteins, Klebsiella & E.coli causing urinary tract infection.

H) SUMMARY

Cefadroxil is almost completely absorbed (85%) after oral administration. No drug accumulation is seen on multiple dosing of Cefadroxil.

Food does not interfere with absorption of Cefadroxil.

High peak serum concentrations are obtained 1½ - 2 hours after oral administration. The Area Under Curve (AUC) is greater indicating greater bioavailability and effective antibiotic therapy.

Slower rate of elimination of CEFADROXIL results in longer duration of action.

In renal and hepatic impairment, CEFADROXIL, accumulates in patients with impaired renal function, but dosage adjustment is not necessary until creatinine clearance falls to less than 25 ml/min. No dose adjustments necessary in patient with hepatic impairment.

I) ADVERSE REACTIONS

Side effects were reported in 6.3% of the patients evaluated. The most frequent complaints during CEFADROXIL therapy have been gastrointestinal disturbances such as nausea and/or vomiting and less frequently diarrhoea.

Hypersensitivity reactions in the form of allergy such as rash, urticaria and dermatitis have been encountered less frequently with CEFADROXIL.

J) CONTRAINDICATIONS

CEFADROXIL is contraindicated in patients with known allergy to the Cephalosporin group of antibiotics.

K) PRECAUTIONS

CEFADROXIL should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73 m2).

In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

L) USE IN PREGNANCY

There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

M) DOSAGE AND ADMINISTRATION

CEFADROXIL is acid stable and may be administered orally with or without meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

The property of CEFADROXIL being unaffected by the presence of food offers patient compliance, particularly to paediatric patients since their eating habits are so difficult to regulate.

a) ADULT DOSAGE

Respiratory Tract Infections/ Pharyngitis and Tonsilllitis

For mild infections - Treatment of Group A hemolytic streptococcal pharyngitis and tonsillitis - 1gm per day in divided doses (B.I.D.) for 10 days.

Lower Respiratory

1 gm per day in divided doses

Tract Infections

For moderate to severe infections, the recommended dose is 1-2 gms daily in two divided doses.

Skin and Soft Tissue Infections

1 gm per day in single or divided doses (b.i.d).

b) PAEDIATRIC DOSAGE

The recommended daily dosage for children is 30mg/kg/day in divided doses for every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of CEFADROXIL should be administered for at least 10 days.

c) Dosage In Renal Impairment

In patients with renal impairment, the dosage of CEFADROXIL should be adjusted according to creatinine clearance rates.

In adults the initial dose is 1,000 mg of CEFADROXIL and maintenance dose is 500mg, the frequency depending on creatinine clearance.

Creatinine Clearance Dosage Interval 0-10 ml/min 36 hrs

10-25 ml/min 24 hrs

25-50 ml/min 12 hrs

Patients with creatinine clearance over 50ml/min may be treated as if they were patients having normal renal function.

N) CLINICAL INDICATIONS

Adults

1. Infections of the Upper Respiratory Tract Acute and Chronic Sinusitis/Pharyngitis

2. E.N.T. Infections

Otitis Media

3. Infections of the Lower Respiratory Tract Bacterial Pneumonia

Acute Bronchitis Chronic Bronchitis

Chronic Obstructive Pulmonary Disease (COPD) Bronchiectasis

4. Urinary Tract Infections

5. Skin and Soft Tissue Infections

Impetigo

Folliculitis

Furuncles and Carbuncles

Paronychia

Erysipelas

Ecthyma

Cellulitis

6. Osteomyelitis
7. Ophthalmic infections
8. Gynaecological conditions

Infants and Children

1. Group A Streptococcal Pharyngitis
2. Sinusitis
3. Otitis Media
4. Bronchitis
5. Pneumonia or Bronchopneumonia
6. Urinary Tract Infections
7. Acute Gastroenteritis

EXCIPIENT USED FOR STUDY

SODIUM BICARBONATE

Synonyms: Backing soda, E500, Monosodium carbonate, Sodium acid carbonate, Sodium hydrogen carbonate.

Nonproprietary Name

B.P.: Sodium Bicarbonate.

USP : Sodium Bicarbonate

Chemical name

Carbonic acid monosodium salt.

Molecular weight: 84.01

Structural formula: $NaHCO_3$

Description

Sodium Bicarbonate occurs as odourless, White crystalline powder with saline, slightly alkaline taste. Crystal structure is monolithic prisms. Commercially different particle size from fine powder to free flowing granules available.

Solubility

Practically insoluble in Ethanol (95%) and Ether at 20^0C. In water 1 in 11 at 20 ^{0}C and 1 in 4 at 100 ^{0}C.

Functional Category: Alkalizing agent, Therapeutic agent.

Application: Pharmaceutical application shows in table.

Table No. 8 : Application

Use	Concentration
Buffer in tablets	10-40%
Effervescent tablets	25-50%
Isotonic injection/Infusion	1.39%

Typical Property

- Density: 2.159g/cm^3
- Melting point: 270 ^{0}C
- Acidity/Alkalinity: pH 8.3 for a freshly prepared 0.1M aqueoussolution at 25^0C.

Stability and Storage Conditions: Stable in dry air but slowly decompose in moist air and therefore be stored in well closed container in cool, dry place.

Safety: Generally regarded as non toxic and non irritant.

MAGNESIUM STEARATE:[59]

Synonyms: Metallic stearic, Magnesium salt.

Nonproprietary Name: NF: Magnesium stearate.

BP/EP: Magnesium stearate.

Functional category: Tablet and capsule lubricant.

Chemical names: Octadecanoic acid, Magnesium salt, Magnesium stearate.

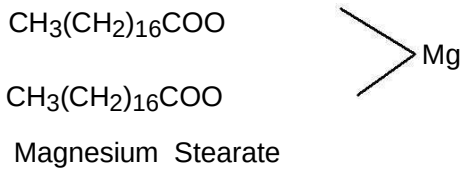
CAS Registry number: 557-04-0

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

Molecular weight: 591.3

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

Structural Formula:



Magnesium Stearate

Description: It is a fine, white, precipitated or milled, impalpable powder of low bulk density.

- Density (He): 1.03-1.08 g/cm^3
- Bulk volume: 3.0-8.4 ml/g
- Tapped volume: 2.5-6.2 ml/g.

Applications: Tablet and capsule lubricant, glidant and antiadherent in the concentration range of 0.25 to 2.0%.

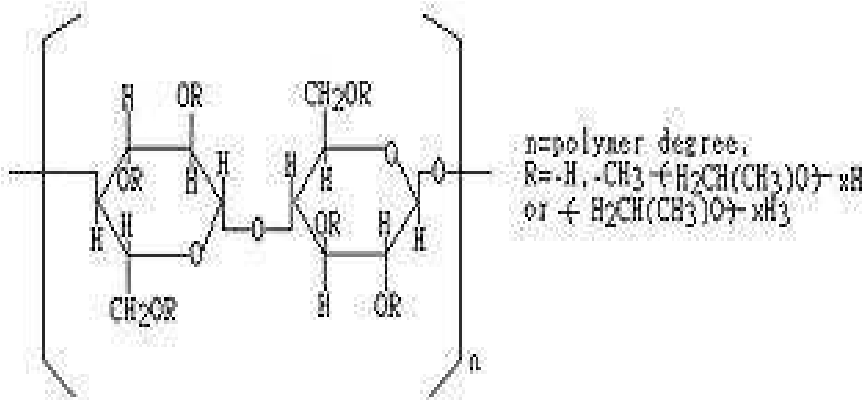
Stability and Storage Conditions: Stable, non-self polymerizable. Store in a cool, dry place in a well closed container.

Incompatibilities: Incompatible with strong acids, alkalies, iron salts and with strong oxidizing materials.

Safety: Described as inert or nuisance dust. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

HYDROXYPROPYL METHYLCELLULOSE (K15M):[59]

Composition and chemical structure:



Synonyms: Cellulose, hydroxypropyl methyl ether, methocel, metolose, pharmacoat, HPMC, methylcellulose propylene glycol ether.

Nonproprietary names: BP: Hypromellose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

Chemical names: Cellulose, 2-Hydroxypropyl methyl ether.

Molecular weight: 10,000 - 15, 00,000.

Category: Coating agent; film former; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Description: It is an odourless and tasteless, white or creamy-white coloured fibrous or granular powder.

Solubility: Soluble in cold water, insoluble in chloroform, ethanol, and ether, but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and dichloromethane.

Viscosity: The viscosity of the polymer ranges from 75-140% of the declared value.

Stability and storage condition: It is stable material although it is hygroscopic after drying. Increase in temperature reduces the viscosity of solutions. It is under goes a reversible solution to get transformation upon heating and cooling respectively. The powder should be stored in a well-closed container in a cool and dry place.

Safety: It is generally regarded as a non-toxic and non-irritant material although excessive consumption may have a laxative effect.

Application:

Chemical ingredient HPMC made by Head Co.,Ltd. are widely used in food, cosmetic and other daily use chemical lines. Typical usage as following:

1. Medical durg.

The product is a medical accessory material of may uses. It can be used for densifiers, dispersing agent, emulsifying agent, lubricator and former etc. It's used as an adhesive and coating film in tablets, increasing markedly rate of dissolution and release, and strengthen water proof for tablets and also be used as mixed dispersing agent, eye drop agent, controlled released matrix tablets. It is combined with other synthetic polymers and gel-type drug products to prevent ethanol separated from transparent gel drug while improve water keep ability.

2. Foodstuff

HPMC can be directly used to food as effective emulsification agent, adhesive, thickening agent as well as can be used as packing materials.

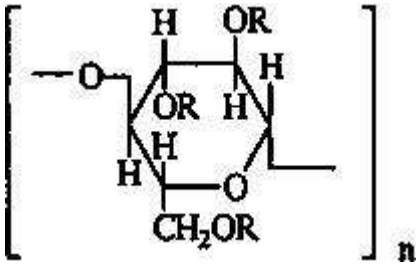
3. Cosmetic.

According to properties of HPMC, it can be used as thickening agent, emulsification agent, suspending agent, stabilizing agent, water retention agent, rheological behavior agent. Thus be used in all kinds of cosmetic products.

Packing, transport and storage

20kg or 25 kg package in polyethylene bag or barrel with inner liners. Keep dry where good ventilated. Do not wet, and keep from sunshine when transport.

SODIUM CARBOXYMETHYLCELLULOSE:[59]



Where R = H, CH_2COONa or CH_2COOH

Synonyms: Akucell, blanose, cekol, cellulose gum, CMC sodium, courlose, E466, nymcel, SCMC, sodium cellulose glycolate, sodium CMC, tylose CB.

Nonproprietary names: USP : Carboxymethylcellulose sodium
PhEur : Carboxymethylcellulosum natricum
BP : Carmellose sodium

Chemical names: Cellulose, carboxymethyl ether, sodium salt.

Molecular weight: 90,000 – 7, 00,000

Category: Coating agent, tablet and capsule disintegrant, tablet binder, stabilizing agent, suspending agent, viscosity-increasing agent.

Description: Carboxymethylcellulose sodium occurs as a white to almost white coloured, odourless, granular powder.

Solubility: Practically insoluble in acetone, ethanol, ether and toluene. Easily dispersed in water at all temperature forming clear colloidal solution.

Viscosity: Various grades of carboxymethylcellulose sodium are commercially available which have differing aqueous viscosities; aqueous 1% w/v solutions with viscosities of 5 – 4000 mPa s may be obtained. An increase in concentration results in an increased in aqueous viscosity.

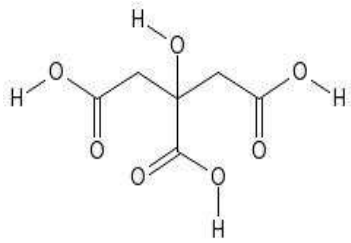
Stability and storage condition: It is a stable, though hygroscopic material. Under high humidity conditions it can absorb a large quantity of water. It may be sterilized in dry state by maintaining it at a temperature of 160^0 C for 1 hr. However, this process results in a significant decrease in viscosity. The bulk material should be stored in a well-closed container in a cool and dry place.

Safety: It is regarded as a non-toxic and non-irritant material.

CITRIC ACID

Citric acid is a weak organic acid found in citrus fruits. It is a good, natural preservative and is also used to add an acidic (sour) taste to foods and soft drinks. In biochemistry, it is important as an intermediate in the citric acid cycle and therefore occurs in the metabolism of almost all living things. It also serves as an environmentally benign cleaning agent and acts as an antioxidant.

Citric acid exists in a variety of fruits and vegetables, but it is most concentrated in lemons and limes, where it can comprise as much as 8% of the dry weight of the fruit.



Citric acid's chemical formula is $C_6H_8O_7$ (structure shown at right). Its structure is reflected in its IUPAC name **2-hydroxypropane-1,2,3-tricarboxylic acid**.

Description: white or colourless, odourless, crystalline solid

Solubility: Very soluble in water, freely soluble in ehanol and slightly soluble in ether

Properties: The physical properties of citric acid are summarized in the table at right. The acidity of citric acid results from the three carboxyl groups COOH which can lose a proton in solution. If this happens, the resulting ion is the citrate ion. Citrates make excellent buffers for controlling the pH of acidic solutions.

Citrate ions form salts called citrates with many metal ions. An important one is calcium citrate or "sour salt", which is commonly used in the preservation and flavoring of food. Additionally, citrates can chelate metal ions, which gives them use as preservatives and water softeners.

At room temperature, citric acid is a white crystalline powder. It can exist either in an *anhydrous* (water-free) form, or as a monohydrate that contains one water molecule for every molecule of citric acid. The anhydrous form crystallizes from hot water, while the monohydrate forms when citric acid is crystallized from cold water. The monohydrate can be converted to the anhydrous form by heating it above 74 °C.

Chemically, citric acid shares the properties of other carboxylic acids. When heated above 175°C, it decomposes through the loss of carbon dioxide and water.

Uses

Most citric acid is used as a flavouring and preservative in food and beverages, especially soft drinks; it is denoted by E number E330. Citrate salts of various metals are used to deliver those minerals in a biologically available form in many dietary supplements. The buffering properties of citrates are used to control pH in household cleaners and pharmaceuticals.

Citric acid's ability to chelate metals makes it useful in soaps and laundry detergents. By chelating the metals in hard water, it lets these cleaners produce foam and work better without need for water softening. Similarly, citric acid is used to regenerate the ion exchange materials used in water softeners by stripping off the accumulated metal ions as citrate complexes.

It is used in the biotechnology and pharmaceutical industry to passivate high purity process piping in lieu of using nitric acid, since nitric acid is a hazardous disposal issue once it is used for this purpose, while citric acid is not.

Citric acid is one of the chemicals required for the synthesis of HMTD; a highly heat, friction, and shock sensitive explosive similar to Acetone peroxide (also know as "Mother of Satan"). Due to this the purchase of large quantities citric acid may be seen by some governments as a indicator of potential terrorist activity.

Citric acid can also be added to ice cream to keep fat globules separate.

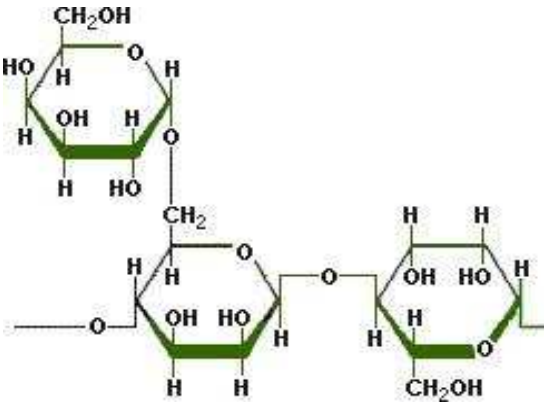
Citric acid can be added to recipes in place of fresh lemon juice.

Safety

Citric acid is recognized as safe for use in food by all major national and international food regulatory agencies. It is naturally present in almost all forms of life, and excess citric acid is readily metabolized and eliminated from the body.

Contact with dry citric acid or with concentrated solutions can result in skin and eye irritation, so protective clothing should be worn when handling these materials.

Guar Gum: Structure Diagram



Guar Gum has excellent cold water solubility because of the high galactose: mannose ratio. The special properties of GUAR GUM known in india make it most suitable for various industrial applications.

Guar Gum Chemical Properties

- Guar gum is an economical thickener and stabilizer. It hydrates fairly rapidly in cold water to give highly viscous pseudo plastic solutions of generally greater low-shear viscosity when compared with other hydrocolloids and much greater than that of locust bean gum.
- High concentrations (~ 1%) are very thixotropic but lower concentrations (~ 0.3%) are far less so.
- Guar gum is more soluble than locust bean gum and a better emulsifier as it has more galactose branch points.
- Unlike locust bean gum, it does not form gels but does show good stability to freeze-thaw cycles.
- Guar gum shows high low-shear viscosity but is strongly shear-thinning. Being non-ionic, it is not affected by ionic strength or pH but will degrade at pH extremes at temperature for e.g. pH 3 at 50°C. With case in, it becomes slightly thixotropic forming a biphasic system containing casein micelles.

Guar Gum Properties

The main properties of Guar gum are

- It is soluble in hot & cold water but insoluble in most organic solvents.
- It has strong hydrogen bonding properties.
- It has excellent thickening, Emulsion, Stabilizing and film forming properties.
- At very low concentration, Guar gum has excellent settling (Flocculation) properties and it acts as a filter aid.
- It is non ionic and maintains a constant high viscosity over a broad range of ph.
- It is compatible with a variety of inorganic and organic substances including certain dyes and various constituents of food.
- The viscosity of Guar gum solution increase gradually with increasing concentration of Guar gum in water.
- The viscosity of Guar gum is influenced by temperature, ph, presence of salts and other solids.
- It has excellent ability to control rheology by economic water phase management.
- It forms highly viscous colloidal dispersions when hydrated in cold water. The time required for complete hydration in water and to achieve maximum viscosities depends on various factors i.e. the ph; temperature; grade of powder used; Equipment etc.

Guar Gum Viscosity: The most important characteristic of guar is its ability to be dispersed in water and hydrate or swell rapidly and almost completely in clod water to form viscous colloidal dispersions or sols.

The viscosity attained is dependent on time, temperature, concentration, pH, rate of agitation and practical size of the powdered gum used. The lower the temperature lower the rate at which viscosity increases and the lower the final viscosity.

Above 80º the final viscosity is slightly reduced. The finer guar powders swells more rapidly than coarse powdered gum.

Uses

- Guar Gum is mainly used as a
- Natural thickener
- Emulsifier
- Stabiliser
- Bonding agent
- Hydrocolloid
- Gelling agent
- Soil Stabiliser
- Natural fiber
- Flocculants
- Fracturing agent

Guar Gum for Pharmaceutical Industries:

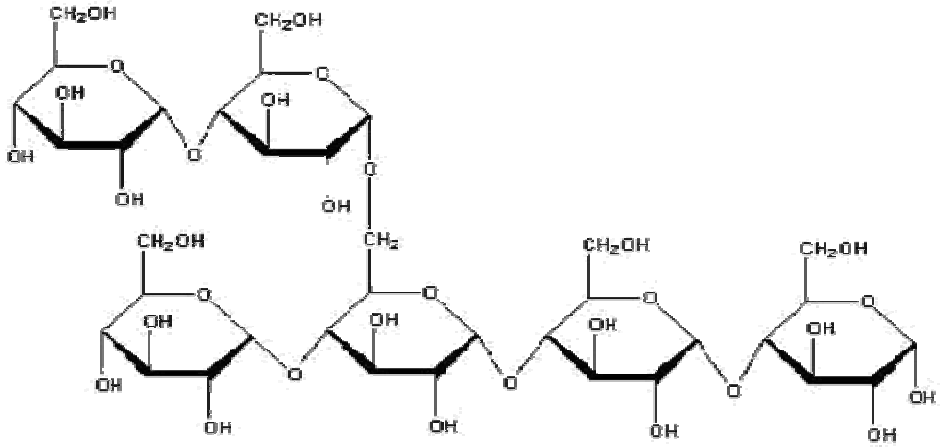
- Guar gum powder is used in pharmaceutical industries as Gelling/ Viscosifying/Thickening, Suspension, Stabilization, Emulsification, Preservation, Water Retention/Water Phase control, Binding, Clouding/Bodying, Process aid, Pour control for following applications.
- In tablet manufacturing it is used as a binder and disintegrating agent and in micro-encapsulation of drugs.
- Suspensions
- Anti-acid formulations
- Tablet binding and disintegration agent
- Controlled drug delivery systems
- Slimming aids
- Nutritional food
- Guar gum has a polymeric structure, containing several hydroxyl groups. The various derivatives or industrial grades of Guar gum are manufactured by reaction of these hydroxyl groups with chemicals that aid in
    - Dispersion
    - Control Viscosity

STARCH

Starch or **amylum** is a polysaccharide carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. Starch is produced by all green plants as an energy store. It is the most important carbohydrate in the human diet and is contained in such staple foods as potatoes, wheat, maize (corn), rice, and cassava.

STRUCTURE OF STARCH

Starch or **amylum** is a polysaccharide carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. Starch is produced by all green plants as an energy store. It is the most important carbohydrate in the human diet and is contained in such staple foods as potatoes, wheat, maize (corn), rice, and cassava.



STRUCTURE

Starch molecules arrange themselves in the plant in semi-crystalline granules. Each plant species has a unique starch granular size: rice starch is relatively small (about 2 **m) while** potato starches **have larger granules (up to 100 m). Although in absolute mass only about** one quarter of the starch granules in plants consist of amylose, there are about 150 times more amylose molecules than amylopectin molecules. Amylose is a much smaller molecule than amylopectin

DESCRIPTION

Pure starch is a white, tasteless and odorless powder that is insoluble in cold water or alcohol. It consists of two types of molecules: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 20 to 25% amylose and 75 to 80% amylopectin.[1] Glycogen, the glucose store of animals, is a more branched version of amylopectin.

Starch can be used as a thickening, stiffening or gluing agent when dissolved in warm water, giving wheatpaste.

SOLUBILITY

Starch becomes soluble in water when heated. The granules swell and burst, the semi-crystalline structure is lost and the smaller amylose molecules start leaching out of the granule, forming a network that holds water and increasing the mixture's viscosity. This process is called starch gelatinization. During cooking the starch becomes a paste and increases further in viscosity. During cooling or prolonged storage of the paste, the semi-crystalline structure partially recovers and the starch paste thickens, expelling water. This is mainly caused by the retrogradation of the amylose. This process is responsible for the hardening of bread or staling, and for the water layer on top of a starch gel (syneresis).

Some cultivated plant varieties have pure amylopectin starch without amylose, known as waxy starches. The most used is waxy maize, others are glutinous rice, waxy potato starch. Waxy starches have less retrogradation, resulting in a more stable paste. High amylose starch, amylomaize, is cultivated for the use of its gel strength.

Glucose is soluble in water, hydrophilic, binds much water and then takes up much space; glucose in the form of starch, on the other hand, is not soluble and can be stored much more compactly.

Since starch is a reserve sugar for the plant, glucose molecules are bound in starch by the easily hydrolyzed alpha bonds. The same type of bond can also be seen in the animal reserve polysaccharide glycogen. This is in contrast to many structural polysaccharides such as chitin, cellulose and peptidoglycan, which are bound by beta-ties and are much more resistant to hydrolysis.

BIOSYNTHESIS

Plants produce starch by first converting glucose 1-phosphate to ADP-glucose using the enzyme glucose-1-phosphate adenylyltransferase. This step requires energy in the form of ATP. The enzyme starch synthase then adds the ADP-glucose via a 1,4-alpha glycosidic bond to a growing chain of glucose residues, liberating ADP and creating amylose. Starch branching enzyme introduces 1,6-alpha glycosidic bonds between these chains, creating the branched amylopectin. The starch debranching enzyme isoamylase removes some of these branches. Several isoforms of these enzymes exist, leading to a highly complex synthesis process.[3] While amylose was traditionally thought to be completely unbranched, it is now known that some of its molecules contain a few branch points.[4]

Glycogen and amylopectin have the same structure, but the former has about one branch point per ten 1,4-alpha bonds, compared to about one branch point per thirty 1,4-alpha bonds in amylopectin.[5] Another difference is that glycogen is synthesised from UDP-glucose while starch is synthesised from ADP-glucose.

HYDROLYSIS

The enzymes that break down or hydrolyze starch into the constituent sugars are known as amylases.

Alpha-amylases are found in plants and in animals. Human saliva is rich in amylase, and the pancreas also secretes the enzyme. Individuals from populations with a high-starch diet tend to have more amylase genes than those with low-starch diets; chimpanzees have very few amylase genes. It is possible that turning to a high-starch diet was a significant event in human evolution.[6]

Beta-amylase cuts starch into maltose units. This process is important in the digestion of starch and is also used in brewing, where the amylase from the skin of the seed grains is responsible for converting starch to maltose (Malting, Mashing).

INDUSTRIAL APPLICATION

- Papermaking
- Corrugated board
- Clothing starch or laundry starch
- Textile chemicals
- Hydrogen production
- Printing industry
- Oil exploration
- Body powder

USES

- As an additive for food processing, food starches are typically used as thickeners and stabilizers in foods such as puddings, custards, soups, sauces, gravies, pie fillings, and salad dressings, and to make noodles and pastas.
- But by far the most common starch based food ingredient are starch sugars (see below) used as sweetener in many drinks and foods.
- Use as a mold. Gummed sweets such as jelly beans and wine gums are not manufactured using a mold in the conventional sense. A tray is filled with native starch and leveled. A positive mold is then pressed into the starch leaving an impression of 1000 or so jelly beans. The mix is then poured into the impressions and then put into a stove to set. This method greatly reduces the number of molds that must be manufactured.
- Starch is used as an excipient, a binder in medications to aid the formation of tablets.
- Resistant starch is starch that escapes digestion in the small intestine of healthy individuals.

MATERIALS AND METHODS

6. MATERIALS AND METHODS

MATERIALS USED

Table No. 9 List of chemicals used with their grade and supplier

SI.No.	Material	Supplier
1.	Cefadroxil	Eleghant Pharmaceutical, Hubli.
2.	Hydroxyl propyl methyl Cellulos K100M	Miltons laboratory, Pondy.
3	Sodium carboxy methyl cellulose	Micro labs, Hosur.
4.	Citric acid	Micro labs, Hosur.
5.	Sodium bicarbonate	Micro labs, Hosur.
6.	Magnesium Stearate	Micro labs, Hosur.
7.	Gum Guar	Micro labs, Hosur.
8.	Starch	Micro labs, Hosur.

Equipments used

Table No.10 Details of Equipments Used

SI. No.	Instrument	Manufacture
1.	Digital balance	Sartorious
2.	Tablet hardness tester	Monsanto
3.	Friability Tester	Roche Friabilitor
4.	Vernier Tester	Mitutoyo
5.	UV spectro photometer (double beam) 1700	Shimadzu
6.	Rotary tablet Punching Machine	Rimek Minipress-1
7.	pH meter	Systronics, Naroda, Ahmedabad
8.	FTIR Spectrophotometer	Shimadzu
9.	Environmental Test Chamber	Heco.
10.	Dissolution Apparatus	Electro lab (Tablet Dissolution Tester USP-24)
11.	Sieve	Jayant Scientific Industry

6.3. LIST OF REAGENT

- Potasium hydrogen phthalate
- Sodium hydroxide
- 0.1N hydrochloric acid

PREFORMULATION STUDIES

Pre formulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bio available dosage forms that can be man produced.

The following preformulation studies are carried out:

- Physical appearance
- Solubility
- Melting point
- Finding the absorption maxima
- Infra red spectroscopy studies (compatibility studies)
- Standard curve of cefadroxil in distilled water
- Standard curve of cefadroxil in 0.1 N HCL

Organoleptic properties

Color

A small quantity of cefadroxil powder was taken in butter paper and viewed in well illuminated place.

Taste and Odour

Very less quantity of cefadroxil was used to get taste with the help of tongue as well as smelled to get the odour.

Melting point:[32,33]

It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals, melting points are very sharp and constant. Since the crude drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure

A small quantity of powder was placed into a fussion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder get melted.

Solubility

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undissolved solute particles. The solubility was expressed in turms of ratio of solute and solvent.

Finding the absorption maxima (λ max)

The absorption maxima was found for drug identification.

Ultraviolet Visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/Ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption.

The drug solutions (5, 10, 15, 20, 25µg/ml) in distilled water was taken in

a standard cuvette and scanned in the range of 200-400 nm in UV spectrophotometer. It exhibits maxima at 263 nm. Therefore further all measurements were taken at 263nm Results given in Fig 23, 24.

Identification By IR [52, 66]

The IR spectrums of the sample of the metoprolol succinate working reference standard in the range of 2000 cm^{-1} to 500 cm^{-1} were taken by preparing dispersion in dry potassium bromide under the same operational conditions. Superimposed these spectra. The transmission minima {absorption maxima) in the spectrum obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the Domperidone working/reference standard. Results given in Table No. 16-20.

Preparation of Standard Curve of Cefadroxil with Distilled Water

Preparation of stock solutions

Weighed accurately 100 mg of cefadroxil and dissolved in a few ml of distilled water in a 100ml volumetric flask. Then the volume was made upto 100ml with the distilled water, which gives 1000 g/ml concentration.

Preparation of Various concentrations:

I) 5 g/ml solution:

0.5ml of stock solution added in 100 ml volumetric flask and made up with distilled water.

II) 10 g/ml solution:

1 ml of stock solution added in 100 ml volumetric flask and made up with distilled water.

III) 15 g/ml solution

1.5 ml of stock solution added in 100 ml volumetric flask and made up with distilled water.

IV) 20 g/ml solution

2 ml of stock solution added in 100 ml volumetric flask and made "up with distilled water.

V) 25 g/ml solution:

2.5 ml of stock solution added in 100 ml volumetric flask and made up with distilled water.

The above concentration solution were checked absorbance at 263 nm by using UV spectrophotometer and distilled water was used as blank solution. The result given in Table No.21

Preparation of Standard Curve of Cefadroxil with 0.1 n HCl

Preparation of stock solutions

Weighed accurately 100 mg of cefadroxil and dissolved in a few ml of 0.1 N HCl in a 100ml volumetric flask. Then the volume was made upto 100ml with the 0.1 N HCl, which gives 1000 g/ml concentration.

Preparation of Various concentrations

I) 5 g/ml solution

0.5 ml of stock solution added in 100 ml volumetric flask and made up with 0.1 N HCl.

II) 10 g/ml solution

1 ml of stock solution added in 100 ml volumetric flask and made up with

0.1 N HCl.

III) 15 g/ml solution

1.5 ml of stock solution added in 100 ml volumetric flask and made up with 0.1 N HCl.

IV) 20 g/ml solution

2 ml of stock solution added in 100 ml volumetric flask and made "up with 0.1 N HCl.

V) 25 g/ml solution

2.5 ml of stock solution added in 100 ml volumetric flask and made up with 0.1 N HCl.

The above concentration solution were checked absorbance at 263 nm by using UV spectrophotometer and distilled water was used as blank solution. The result given in Table No 22

FORMULATON OF FLOATING TABLETS

Method of Preparation of Floating Tablets

Matrix type floating tablets were prepared by wet granulation method. The floating tablets were prepared by using various polymer like HPMC K100M (different concentrations) & SCMC by effervescent method. The two different strength(125& 250) was prepared for comparision.

PROCEDURE

Sifting

Cefadroxil was sifted from mesh No. 60# then Hydroxy Propyl Methyl Cellulose – K 15 M (cps), sodium carboxy methyl cellulose, sodium bicarbonate , citric aid and guar gum Sifted through mesh No. 30#. Sodium bicarbonate

Mixing

All sifted ingredient is dry mixed thoroughly for not less than 5 min, until to get uniform mixed powder.

Preparation of Granulating Fluid

Starch paste-10%

Granulation

Granulating fluid was added on mixed material to get dough mass.

Milling and Drying

Dough mass was milled through sieve No.10 and dried by hot air oven at 60^{o} C for 30 min to get dry granules. These dried granules were against passed through sieve No. 22# The portion retained on sieve was collected.

Lubrication / Blending

Lubricating material magnesium stearate previously were passed through sieve No.30 # and mixed thoroughly with granules for not less than 5 min. to get uniform granules.

Compression

The lubricated granules were compressed into tablet using minipress 10 station tablet punching machine.

Table-10 Formulation Table

CEFADROXIL STRENGTH 125 MG

SI. No	Ingredients	F1	F2	F3	F4	F5
1.	Cefadroxil	125	125	125	125	125
2.	HPMC K100M	0	50	100	150	200
3.	SCMC	50	50	50	50	50
4.	Sod bicarbonate	140	140	140	140	140
5.	Citric acid	70	70	70	70	70
6.	Gum Guar	10	10	10	10	10
7.	Starch	Q.S	Q.S	Q.S	Q.S	Q.S
8.	Magnesium Sterate	5	5	5	5	5
	TOTAL	400	450	500	550	600

Table -11 Formulation Table

CEFADROXIL STRENGTH 250 MG

SI. No	Ingredients	F6	F7	F8	F9	F10
1.	Cefadroxil	250	250	250	250	250
2.	HPMC K100M	0	50	100	150	200
3.	SCMC	50	50	50	50	50
4.	Sod bicarbonate	200	200	200	200	200
5.	Citric acid	85	85	85	85	85
6.	Gum Guar	10	10	10	10	10
7.	Starch	Q.S	Q.S	Q.S	Q.S	Q.S
8.	Magnesium Sterate	5	5	5	5	5
	TOTAL	600	650	700	750	800

OPTIMIZATION

Evaluation of granules

Flow properties

The flow properties of powders are critical for an efficient tabletting operation. A good flow of powder or granulation to be compressed is necessary to assure efficient missing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the pre formulation stage to be "poorly flowable", the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be pre-compressed or granulated to improve their flow properties. During pre formulation evaluation of drug substance, therefore, its flowability characteristic should be studied, especially when the anticipated dose of the drug is large.

Angle of repose

It is defined as the maximum angle formed beween the pile of powder heap and the radius of powder. The results are discussed in table :23,24

Procedure

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose are calculated by using the following formula.

$\tan \theta = h/r$

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

Where, h; height of the heap

r: radius of the heap

Table -11 Angle of Repose

S.NO	ANGLE OF REPOSE	FLOW PROPERTY
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Bulk density

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease.

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (method 1) or through a volumetric measuring apparatus into a cup (method 11).

Procedure:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, Refer table 23,24

$$Bulk\ density = \frac{m}{v_o}$$

Tapped density

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are take until little further volume changes is observed. The mechanical tapping is achieved by rising the cylinder and allowing it to drop under its own weight a specific distance (by either two method). Device that rotate the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Cylinder dropping distance: 14± 2 mm at a normal rate of 300 drops / minute.

Unless otherwise specified, tab the cylinder 500 times initially and measure the tapped volume, Va, to the nearest graduated unit. Repeat the tapping an additional 750 times and measured the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volume is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

$$Tapped\ density = \frac{m}{Vf}$$

Generally replicate determinations are desirable for the determination of this property.

Note; method II: Same as method 1 except that a suitable mechanical tapped density tester that provides a fixed drop of 3 mm (±10 %) at a nominal rate of 250 drops per minute was used. Results given in Table No. 23, 24

Measurement of Powder Compressibility

The compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing power, such

interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner Ratio Calculated by the formula. Result given in Table No. 23,24

$$Compressibility\ Index = 100\ \frac{(V_0 - Vf)}{V_o}$$

Table No.12 Compressibity index

S.NO	COMPRESSIBILITY INDEX	FLOW PROPERTY
1	5-15	Excellent
2	12-16	Good
3	18-23	Fair to passable
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

8.2.1.5 Hausners ratio

It is the ratio of tapped density to the bulk density.

Hausners ratio= tapped density / bulk density.

Table-13 Hausners ratio

S.NO	HASNER RATIO	FLOW PROPERTY
1	< 1.25	Good
2	1.25-1.5	Moderate
3	> 1.5	Poor

REFER TABLE NO.23, 24

RESULTS AND DISCUSSION

RESULTS

Weight Variation Test

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was -calculated. As per Indian Pharmacopoeial Specification, tablets with an average weight between 80 – 250 mg, the percentage deviation should not more than ± 7. 5 % and tablets with an average weight more than 250 mg should not be more than ±10 %. Results given in Table No. 25,26

Weight variation (TABLE-14)

SI.NO	AVERAGE WEIGHT	% DEVIATION
1	80 mg or less	10
2	More than 80 but less than 250 mg	7.5
3	250 mg or more	5

Friability Test

Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets. Friability was calculated by the following formula.

$$F = 1\left[00\frac{W_0 - W}{W} \right]$$

F = Friability, W = Final weight, Wo = Initial weight

The result are give in table no. Results given in Table No.25,26 .

Hardness Test

The hardness of tablet was carried out by using Monsanto type hardness tester. The hardness of the tablet kg / cm^2 was measured. The result are give in table no. Results given in Table No 25,26..

Assay of the tablets (UV spectrophotometer method)

Ten tablets from the batch were weighed and powdered . power equivalent to the average weight of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of the 0.1 N HCL. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer(double beam 1700 shimadzu, japan) at 263 nm.

Assay (HPLC method)

Determined by liquid chromatography method

Test solution: a freshly prepared 0.1 percent w/v solution of the substance under examination in phosphate buffer pH 5

Reference solution: a freshly prepared 0.1 percent w/v solution of cefadroxil RS in phosphate buffer pH 5

Chromatography system

- A stainless steel column 25 cm × 4mm, packed with octadecylsilyl silica gel (30 to 10 µm)
- Mobile phase: a mixture of 96 volumes of phosphate buffer pH 5 and volume of acetonitrile,
- Flow rate 1.5 ml per minute,
- Spectrophotometer se at 230 nm,

- A 20µl loop injector.

Inject the reference solution. The test is not valid unless th e relative standard deviation for replicate injections is not more 2.0 percent. Refer table-27, 28

Assay preparation

Weigh and finely powder NLT 10 tablets. transfer an accurately weighed portion of the powder, equivalent to about 200 mg of cefadroxil, to a 200 ml volumetric flask, dilute with pH 5 buffer to volume, and stir by mechanical means for 5 minutes. Use this solution on the day prepared. calculate the quantity in mg, of C_{16} H $_{17}$ N_3 0_5 S in the portion of tablets taken by the formula.

0.2 CE $r_{u/}$ r_s

$$\text{Sample to be taken} = \frac{\text{Avg. wt of the tablet} \times \text{amount equivalent to be taken}}{\text{Label claim}}$$

$$\text{Amount of the tablet} = \frac{\text{Average sample area} \times \text{standard weight} \times \text{purity} \times \text{avg.wt of the tablet} \times 1000}{\text{Standard area} \times \text{sample area}}$$

Preparation of Dissolution Medium pH 1.2

Placed 76.5 ml of the of concentrated hydrochloric acid in 823.5 ml of distilled water.

Dissolution Study

Medium : 900 ml of 0.1 N hydrochloric acid. pH 1.2

Apparatus : USP (paddle)

Speed : 50 rpm

Time : 0.5,1,2,3, 4,5,6,7,8……24 hours

Temperature : 37C ± 0.5 C

λ : 263 nm

Perform the test on six tablets place one tablet in each dissolution vessel containing 900 ml of of 0.1 M hydrochloric acid (pH 1.2). Maintained at 370C ± 0.50C. At specified time withdrawn required amount of sample and take absorbance and calculate percentage release. Results were illustrated in tables. Results given in Table No. .29-38

Floating property study

The time taken for dosage form to emerge on surface of medium called buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerge on surface of medium called Total floating time (TFT).

Tablets were placed in a 400 ml flask of pH 1.2, time needed to go upward and float on surface of the liquid and floating duration were determined. Results given in Table No. 39 & 40

Dertermination of Swelling Index

The Swelling Index of the tablets was determined in gastric fluid (0.1 N)at room temperature. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was gastric fluid(0.1 N),900 ml, rotated at 50 rpm. The medium was maintained at 37±0.5 ◦ C throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. The swelling characteristics of the tablets were expressed as, Results given in Table No. 41&.42

$$\text{Swelling Index} = \frac{\text{Weight of the swollen tablet- initial weight of the tablet}}{\text{initial weight of the tablet}}$$

Kinetics of Drug Release

The order of drug release can be assessed by graphical treatment of drug release data.

A plot of % drug remaining versus time would be linear if the drug release follows zero order (ie. Concentration independent release).

A plot of log of % remaining drug versus time would be linear, if the drug release follows first order (ie. concentration dependent release)

The linear equation for zero order drug release plot is:

$C_t = C_0 - Kt$

Where, C_t = concentration remaining at time t,

C_o = original concentration,

t = time,

K = release rate

The linear equation for first order release plot is

$$\log C = \frac{\log C_0 Kt}{2.303}$$

A matrix device as the name implies, consists of drug dispersed homogeneously through out a polymer matrix.

In this model, drug in the out side layer exposed to the bathing solution is dissolved first and than diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior.

Obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles with in the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Deviation of the mathematical model to describe this system involves the following assumptions.

1) A pseudo study state is maintained during drug release.
2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
3) The bathing solution provides sink conditions at all times and
4) The diffusion coefficient of drug in the matrix remains constant (ie. no change occurs in the characteristics of the polymer matrix).

Hydrophilic matrix tablets contain a water swellable polymer. On contact with gastric juices the tablet surface gels, impeding further liquid penetration into the tablet core and providing a rate controlling layer. Dissolution occurs at the gel core interface and drug diffuse out through the gelled layer.

Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion. The extent to which diffusion or erosion controls release depends on the polymer ration.

Mechanism of release from erodable matrix has been described by Hopfenberg. A simple expression describing release from erodable is

$$\left(1-\frac{Mt}{M}\right)^{1/3} = 1 - Kt$$

Where, Mt = mass of drug release at time t,

M = mass release at the infinite time,

K = rate of erosion,

t = time

Thus a plot of $[1 - Mt / M]^{1/3}$ versus the time will be linear. If the release of drug from the matrix is erosion controlled.

In order to ascertain whether the drug release occurs by diffusion or erosion, the drug release data was subjected to following modes of data treatments.

1) Amount of drug release versus square root of time (Higuchi Plot).

2) $[1 - Mt / M]^{1/3}$ versus time.

The results are discussed in table 43-46

Accelerated stability studies

Stability

Stability is officially defined as the time lapse during which the drug product retains the same property and characteristics that it possessed at the time of manufacture. This process begins at early development phases.

Instability in modern formulation is often undetectable only after considerable storage period under normal conditions. To assess the stability of a formulated product it is usual to expose it to high stress conditions to enhance deterioration and therefore the time required for testing is reduced. Common high stresses are temperature and humidity. This will eliminate unsatisfactory formulation.

Strategy of stability testing

- The study of drug decomposition kinetics
- The development of stable dosage form
- Establishment of expiration date for commercially available drug product is some of the needs of stability testing

- Data from which study should be provided on at least 3 primary batches of the drug product
- The batches should be manufactured to a minimum of pilot scale
- Important point of view of the safety of the paient, patient relieves a uniform dose of drug throughout the shelf life of the product.

Table-15 : The Stability Storage Condition

SI.NO	STUDY	STORAGE CONDITION	MINIMUM PERIOD
1	Long-term	25ºC ± 2ºC	12 months
2	Intermediate	30ºC ± 2ºC	6 months
3	Accelerated	40ºC ± 2ºC	6 months
		75% ± 5% RH	

PROCEDURE

Selected batches were placed in a high density polyethylene container, blister pack, strip pack etc. They are kept in stability chamber maintained at 40ºc and 75% RH.The stability studies were carried out for a period of one month. The tablets were tested and checked at regular intervals for changes in physical appearance and percentage of drug content. The results are discussed in Table 47-50.

FT-IR STUDIES

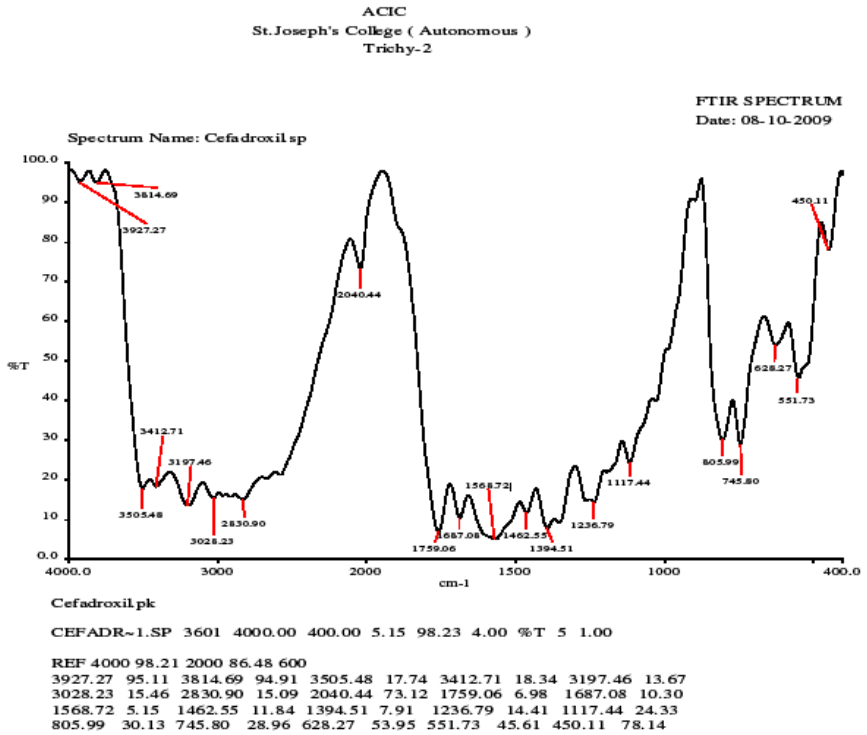


Figure16 Ft-Ir Study For Cefadroxil

Table-16 Interpretation (Cefadroxil)

S.NO	WAVE NUMBER	Interpretation
1 2 3	1117.44 1236.79 1568.72	C-S C-O-C(asymmetric) **S**NH (amide)
4 5 6 7	1759.06 2830.90 3028.33 3197.46, 3412.71	COOH Csp^3H Csp^2H OH Stretch

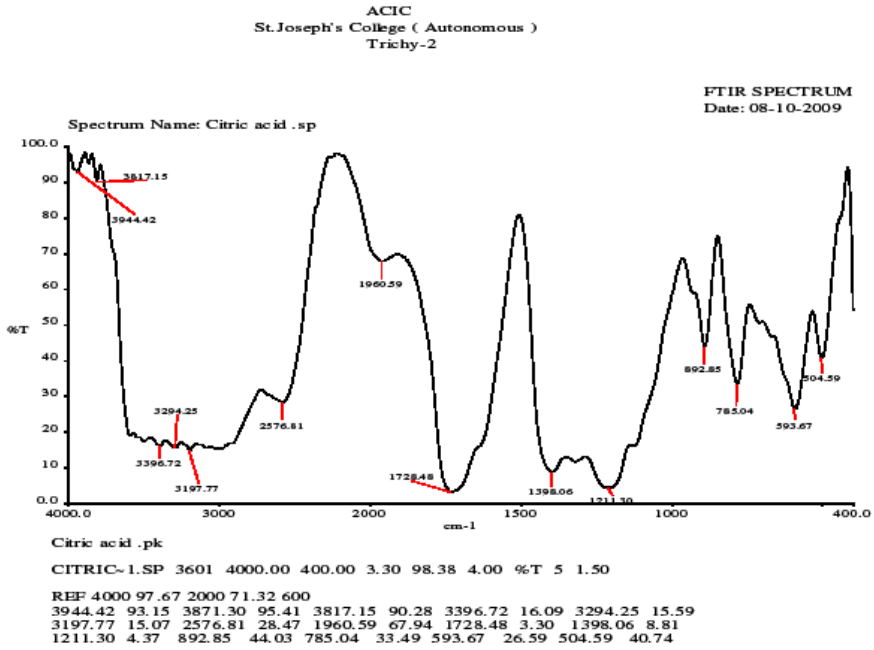


Figure-17 FT-IR Study For Citric Acid

Table-17 Interpretation (Citric Acid)

S.NO	WAVE NUMBER	INTERPRETATION
1	1728.48	COOH
2	3396.72, 3294.25,	OH Stretch
	3197.77	

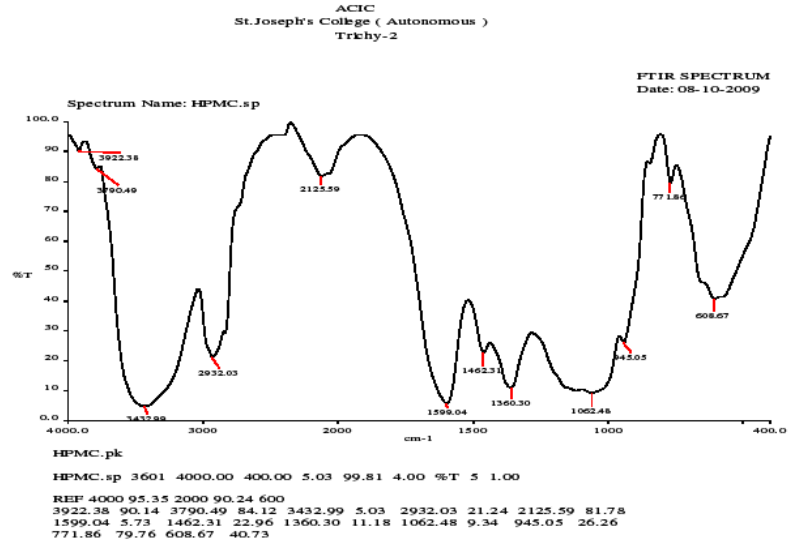


Figure-18 FT-IR Study For HPMC

Table-18 Interpretation (Hpmc)

S. NO	WAVE NUMBER	INTERPRETATION
1	1360.30	C-O-C
2	1599.04	C = O
3	2932.30	CH Stretching
4	3432.99	OH stretching

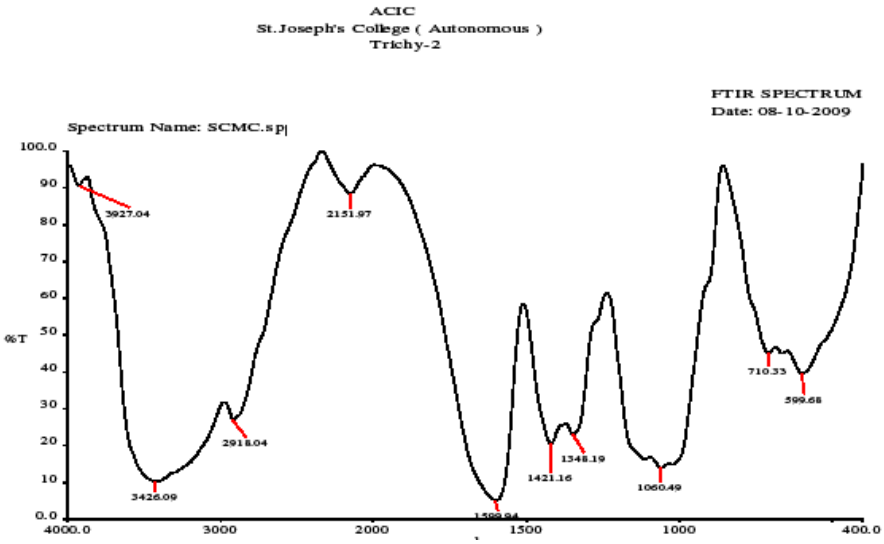


Figure-19 FT-IR Study for SCMC

Table-19 Interpretation (SCMC)

S.NO	WAVE NUMBER	INTERPRETATION
1	1348.19	C=0
2	1599.94	OCH3
3	2918.04	CH Stretch
4	3426.09	OH Stretch

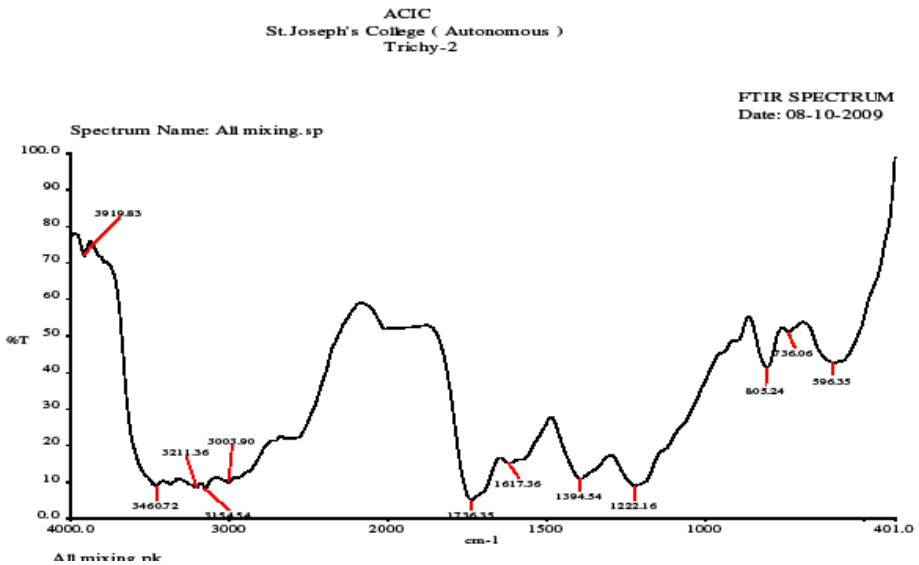


Figure-20 FT-Ir Study For Polymer And Drug

Table-20 Interretation (Drug and Polymer)

S.NO	WAVE NUMBER	ASSIGNMENT
1	1222.16	C-O-C
2	1617.36	SNH amide
3	1736.35	COOH
4	3003.90	Csp^3H
5	3154.54, 3460.72	OH Stretch

Table-21 standard Curve Standard Curve Of Cefadroxil In Distilled Water

SINo.	Concentration (µg/ml)	Absorbance at 263 nm
1.	**5**	**0.0911**
2.	**10**	**0.1926**
3.	**15**	**0.2709**
4.	**20**	**0.3521**
5.	**25**	**0.4479**
6.	**30**	**0.5446**
7.	**35**	**0.6656**
8.	**40**	**0.7306**

a = 0.0370
b = 0.0184
r = 0.9985

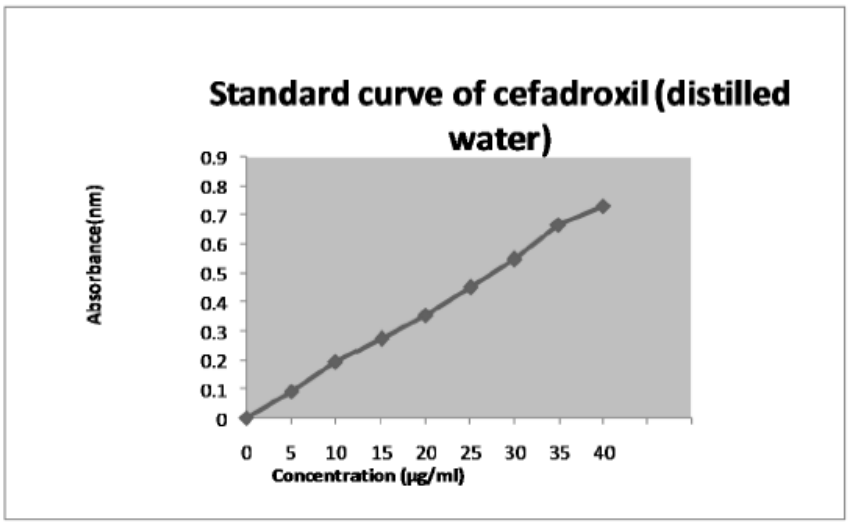


Figure-21 Standard Curve of Cefadroxil (distilled Water)

Table-22 Standard Curve Of Cefadroxil in 0.1 N HCL

SI No.	Concentration (µgl ml)	Absorbance at 263 nm
1.	5	0.0710
2.	10	0.1646
3.	15	0.2662
4.	20	0.3727
5.	25	0.4613
6.	30	0.5486
7.	35	0.6536
8.	40	0.7621

a = - 0.02776
b = 0.01956
r = 0.9996

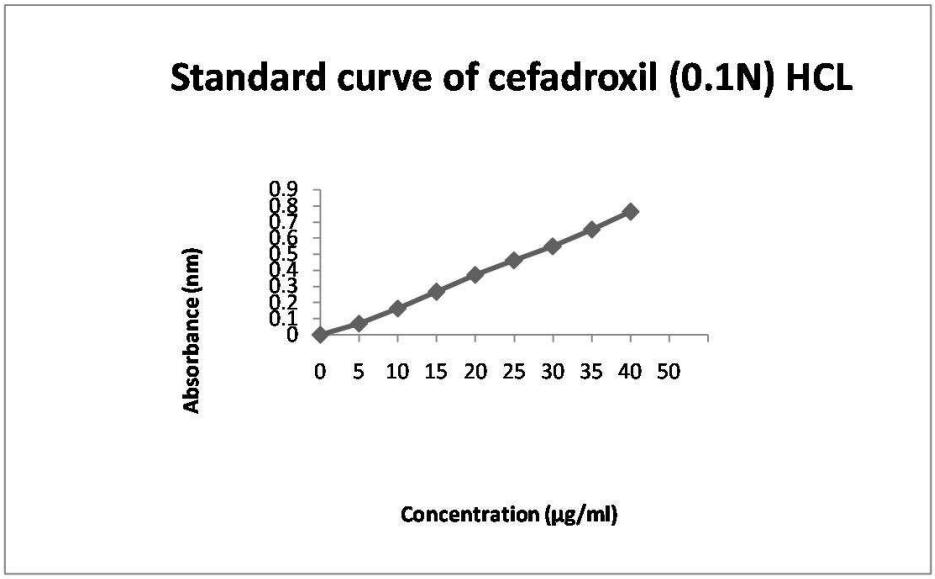


Figure-22 Standard curve of cefadroxil (0.1N) HCL

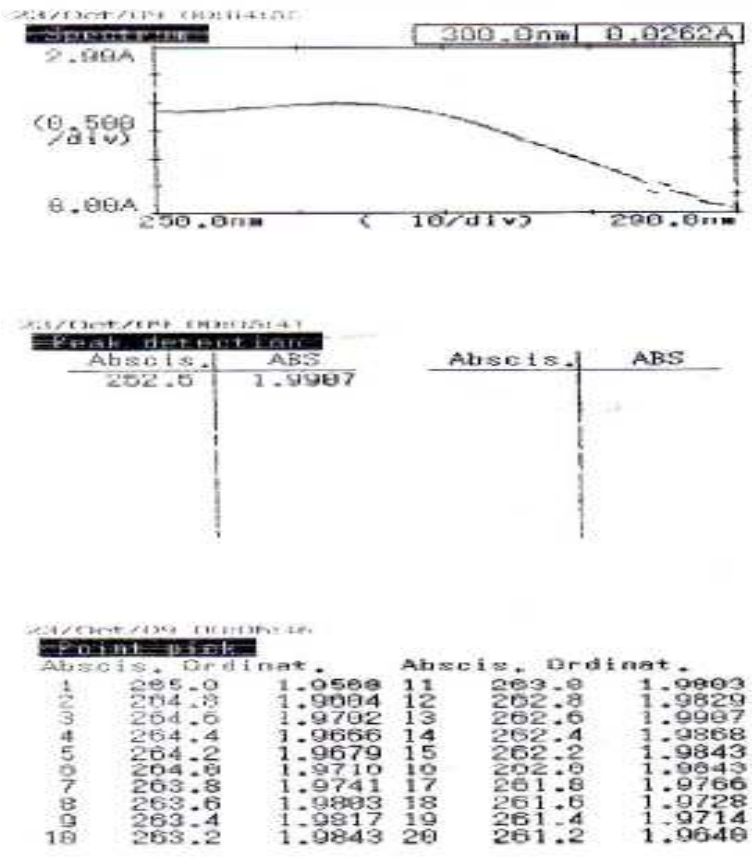
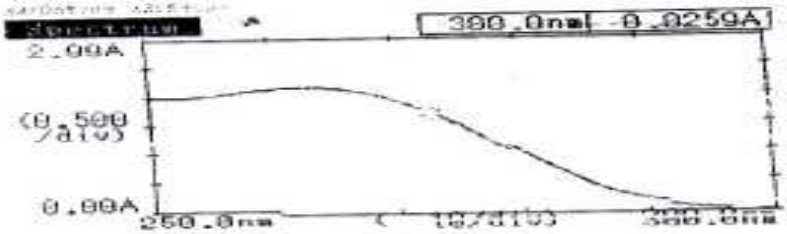
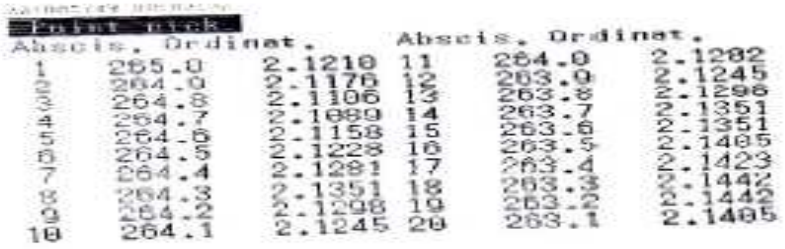


Figure -23 & 24 Predicting the absorption maxima in two solvent(distilled water & 0.1N HCL)





Finding Absorption maxima

The Absorption maxima was found in two solvents.

1) Distilled water - 262.5
2) 0.1 N HCl - 263.3

Evaluation of Powder Blend Ready for Compression

The powder blend ready for compression was evaluated for its physicochemical parameters. The various Physical parameters are shown in table 15 given below.

CEFADROXIL STRENGTH 125 mg

Table-23 Evaluation of powder blend ready for compression

FORMULATION CODE	BULK DENSITY	TAPPED DENSITY	CARR'S INDEX	HAUSNER'S RATIO	ANGLE OF REPOSE
F1	0.35	0.44	12.00	0.88	24.70 º
F2	0.32	0.38	14.47	1.18	20.80 º
F3	0.34	0.38	11.00	1.11	21.80 º
F4	0.33	0.37	12.38	1.14	24.22 º
F5	0.40	0.46	12.24	0.87	25.25 º

CEFADROXIL STRENGTH 250 mg

Table-24 Evaluation of powder blend ready for compression

FORMULATION CODE	BULK DENSITY	TAPPED DENSITY	CARR'S INDEX	HAUSNER'S RATIO	ANGLE OF REPOSE
F6	0.41	0.46	10.57	1.12	22.78º
F7	0.37	0.43	13.48	0.86	23.70º
F8	0.36	0.41	11.54	1.13	27.02º
F9	0.35	0.42	13.07	1.14	24.22º
F10	0.45	0.54	15.96	1.18	26.56º

9.6 PHYSICAL EVALUATION OF TABLET

9.6.1 Physico chemical parameters:

a) Uniformity of weight test:

Weight variation test was performed for 20 tablets from each batch and Results are showed in table 24

b) Hardness

The average hardness of three tablets of from each batch and results are shown in table 24

c) Friability

% Friability was determined for 20 tablets from each batch and was found to lie within limited range of less than 1%. So all the tablets comply with the test for friability. Results are shown in table 24

Table-25 Cefadroxil Strength 125 mg

Formulation code	Average weight of tablet (mg) ± limit	Average Hardness * (Kg/cm^2)	% Friability*
F1	0.4177	5.43	0.72
F2	0.4612	5.76	0.87
F3	0.5099	5.46	0.48
F4	0.5522	5.73	0.53
F5	0.6162	5.33	0.47

Table-26 Cefadroxil Strength 250 mg

Formulation code	Average weight of tablet (mg) ± limit	Average Hardness * (Kg/cm^2)	% Friability*
F6	0.6172	5.64	0.65
F7	0.6629	5.76	0.86
F8	0.7115	5.40	0.98
F9	0.7615	5.36	0.79
F10	0.8125	5.30	0.61

D) Content uniformity (uv spectrophotometeric method)

The percentage drug content of the different formulations is as shown in table 20. The percentage drug content of all formulation batches was found to be in the range of IP limits. Drug content was found to be uniform with all formulations.

Table-27cefadroxil Strength 125 mg

Formulation code	Amount of cefadroxil (mg/tablet)	Percentage drug content
F1	115.10	92.10
F2	123.30	98.64
F3	120.05	96.04
F4	122.08	97.66
F5	123.64	98.02

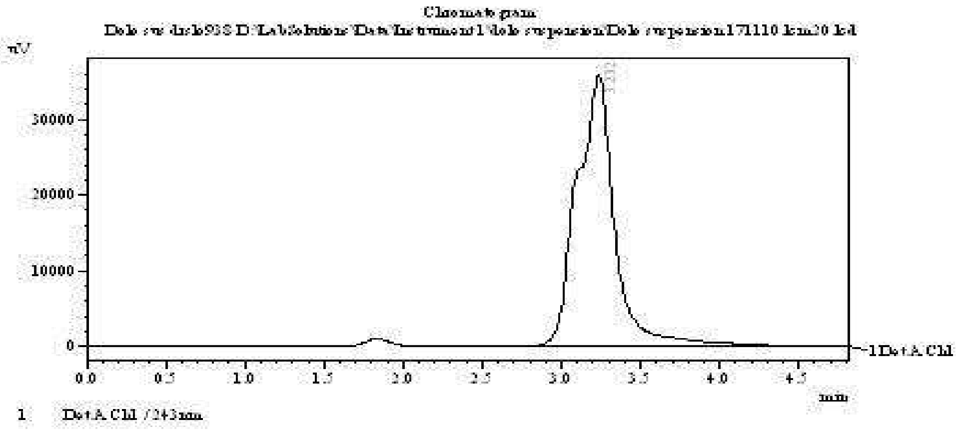
Table-28 Cefadroxil Strength 250mg

Formulation code	Amount of cefadroxil (mg/tablet)	Percentage drug content
F6	226,0	90.78
F7	246.70	98.68
F8	244.01	97.60
F9	247.01	98.80
F10	244.60	97.84

STERLING LAB

Sample Information

Acquired by	: Admin
Sample Name	: Dolo sus disb938std01
Sample ID	: std01
Injection Volume	: 20
Data Filename	: Dolo suspension171110.lcm20.lcd)



PeakTable

Detector A Ch1 243nm

Name	Ret. Time	Area	Height %	Theoretical Plate#	Area %
RT3.232	3.232	593718	100.000	974.981	100.000
		593718	100.000		100.000

Figure- 25,26 & 27 Assay of the Tablet by Hplc Method (F5 & F10)

Standard:

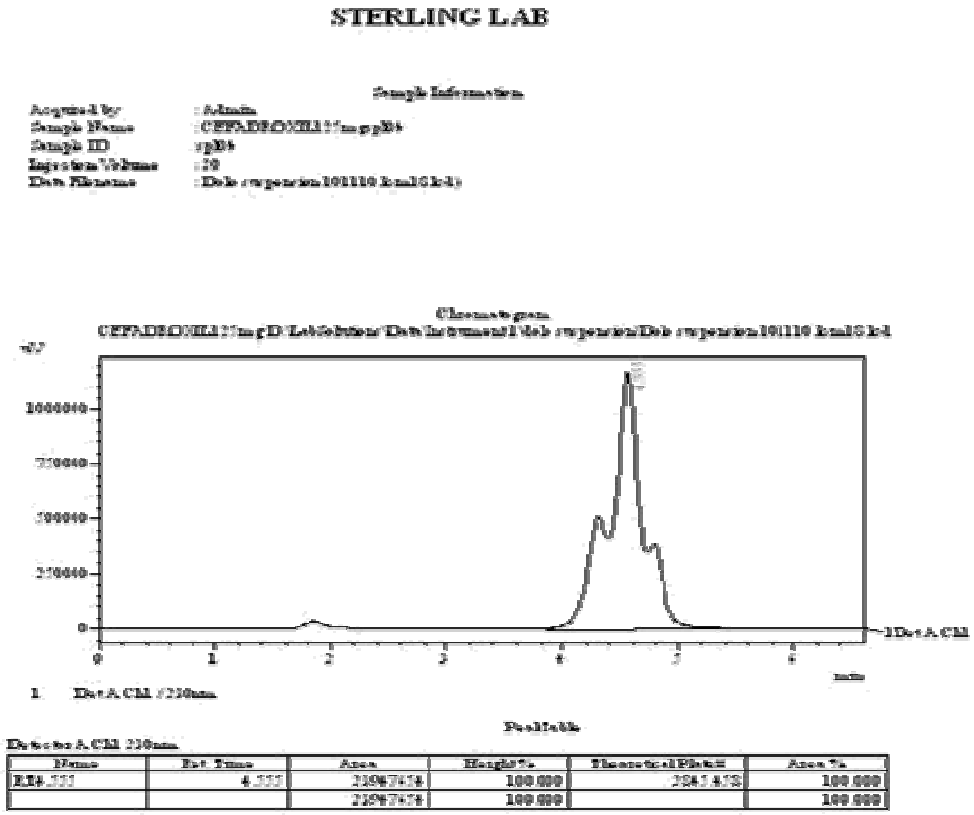
Area –33189989

CEFADROXIL STRENGTH 125 mg (F5)

Area-29968719

CEFADROXIL STRENGTH 250 mg (F10)

Area-27668103



CALCULATION

Avg. Wt of the tablet × equi. amount to be

$$\textbf{Sample to be taken} = \frac{\textbf{taken}}{\textbf{label claim}}$$

$$= (0.6679/0.1250)*0.1$$

$$= 0.539 \text{ gm}$$

$$\textbf{Amount Of The Tablets} = \frac{\textbf{Avg. Sample Area} \times \textbf{Standard Weight} \times \textbf{Purity} \times \textbf{Avg. wt of the tablet} \times 1000}{\textbf{Avg. Standard area} \times \textbf{Sample wt}}$$

$$= \frac{29968719 \times 0.1199 \times 97.25 \times 0.6267 \times 1000}{33189989 \times 0.5399 \times 100}$$

$$= 122.21\text{mg.}(97.76\%)$$

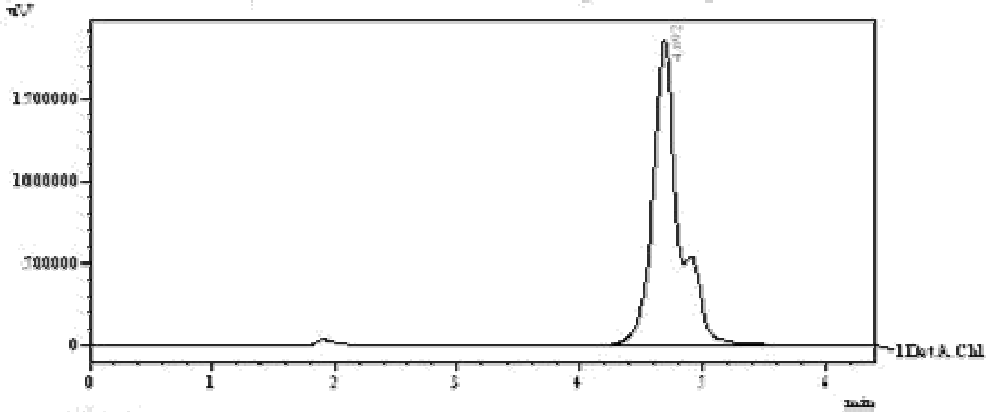
STERLING LAB

Sample Information

Acquired by	: Admin
Sample Name	: CEFADROXIL250mg sp02
Sample ID	: sp02
Injection Volume	: 20
Data Filename	: Dolo suspension101110 kml (kd)

Chromatogram

CEFADROXIL250mg D:\LabSolutions\Data\Instrument1\dolo suspension\Dolo suspension101110 kml (kd)



1 Det.A Ch1 / 230nm

PeakTable

Detector A Ch1 230nm

Name	Ret. Time	Area	Height %	Theoretical Plate #	Area %
RT4.492	4.492	27917143	100.000	3459.827	100.000
		27917143	100.000		100.000

Sample to be taken

$$= \frac{\textbf{Avg. Wt of the tablet} \times \textbf{equi. Amount to be taken}}{\textbf{Label claim}}$$

$= (0.821/0.250) \times 0.1$

$= 0.3275$ gm

$$= \frac{2766103 \times 0.119 \times 97.25 \times 0.821 \times 1000}{33189989 \times 0.3275 \times 100} = 243.67 \text{ gm } (97.46\%)$$

CEFADROXIL STRENGTH 125 mg

Dissolution study

Dissolution study of F1 (TABLE-29) Medium: 0.1 N HCL

Label claim: 115.1 mg

TIME (hrs)	ABSORBANCE * (nm)	CONCENTRATION (g/ml)	AMOUNT RELEASED (mg)	% AMOUNT RELEASED
2	1.8075	93.67	84.30	73.24
4	2.4210	125.19	112.67	97.89
6				
8				
10				
12				
14				
16				
18				
20				
22				
24				

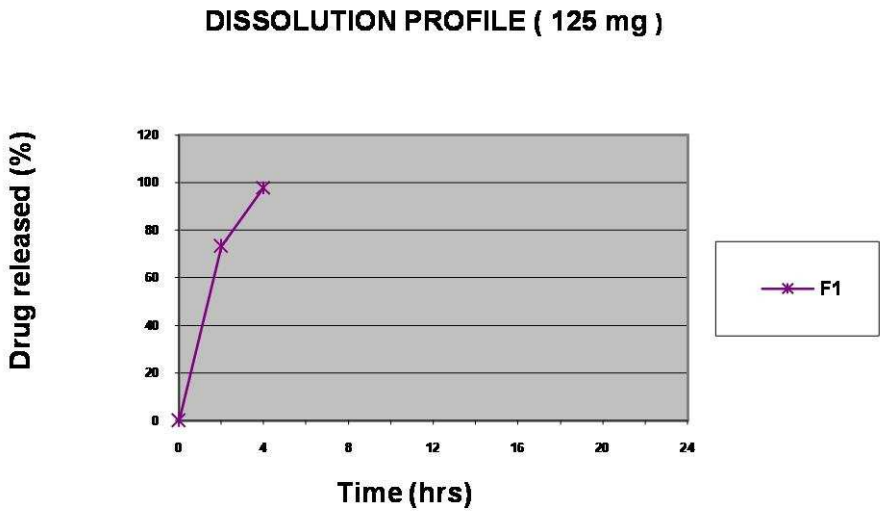


Figure-28 Dissolution Profile (125 mg)

Dissolution study of F2

Medium: 0.1 N HCL

Label claim: 123.3 mg

TABLE-30

TIME (hrs)	ABSORBANCE * (nm)	CONCENTRATION (µg/ml)	AMOUNT RELEASED (mg)	% AMOUNT RELEASED
2	0.9227	48.58	43.73	35.46
4	1.8255	94.74	88.26	69.14
6	2.4996	129.20	116.28	94.30
8	2.6221	135.47	121.92	98.88
10				
12				
14				
16				
18				
20				
22				
24				

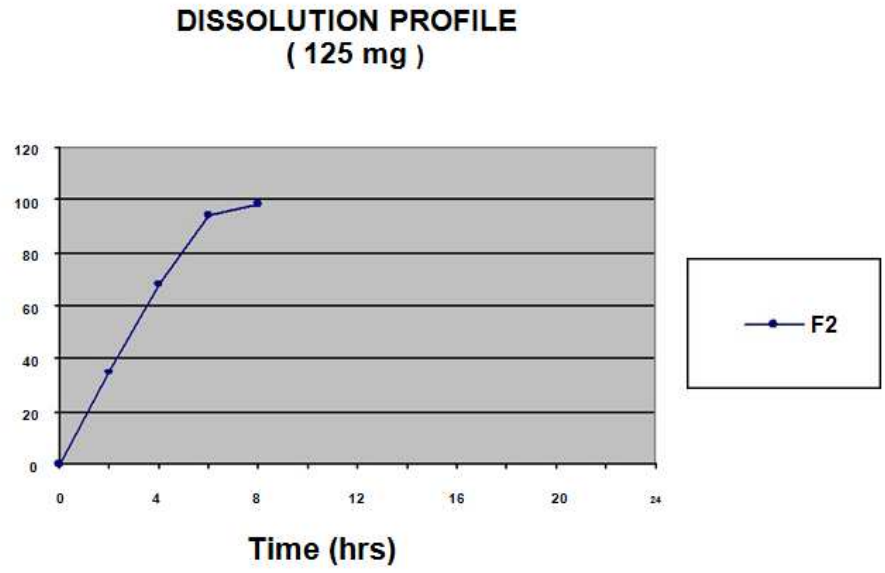
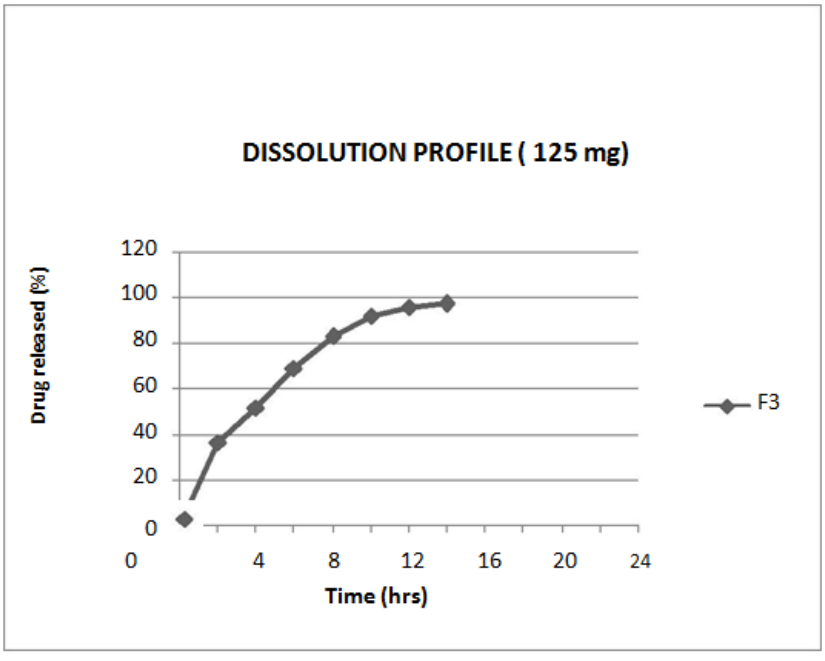


Figure-29

Dissolution study of F3 Medium: 0.1 N HCL Label claim: 120.08 mg

Table-31

TIME (hrs)	ABSORBANCE * (nm)	CONCENTRATION (g/ml)	AMOUNT RELEASED (mg)	% AMOUNT RELEASED
2	0.9224	48.57	43.71	36.42
4	1.3214	68.97	62.07	51.72
6	1.7791	92.37	83.13	69.27
8	2.1431	110.98	99.88	83.23
10	2.3912	23.66	111.30	92.36
12	2.4795	128.18	115.36	96.01
14	2.5095	129.71	116.74	97.22
16				
18				
20				
22				
24				



Dissolution study of F4

Medium: 0.1 N HCL

Label claim: 122.08 mg

Table-32

TIME (hrs)	ABSORBANCE * (nm)	CONCENTRATION (g/ml)	AMOUNT RELEASED (mg)	% AMOUNT RELEASED
2	0.4284	23.31	20.98	17.20
4	0.8499	44.86	40.38	33.09
6	1.2451	65.07	58.56	48.00
8	1.6692	86.75	78.07	63.99
10	2.0014	103.73	93.36	76.41
12	2.2341	115.63	104.07	85.30
14	2.4562	126.98	114.28	93.68
16	2.5402	131.28	118.15	96.84
18	2.5861	133.62	120.26	98.57
20				
22				
24				

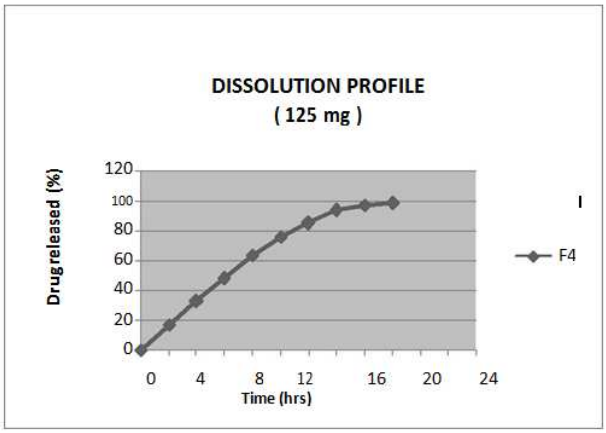


Figure-31

SUMMARY AND CONLCUSION

8. SUMMARY

In present work, attempts have been made to formulate floating matrix extended release tablets of cefadroxil, by using different ratio of hydrophilic polymer HPMC K100M and sodium carboxy methyl cellulose and sodium bicarbonate as a gas generating agent. Cefadroxil is a acid stable broad-spectrum antibiotic of the cephalosporin type, effective in Gram-positive and Gram-negative bacterial infections. It is a bactericidal antibiotic. The floating Matrix tablets were prepared by wet granulation technique. Cefadroxil meets all the ideal characteristics to formulate in the form of extended release drug delivery system.

Under preformulation study, the organoleptic properties were complied with the IP specification. Physical properties such as bulk density and tapped density were more in case of granules ready for compression than that on cefadroxil raw powder. melting point determination were given the information about the purity of the drug powder respectively. the result of angle of repose of drug powder showed the poor flow properties.

Solution properties i.e pH of the solution and solubility were evaluated, results were complied with the pharmacopoeial specification.

All the formulations were evaluated on the basis of pharmacopoeial specifications. Shape of the tablets was round standard concave hardness, weight variation, floating time study, dissolution test were carried out.

Assay of cefadroxil was carried out by both uv spectrophotometric method and hplc method.

Assay (UV METHOD) was carried out for F5 and F10 was found to be 98.02% and 97.84%

Assay (HPLC METHOD) was carried out for F5 mg) and F10 was found to be 97.76% and 97.46%

Infra Red spectrum of cefadoxil matches with the standard spectrum as well in tablet there are no any additional peak formation.

Stability studies of the selected formulated tablets were carried out by keeping the tablets at room temperature and at 40 ^{o}C $\pm$ 2 ^{o}C/ 75 $\pm$ 5 % RH (stability chamber) for 30 days. All the parameters were within the limit after 30 days.

The mechanism of drug release form matrix tablets were combination of swelling diffusion and erosion in all cases.

The release rate of cefadroxil matrix floating tablets followed near mixed order kinetics, which was obtained by plotting, a graph of cumulative percentage drug release Vs time.

CONCLUSION

In the present study attempts were made to formulate two different strength(125mg & 250 mg) of cefadroxil floating matrix extended release tablet, by wet granulation.

The In Vitro study, shows formulation No.5 & 10 were well suited to be extended release formulation due to floating up to 24 hrs.

Formulation F5 & F10 was found 0074o obey nearly zero to zero order drug release governed by diffusion through swollen matrix, showing anlomous diffusion or non fickian transport.

Infrared spectrum of tablet reveals that there is no interaction of the polymer and tablet matrix with cefadroxil

Stability study is passed as per specification.

Further *in-vivo* and continuation of stability study are recommended.

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