# FORMULATION AND EVALUATION OF CINITAPRIDE TABLETS AS FLOATING DRUG DELIVERY SYSTEM

**A Dissertation Submitted to**

**THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSTIY, CHENNAI**

***In partial fulfillment for the award of degree of***

**MASTER OF PHARMACY**

**IN**

**PHARMACEUTICS**


**Submitted by**

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**CERTIFICATE**

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF CINITAPRIDE TABLETS AS FLOATING DRUG DELIVERY SYSTEM** " submitted by **DINESH.S (26107706)** in partial fulfillment of the degree of Master of Pharmacy in Pharmaceutics of The TamilNadu Dr.M.G.R Medical University, Chennai at Annai Veilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by his/her under my guidance and supervision during the academic year 2011-2012. The dissertation or any part of this has not been submitted elsewhere for any other degree.

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R_H Richer Healthcare

## To Whom So Ever It May Concern

This is a bonafide dissertation work entitled **"Formulation And Evaluation Of Cinitapide Tablets As Floating Drug Delivery System "** which has been carried out by **Mr.S.Dinesh** from Annai Veilankanni's College Of Pharmacy, affiliated to the Tamil nadu Dr.M.G.R Medical University-Chennai, in partial fulfillment of the requirement for the award of the degree of Master Of Pharmacy In Pharmaceutics. This thesis work was carried out at "Richer Health Care Pvt Ltd-hyderabad,under my supervision and guidance during the academic year 2011-2012.

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## DECLARATION

**I hereby declare that the dissertation work entitled "FORMULATION AND EVALUATION OF CINITAPRIDE TABLETS AS FLOATING DRUG DELIVERY SYSTEM" is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Saidapet, Chennai and Richer Health Care Pvt Ltd., Hyderabad under the guidance of Dr. M.Senthil Kumar and Mr. Ajay kumar ,for submission to The Tamilnadu Dr.M.G.R University in the partial fulfillment of the requirement for the award of degree Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.**

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## *Acknowledgement*

***At the outset, I thank the God who brought this opportunity, gave me the abundance of requisite determination and strength to pursue and complete this course and dissertation successfully. It is my immense pleasure privileges to acknowledge the untold contributions, thankfully received, the blessed inspiration and the unreserved support I have had from the individual and institutional sources with whom I have been in association during the course of my last two years of pursuit I hereby take this opportunity to acknowledge all those who have helped me in the completion of this dissertation work.***

***I am extremely grateful to Dr. S.Devaraj, Chairmen and Mr.D. Devanand, Secretary Annai Veilankanni's Pharmacy College , saidapet, Chennai – 600015 for providing me the opportunity to do my project at Richer Health Care (P) Ltd., Hyderabad.***

***It's a fact that every mission needs a spirit of hard work and dedication but it needs to be put on the right path to meet its destination and in my case this credit goes to my respected teacher and guide, Dr.M.Senthil Kumar, Principal , Department of Pharmaceutics, Annai Veilankanni's Pharmacy College. I am very much thankful to him for his inspiration, kind co-operation, caring attitude, timely help, valuable guidance and constant encouragement during every phase of this dissertation. His patience way of sharing knowledge, our numerous discursions support always propelled and boosted me to perform better. I would remain grateful to him.***

***My sincere and heartful thanks to my teachers, Mrs.S.Valarmathi for their help and co-operation.***

***I am indebted to industrial guide Mr.Ajay kumar, Richer Health Care India (P) Ltd., Hyderabad for allowing me to accomplish the project work in this industry. He was always there with his enthusiastic suggestions and corrections, despite of his extremely busy schedule rendered me the freedom to explore the facilities in the laboratory and utilize them up to my learning capabilities. His innovative ideas helped***

***me to successfully complete my project and my thesis work with spontaneity and enthusiasm.***

***I profoundly express my sincere thanks to Mr.Ajay, Manager , Richer Health Care India (P) Ltd., Hyderabad for their valuable suggestions and kind encouragement during the dissertation work.***

***I would also like to extend my sincere thanks to the entire staff of the Annai veilankanni's pharmacy college., saidapet, Chennai, formulation department, Richer Health Care India (P) Ltd., Hyderabad.***

***I would like to thank my friends Ashokkumar, Venkanna Babu, Chandra , Jenish, and Marshal for their co-operation and help in carrying out my project work.***

***I thank everyone who helped me directly or indirectly in the successful completion of this dissertation.***

***And at last but not least my heartiest and dearest gratitude to my lovable friends Ashok, Venkanna Babu, Chandra Jenish, Marshal, john and ashok for their love, faith, care and support.***

***I would like to express my deep sense of love and affection to my family members especially to my dad Mr.V.Soundararajan and my mom Mrs.G.Mahalakshmi , my beloved sister Mrs.Thilagavathy and my aunt Mrs.G.Shantha bhai for their strong piety and pantheism enable me to face the world without fear and with pedantic strength.***

## ABBREVIATIONS USED

| | |
|---|---|
| **e.g.** | **Example** |
| **i.e.** | **That is** |
| **%** | **Percentage** |
| **Kg** | **Kilogram** |
| **Gm** | **Gram** |
| **Mg** | **Milligram** |
| **µg** | **Microgram** |
| **Ml** | **Millilitre** |
| **Cm** | **Centimetre** |
| **Mm** | **Millimetre** |
| **Nm** | **Nanometre** |
| **W/w** | **Weight by weight** |
| **V/v** | **Volume by volume** |
| **Avg** | **Average** |
| **Hrs** | **Hours** |
| **pH** | **Hydrogen ion concentration** |
| **°C** | **Degree centigrade** |
| **RH** | **Relative Humidity** |
| **HCL** | **Hydrochloric acid** |
| **RPM** | **Revolution per minute** |
| **Abs** | **Absorbance** |
| **Conc.** | **Concentration** |
| **Fig** | **Figure** |
| **UV- VIS** | **Ultra violet and visible spectroscopy** |
| **FTIR** | **Fourier Transform Infra Red spectroscopy** |
| **C.I** | **Compressibility Index** |
| **CR** | **Cumulative Release** |
| **HPMC** | **Hydroxy propyl methyl cellulose** |
| **GRDDS** | **Gastro Retentive Drug Delivery System** |
| **FT** | **Floating Tablet** |

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# INTRODUCTION

**Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.** [1]

**The de novo design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the (GIT) and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hrs. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2–3 hrs through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the (DDS) leading to diminished efficacy of the administered dose. Thus, control of placement of a (DDS) in a specific region of the (GIT) offers numerous advantages, especially for drugs exhibiting an absorption window in the (GIT) or drugs with a stability problem. These**

**considerations have led to the development of oral controlled-release (CR) dosage forms possessing gastric retention capabilities.** [2]

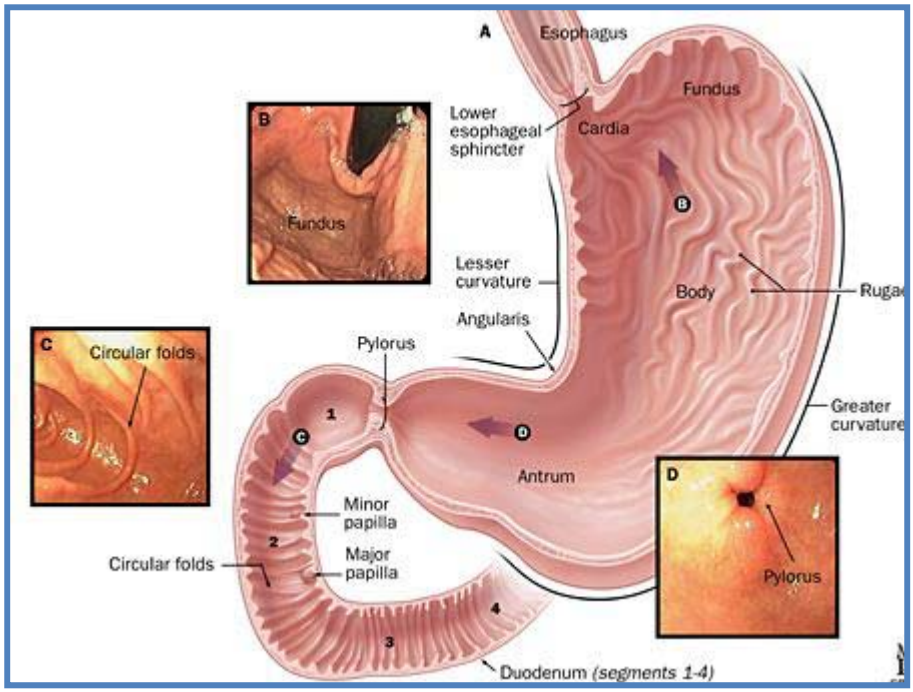
**After oral administration, such a drug delivery system would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the (GIT). Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects.**

## BASIC GASTROINTESTINAL TRACT PHYSIOLOGY: [3]

### Stomach Physiology:

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

**Fig. 1: Physiology of stomach**



**Gastric emptying:**

**Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both 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 following 4 phases as described by Wilson and Washington, (table: 1).** [3]

**Table - 1: Phases of migrating myloelectric cycle (MMC)**

| Phases | Name | Duration | Nature |
|---|---|---|---|
| Phase 1 | Basal phase | 45-60min | Rare contractions. |
| Phase 2 | Pre-burst phase | 30-45 min | Intermittent peristaltic contractions which gradually increase in intensity and frequency. |
| Phase 3 | Burst phase or "house keeper waves" | 5-15 min | Large intense peristaltic contractions. |
| Phase 4 | Brief transitional phase | 0-5 min | Occurs between phase 3 and phase 1 of the 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 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.**

**FACTORS AFFECTING GASTRIC RETENTION: [5]**

**The gastric retention time (GRT) of dosage form is controlled by several factors, which affect their efficacy as a gastroretentive system.**

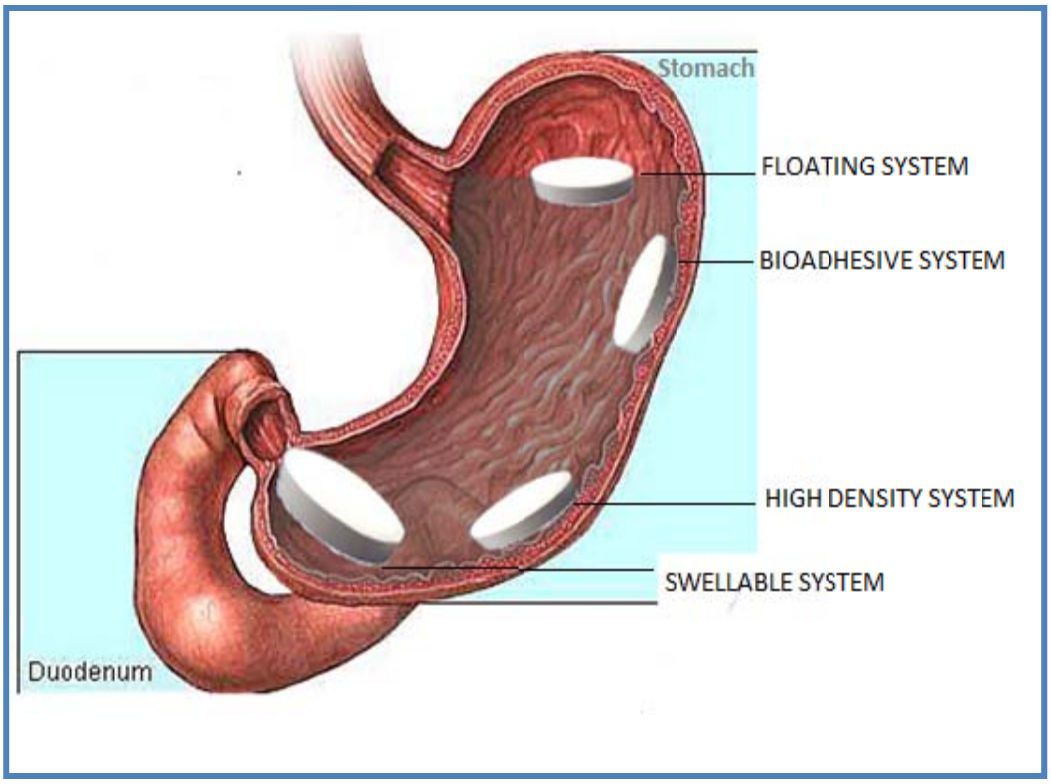
- **Density – GRT is a function of dosage form buoyancy that is dependent on the density.**
- **Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.**
- **Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.**
- **Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric cycle (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.**
- **Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.**
- **Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.**
- **Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.**

- **Gender – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.**
- **Age – Elderly people, especially those over 70, have a significantly longer GRT.**
- **Posture – GRT can vary between supine and upright ambulatory states of the patient.**
- **Concomitant drug administration– Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.**
- **Biological factors – Diabetes and Crohn's disease.**

**TYPES OF GASTRORETENTIVE DOSAGE FORMS:**

1. **Floating drug delivery systems (FDDS)**
    - **Effervescent.**
    - **Non effervescent.**
2. **High density systems.**
3. **Swelling or Expandable systems.**
4. **Bioadhesive or Mucoadhesive systems.**

**Fig.2: Various Gastro retentive Dosage forms**




**FLOATING DRUG DELIVERTY SYSTEMS (FDDS):** [6]

**Floating drug delivery systems also called as hydrodyanamically balanced systems float on the gastric contents to release the drug slowly from the dosage form. The density of the FDDS should be less than the density of gastric fluid.**

**1. Effervescent Systems:**

**The concept of this system involves formation of carbon dioxide gas thereby causing reduction in density which makes the system easy to float in GI fluids. The effervescent systems further classified into two types:**

**a. Gas generating systems.**

**b. Volatile Liquid/Vacuum containing systems.**

**A. Gas generating systems:**

**a) Intra gastric single layer floating tablets: These systems can be prepared by compressing the drug with gas ($CO_2$) generating agents. These systems have low density than the GI fluid so that it can float for a prolonged period. The drug is released in controlled manner for a specified period of time.**

**b) Intra gastric bilayer floating tablets: These are also tablets which contain two layers, namely immediate release layer which is required to maintain the loading dose and sustained release layer which releases drug for sustained period.**

**c) Multiple unit type floating pills: These systems consist of effervescent agents inside and swelling membrane in outer layer. When it is placed in dissolution medium it swells, subsequently the density is reduced which makes it suitable for floating.**

**B. Volatile liquid containing systems: The concept involved in this system is sustaining the gastric retention by incorporating an inflatable chamber. This chamber contains a volatile liquid e.g. ether, cyclopentane, that gasifies at body temperature.**

**2. Non-effervescent Systems:**

**These systems form gel or swells when it contacts gastric fluids. This is due to the presence of hydrocolloids. Due to the air entrapment in swollen matrix the density of this system becomes less than one, so that it floats.**

❖ **The major requirements for floating drug delivery system are:**

- **It should release contents slowly to serve as a reservoir.**
- **It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm$^3$).**
- **It must form a cohesive gel barrier.**

**Advantages of Floating Drug Delivery:**

- **Improved bioavailability.**
- **Reduced dose and dosing frequency.**
- **Minimized fluctuation of drug concentration in blood.**
- **Targeting of drugs.**
- **Local action can be achieved in GIT e.g. Antacids.**
- **Reduced side effects.**
- **Can be used for wide range of drugs.**

- **Sustained release can be achieved.**
- **Safest route of administration.**
- **Economic.**

**Limitations of Floating Drug Delivery:** [4]

- **Should be administered with plenty of water.**
- **Drugs with solubility or stability problem in GIT can't be administered.**
- **Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.**
- **Drugs which are irritant to gastric mucosa are not suitable.**
- **These systems do not offer significant advantages over the conventional dosage forms for drugs which are absorbed throughout the gastrointestinal tract.**

**Application of Floating Drug Delivery Systems:** [7]

**Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.**

1. **Sustained Drug Delivery: These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems.**
2. **Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine.**
3. **Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.**

**POTENTIAL DRUG CANDIDATES FOR FLOATING DRUG DELIVERTY SYSTEMS (FDDS):** [1]

1) ***Drugs those are locally active in the stomach:*** **e.g. misroprostol, antacids etc.**
2) ***Drugs that have narrow absorption window in gastrointestinal tract (GIT):*** **e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.**
3) ***Drugs those are unstable in the intestinal or colonic environment:*** **e.g. captopril, ranitidine, metronidazole.**
4) ***Drugs that disturb normal colonic microbes:*** **e.g. antibiotics against Helicobacter pylori.**
5) ***Drugs that exhibit low solubility at high pH values:*** **e.g. diazepam, chlordiazepoxide, verapamil HCl.**

**CINITAPRIDE :**

**Cinitapride1-2,chemically4-amino-*N*-[3-(Cyclohexan-1-yl-methyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide has the molecular formula C21H30N4O4 and molecular weight 402.49 g.mol-1 .Cinitapride is a drug that has against action to the serotoninergic 5-HT2 and D2 dopaminergic receptors that has been indicated in the gastro esophageal reflux and in the functional disorders of gastrointestinal motility treatment.**

**The therapeutic effect of cinitapride lies on the capacity of increasing lower esophageal sphincter tone and has strong gastro kinetic activity, which generates significant increases in the gastric emptiness; besides, through the serotoninergic system it stimulates the intestinal activity. The use of cinitapride is efficient and safe in treatment of patients with disorders in the gastric emptiness related to gastro esophageal reflux and functional dyspepsia as well as in individuals that present irritable bowel syndrome with constipation and abdominal pain.**

**Literature survey reveals a polarographic3 method for its determination. Further, a fast, sensitive and selective method for measuring plasma cinitapride using LC-MS/MS with positive ion electrospray ionization using multiple reaction-monitoring (MRM) mode to quantify cinitapride in human plasma using respridone as the internal standard is also reported 4.To best of our knowledge, there is no work in the literature reported about the spectrophotometric method for the analysis of cinitapride in biological fluids or pharmaceutical formulations. Hence, the authors has made an attempt to develop few simple and rapid spectrophotometric methods 5-7 for the estimation of cinitapride [8]**

- **Roy *et al.* 2008[9] described rapid, sensitive and specific method to quantitify cinitapride in human plasma using risperidone as the internal standard. Sample preparation involved simple solid phase extraction procedure. Plasma concentrations of cinitapride were determined by LC-MS/MS with a LOQ (limit of quantification) of 20.118 pg $mL^{-1}$ that allowed an appropriate characterization of the pharmacokinetic profile of cinitapride at the therapeutic dose. The method was successfully applied to the bioequivalence study of cinitapride tablet (1.0 mg) administered as a single oral dose.**

- **Sangeetha *et al*[10] design and evaluate oral sustained release tablet of lamotrigine using polymer such as HPMC K 4M, HPMC K 100M and methocel E50 LV at 15%, 25%, and 35% Concentration range. *In vitro* release profile was studied using HPMC K4M, HPMC K 100M and methocel E50 LV at three different concentration. The percentage cumulative amount of drug release was found to be 82.72% in 12 hrs, 70.69% in 12hrs and 97.80% in 4hrs respectively for the entire batch at 15% polymer concentration. The study proves that fluctuation in the drug release is overwhelmed when lamotrigine is administered in the form of SR tablet.**

- **DESIGN AND EVALUATION OF LAMOTRIGINE ORAL SUSTAINED RELEASE TABLETS[11]**

  **The purpose of writing 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 recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are**

**useful to several problems encountered during the development of a pharmaceutical dosage form.**

- **Anuradha K. Salunkhe *et.al* (2011); [12] prepared and evaluated a floating pulsatile drug delivery system of metoprolol tartrate. The prepared floating pulsatile delivery system consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of hydroxy propyl methyl cellulose (HPMC) E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. Developed formulations were evaluated for their physical characteristics, drug content, in-vitro disintegration time, in-vitro drug release profile (lag time), floating lag time, floating time and in-vivo X-ray study. On the basis of these evaluation parameters it was found that optimized floating pulsatile release formulation (FPRT) showed floating lag time of 4 min.**

- **Vikrant K. Nikam *et.al* (2011); [13] designed and evaluated verapamil HCL floating controlled release gastroretentive tablets using different hydrocolloid polymers including Carbopol, Hydroxy propyl methyl cellulose, and Xanthan gum incorporated for gel forming agent by direct compression technology. The tablets were evaluated for the physicochemical parameters such as weight variation, thickness, friability, hardness, drug content, in-vitro buoyancy studies, in-vitro dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. Tablet buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The in-vitro dissolution studies were carried out in a USP XXII apparatus II in 0.1N HCl. All the gastroretentive tablets showed good in-vitro buoyancy. The selected tablets containing Xanthan gum released approximately 94.43% drug in 24 h, while the buoyancy lag time was 25.8 ± 4.2 second and the**

**tablet remained buoyant for > 24 h. Zero order and non-Fickian release transport was confirmed as the drug release mechanism for the selected tablets.**

- **Liandong Hu *et.al* (2011); [14] developed dextromethorphan hydrobromide sustained-release (DMB-SR) tablets using floating technique to prolong the gastric residence time and compared their pharmacokinetic behavior with conventional sustained release tablets. DMB-SR floating tablets were prepared employing hydroxy propyl methyl cellulose (HPMC) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and hexadecanol as floating assistant agent. An orthogonal experiment design method was used to select the optimized formulation. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, floating characteristics, in-vitro release and in-vivo bioavailability. The optimized tablets were prepared with HPMC K4M 25 mg, sodium bicarbonate 20 mg and hexadecanol 18 mg. The prepared tablets could float within 3 min and maintain for more than 24 h. The data of physical parameters were all lie within the limits. Drug release at 12 h was more than 85%. The comparative pharmacokinetic study was performed by administration of the DMB-SR floating tablets and conventional DMB-SR tablets. The area under curve of plasma concentration–time (AUC) of floating tablets was slightly higher than that of reference tablets, Tmax was prolonged apparently. The results showed the floating tablets are a feasible approach for the sustained-release preparation of drugs, which have limited absorption sites in the stomach.**

- **Nanjan Sockan Ganesh *et.al* (2011); [15] prepared floating drug delivery system of Ketoprofen using variable concentration of polymers (HPMC K4M and Ethyl cellulose). Formulations were evaluated for physico-chemical, pre-formulation parameters and formulation parameters, in-vitro buoyancy studies, in-vitro release studies and results obtained in in-**

**vitro release studies were plotted in different models of data treatment (Zero Order, First Order, Higuchi's and Peppa's). Compatibility studies were performed using FTIR, there was no interaction between Ketoprofen and the polymers used. The measured hardness of tablets of each batch ranged between 4.3 to 6.4 kg/cm² which ensured good handling characteristics of all batches. The percentage drug content for all formulations ranged from 97.04% to 99.69% of Ketoprofen which complies with official specifications. All the batches were subjected to in-vitro release studies at 0.1N HCL (pH 1.2) and Phosphate buffer (pH 6.8). The best release was observed with formulation containing (3:1 ratio of HPMC K4M and Ethyl cellulose).**

- **Pramod Patil *et.al* (2011); [16] developed floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymers like guar gum, locust bean gum, either alone or in combination with HPMC K100M as swelling polymers, with sodium bicarbonate as gas generating agent and were evaluated for parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, in-vitro buoyancy study, in-vitro drug release study. All the formulation showed compliance with pharmacopieal standards. The selected best formulations were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release profile of the best formulations was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation.**

- **M.I. Tadros (2010); [17] developed a gastroretentive controlled release drug delivery system of Ciprofloxacin hydrochloride with swelling, floating, and adhesive properties. Tablet formulations were designed using hydroxy propyl methyl cellulose (HPMC K15M) and/or sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate**

**($NaHCO_3$) or calcium carbonate ($CaCO_3$) as a gas former. Swelling ability, floating behavior, adhesion period and drug release studies were conducted in 0.1 N HCL (pH 1.2) at 37 ± 0.5 ˚C. The tablets showed acceptable physicochemical properties. Drug release profiles of all formulae followed non-Fickian diffusion. Statistical analyses of data revealed that tablets containing HPMC K15M (21.42%, w/w), Na alginate (7.14%, w/w) and $NaHCO_3$ (20%, w/w) or $CaCO_3$ (20%, w/w) were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics. Both formulae were stored at 40 ˚C/75% RH for 3 months according to ICH guidelines. Formulation showed better physical stability. Abdominal X-ray imaging of formulation, loaded with barium sulfate, in six healthy volunteers revealed a mean gastric retention period of 5.50 ± 0.77 h.**

- **Kar *et.al* (2010); [18] prepared and characterized gastro retentive floating tablets of Cefuroxime Axetil. Hydrophilic polymers such as HPMC K15M and HPMC E5LV were used for its gel forming and release controlling properties. Sodium bicarbonate was incorporated as gas generating agent and Sodium Laurayl Sulfate (SLS) was used as solubility enhancer. The effects of gel forming agent (HPMC K15M and HPMC E5LV) and surfactant on drug release profile and floating properties were investigated. It has been observed that release characteristics were decreased with high viscous polymer due to increased tortuosity and length of drug diffusion path. Significant difference in release rate was found in different concentration of SLS. The release mechanisms were explored and explained with zero order, first order, Higuchi, Korsmeyer and Hixon-Crowell equations. The release rate, extent and mechanisms were found to be governed by the content of polymer. It was found that polymer content and amount of floating agent significantly affected the time required for 50% of drug release (T50%), Mean dissolution time (MDT), release rate constant, and diffusion exponent (n).Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was co-**

**dominated by both diffusion and polymer erosion in the release mechanism.**

- **Ramanathan *et.al* (2010); [19] fabricated a hydro-dynamically balanced system (HBS) of Mefenamic Acid. The different viscosity grades of hydroxy propyl methyl cellulose polymer like HPMC K100, HPMC K4M, HPMC KV600, and HPMC K50 was incorporated as hydrophilic swellable polymers for preparing matrix-floating tablets. Sodium bicarbonate was incorporated as a gas-generating agent. The prepared floating tablets were evaluated for the physical parameters like thickness, hardness, friability, drug content, floating lag time, floating time and in-vitro dissolution studies. The mechanism of drug release was anomalous type and depends upon the viscosity of polymers, which was mainly concluded as the major controlling factor for the drug release. The results showed that the formulation containing Drug: HPMC KV600 in the ratio of 1:0.5 is suitable for the formulation of gastro-retentive floating tablets of mefenamic acid.**

- **Margret Chandira *et.al* (2010); [20] formulated floating tablets of Itopride hydrochloride a gastroprokinetic drug using an effervescent approach for gastroretentive drug delivery system. Floating tablets were fabricated; using direct compression method; containing polymers HPMC K100M, HPMC K15M and Carbopol 934 P, along with gas generating agent sodium bicarbonate and citric acid. The addition of Carbopol aided in the reduction of the drug dissolution due to their hydrophobic nature. The concentration of these agents was also optimized to get desired controlled release of drug. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, in-vitro drug release, hardness, friability and weight variation. The results indicated that gas powered floating tablets of Itopride hydrochloride containing 125 mg HPMC K100M, 40 mg HPMC K15M, and 40 mg Carbopol provides a better option for 24 hours release action and improved bioavailability. The drug release pattern of this optimized formulation was found to be non-fickian diffusion mechanism. The accelerated stability studies, at**

**40˚C / 75% RH, of the optimized formulation were carried out for one month and no significant change was observed.**

- **Pare *et.al* (2008); [21] developed Amlodipine besylate effervescent floating tablets by employing hydrophilic polymers (HPMC K100M, HPMC K15M) and hydrophobic polymer (carbopol 934P) along with effervescing agent sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug release mechanisms. Formulations showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.**

- **Sanjay S. Patel *et.al* (2006); [22] designed floating dosage form containing clarithromycin for the treatment of *Helicobacter pylori*. Tablets containing hydroxyl propyl methyl cellulose (HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique. The study showed that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 s; total floating time >10 h). The drug release was sufficiently sustained (more than 8 h) and anomalous diffusion as well as zero-order was confirmed. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 s with a total floating time > 10 h, in-vitro release profile very near to the target in-vitro release profile and follows anomalous diffusion as well as zero order pattern of release.**

# AIM AND OBJECTIVE

**AIM:**

**To design, formulate & evaluate floating tablets containing Cinitapride based on floating technique in order to increase gastric retention time for enhancing site-specific absorption in the stomach or upper parts of the small intestine as well as to produce controlled release of the drug for a longer time.**

**To evaluate the influence of preparative parameters and its effect on drug release, The floating ability of the formulation and the release mechanism on the basis of various kinetic models.**

**OBJECTIVES :**

**To design of sustained release dosage form of Cinitapride that will help in releasing only small quantities of drug over a prolonged period of time.**

**To study the effect of type of polymers and polymer concentration on release profiles of controlled release cinitapride formulations.**

**To study the different types of schemes on release profiles of controlled release Cinitapride formulations.**

**To arrive at better formulation based on comparison amongst the studied ones.**

**To perform stability studies as per ICH guidelines.**

# PLAN OF WORK

1. **Literature review.**
2. **Pre-formulation studies.**
3. **Preparation of floating tablets of Cinitapride.**
4. **Evaluation of tablets for:**
    a. **Hardness**
    b. **thickness**
    c. **Friability**
    d. **Weight variation**
    e. **Assay**
    f. **Dissolution studies.**
5. **Kinetic models analysis:**
    a. **First order**
    b. **Zero order**
6. **Stability studies.**

# DRUG PROFILE

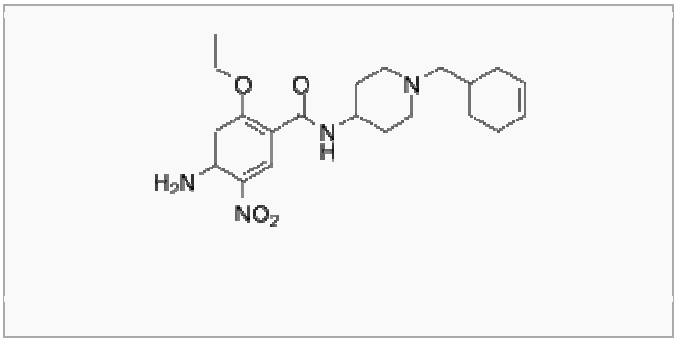
## CINITAPRIDE[23,24]

**CHEMICAL IUPAC NAME**

***RS*)-4-amino-*N*-[1-(1-cyclohex-3-enylmethyl)-4-piperidyl]-2-ethoxy-5nitrobenzamide**

**EMPIRICAL FORMULA : $C_{21}H_{30}N_4O_4$**

**STRUCTURAL FORMULA:**




**DESCRIPTION : Solid and Amarphors**

.

**CATEGORY : Anti ulcer agent**

**SOLUBILITY : Soluble in water**

**MECHANISM OF ACTION**

**Cinitapride is a substituted benzamide with 5-HT receptor antagonist and agonist activity.[1] It acts as an agonist of the 5-HT1 and 5-HT4 receptors and as an antagonist of the 5-HT2 receptors**

**ABSORPTION**

**Absorption of cinitapride (12mg) following oral administration was rapid, with peak levels being achieved 2 h after dosing; absorption following intramuscular administration (4mg) was even more rapid, with peak levels (50% more that oral levels) being achieved 1 h after dosing.**

**TOXICITY**

**The symptoms of overdose include drowsiness, confusion and extrapyramidal effects.**

**BIOAVAILABILITY: 50 – 95%**

**HALF LIFE: 3-5 h during the first 8 h and a residual half-life greater than 15 h thereafter.**

**PHARMACOKINETICS**

**Pharmacokinetic studies in man following oral and intramuscular administration have been made using doses substantially higher than the therapeutic dose due to the absence of a sufficiently sensitive analytical method for the detection of plasma concentrations following very low doses of cinitapride. The absorption of cinitapride (12mg) following oral administration was rapid, with peak levels being achieved 2 h after dosing; absorption following intramuscular administration (4mg) was even more rapid,with peak levels (50% more that oral levels) being achieved 1 h after dosing.**

**The elimination profile in man was similar by either route of administration, with a half-**
**life of some 3-5 h during the first 8 h and a residual half-life greater than 15 h thereafter.**
**The plasma levels during this slow phase were, however, negligible and the overall**
**pharmacokinetic profile is indicative of 3 time's daily dosing schedule being the most**
**appropriate. Since the urinary 24-h excretion of cinitapride and its two major metabolites**
**(principally the de-alkylated product) was no greater than 7% of the administered dose, this is obviously only a minor elimination pathway**

**PHARMACODYNAMICS**

**These drugs may increase acetylcholine concentrations by antagonizing the $M_1$ receptor which inhibits acetylcholine release, or by inhibiting the enzyme acetylcholinesterase which metabolizes acetylcholine. Higher acetylcholine levels increase gastrointestinal peristalsis and further increase pressure on the lower esophageal sphincter, thereby stimulating gastrointestinal motility, accelerating gastric emptying, and improving gastro-duodenal coordination.**

**The 5-HT4 receptor is thought to play a significant role in both the physiology and pathophysiology of GI tract motility.[2] Therefore, 5-$HT_4$ receptors have been identified as potential therapeutic targets for diseases related to GI dysmotility such as chronic constipation. Some of these prokinetic agents, such as mosapride and cisapride, classic benzamides, have only moderate affinity for $5HT_4$ receptors. In recent years, it has become clear that the selectivity profile is a major determinant of the risk-benefit profile of this class**

**DOSE AND ADMINISTRATION**

**Administrated by oral route**

**Adult: 1mg tab t,i,d**

**USES**

**Delayed gastric emptying,**

**Gastro-esophageal reflux disease,**

**Non-ulcer dyspepsia.**

## HYPROMELLOSE[25]

**Nonproprietary names:**

**BP : Hypromellose**

**JP : Hydroxypropyl methylcellulose**

**PhEur : Hypromellosum**

**USP : Hypromellose**

**Synonyms:**

**Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropyl cellulose; Metolose; Tylopur.**

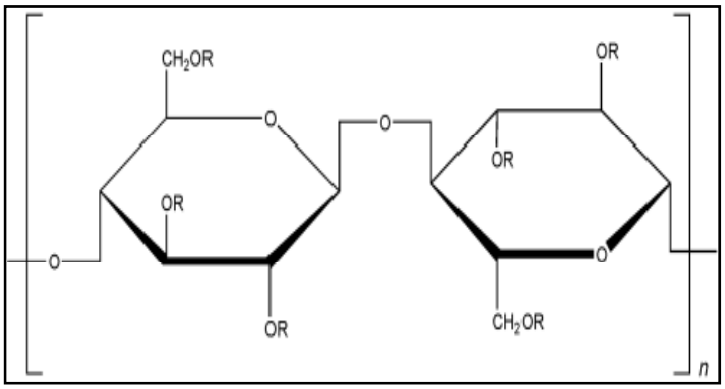
**Chemical name and CAS registry number:**

**Cellulose 2- hydroxypropyl methyl ether [9004-65-3]**

**Molecular weight:**

**Molecular weight is approximately 10,000-1,500,000.**

**Structural formula:**




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

**Functional category:**

**Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder and viscosity increasing agent.**

**Applications in pharmaceutical formulation or technology:**

**Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.**

**High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose at concentrations between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.**

**Typical Properties:**

| | | |
|---|---|---|
| **Acidity/alkalinity** | **:** | **pH = 5.5–8.0 for a 1% w/w aqueous solution.** |
| **Density (bulk)** | **:** | **0.341 g/cm$^3$** |
| **Density (tapped)** | **:** | **0.557 g/cm$^3$** |
| **Density (true)** | **:** | **1.326 g/cm$^3$** |
| **Melting Point** | **:** | **browns at 190 – 200°C; chars at 225 – 230°C**<br>**Glass transition temperature is 170 - 180$^o$ C** |

**Table 5.3: Various grades of hypromellose**

| Methocelproduct | USP 28 designation | Nominal viscosity (mPa s) |
|---|---|---|
| Methocel K100 Premium LVEP | 2208 | 100 |
| Methocel K4M Premium | 2208 | 4000 |
| Methocel K15M Premium | 2208 | 15 000 |
| Methocel K100M Premium | 2208 | 100 000 |
| Methocel E4M Premium | 2910 | 4000 |
| Methocel F50 Premium | 2906 | 50 |
| Methocel E10M Premium CR | 2906 | 10 000 |
| Methocel E3 Premium LV | 2906 | 3 |
| Methocel E6 Premium LV | 2906 | 6 |
| Methocel E15 Premium LV | 2906 | 15 |
| Metolose 60SH | 2910 | 50, 4000, 10 000 |
| Metolose 65SH | 2906 | 50, 400, 1500, 4000 |
| Metolose 90SH | 2208 | 100, 400, 4000, 15 000 |

**Description:**

**Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.**

**Melting point:**

**Browns at 190-200°C; chars at 225-230°C, glass transition temperature is 170-180°C.**

**Moisture content:**

**Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.**

**Solubility:**

**Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether but its soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol and other organic solvents.**

**Viscosity (dynamic):**

**A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.**

**Stability and storage conditions:**

**Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90°C, depending upon the grade and concentration of material.**

## MICROCRYSTALLINE CELLULOSE: [26]

**Nonproprietary Names:**

**BP : Microcrystalline cellulose**

**JP : Microcrystalline cellulose**

**PhEur : Cellulosum microcristallinum**

**USPNF : Microcrystalline cellulose**

**Synonyms:**

**Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.**

**Chemical Name : Cellulose**

**CAS Registry Number : [9004-34-6]**

**Molecular Weight : 36, 000**

**Functional Category:**

**Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.**

**Description:**

**Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.**

**Typical Properties:**

**Density (bulk) : 0.337 g/cm3;**

**Density (tapped) : 0.478 g/cm3;**

**Density (true) : 1.512–1.668 g/cm3**

**Flowability : 1.41 g/s**

**Melting point : chars at 260–270°C.**

**Specific surface area: 1.06–1.12 m2/g for Avicel PH-101;**

**1.21–1.30 m2/g for Avicel PH-102;**

**0.78–1.18 m2/g for Avicel PH-200.**

**1.21–1.30 m2/g for Avicel PH-102;**

**Moisture content:**

**Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic. (Avicel PH- 102= • 5.0)**

**Solubility:**

**Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.**

**Applications in Pharmaceutical Formulation or Technology:**

**Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and directcompression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.**

**Uses of microcrystalline cellulose**

**1. Adsorbent**

**2. Capsule binder/diluents**

**3. Tablet disintegrants**

**4. Tablet binder/diluents**

**Stability and Storage Conditions:**

**Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.**

**Incompatibilities:**

**Microcrystalline cellulose is incompatible with strong oxidizing agents.**

**MAGNESIUM STEARATE:[25]**

**Nonproprietary names:**

**BP : Magnesium stearate**

**JP : Magnesium stearate**

**PhEur : Magnesii stearas**

**USPNF : Magnesium stearate**

**Synonyms : Magnesium octa decanoate, Magnesium salt.**

**Chemical name and CAS registry number**

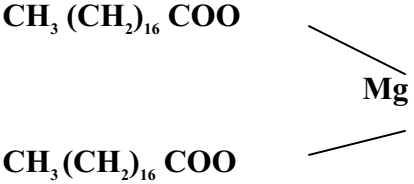
**Octa decanoic acid magnesium salt [557-04-0]**

**Functional category : Tablet and capsule lubricant**

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

**Molecular weight : 591.3**

**Structure :**




**Description:**

**It is a fine, white, precipitated or milled, impalpable powder of low bulk density and having a faint odor of stearic acid, characteristic taste.**

**Solubility:**

**It is insoluble in water, ethanol and ether. It can slightly soluble in warm ethanol and benzene.**

**Stability and storage conditions:**

**Stable, Store in a well closed container in a cool, dry place.**

## TALC:[25]

**Nonproprietary names:**

**BP : Purified talc**

**JP : Talc**

**PhEur : Talcum**

**USPNF : Talc**

**Synonyms:**

**Purified chalk, altalc, powdered talc and soapstone**

**Chemical name and CAS registry number: Talc [14807-96-6]**

**Description:**

**A very fine, white to grayish white, impalpable, odorless crystalline powder,**

**Unctuous, adheres readily to skin, soft to touch and free from granules.**

**Empirical formula : $Mg_6(Si_2O_5)_4(OH)_4$**

**Functional category:**

**Tablet, capsule it can use as a lubricant and diluents. During compression used as glidant and anticaking agent.**

**Solubility:**

**Insoluble in water, organic solvents, dilutes acids and alkalis.**

**Storage conditions:**

**Stable, Preserve in a well-closed container in a cool, dry place.**

## CARBOPOL -940[27]

**Nonproprietary Names:**

**BP, PhEur and USP-NF : Carbomer.**

**Synonyms:**

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

**Chemical Name:**

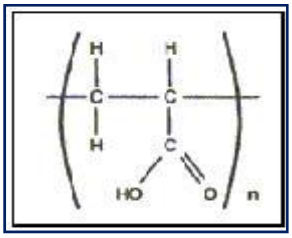
**Polyacrylate – 1- cross polymer.**

**Empirical Formula:**

**Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol.**

**Structural Formula:**

**General Structure of Carbopol Polymers**




**Description:**

**Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor.**

**Typical Properties:**

**Density (bulk): 0.2 g/cm$^3$ (powder); 0.4 g/cm$^3$ (granular).**

**Density (tapped): 0.3 g/cm$^3$ (powder); 0.4 g/cm$^3$ (granular).**

**Dissociation constant (pKa): 6.0±0.5**

**Glass transition temperature: 100–105˚C.**

**Melting point: Decomposition occurs within 30 minutes at 260˚C.**

**pH: 2.5–4.0 for a 0.2% w/v aqueous dispersion.**

**Moisture content: 2.0%w/w maximum.**

**Specific gravity: 1.41**

**Viscosity of Carbomer 940 (0.5% w/v): 40,000-60,000 (mPa s).**

**Solubility:**

**Swellable in water and glycerin and, after neutralization, in ethanol (95%). Carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels.**

**Functional Category:**

**Bioadhesive material; controlled-release agent; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.**

**Applications in Pharmaceutical Formulation:**

| Use | Concentration (%) |
|---|---|
| Emulsifying agent | 0.1 – 0.5 |
| Gelling agent | 0.5 – 2.0 |
| Suspending agent | 0.5 – 1.0 |
| Tablet binder | 0.75 – 3.0 |
| Controlled-release | 5.0 – 30.0 |

| | |
|---|---|
| **agent** | |

**Safety:**

**Carbomers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. Grades polymerized in ethyl acetate may also be used in oral formulations. There is no evidence of systemic absorption of carbomer polymers following oral administration.**

# MATERIALS AND METHODS

**Table no-2**

| INSTRUMENTS | SUPPLIER/ MANUFACTURER |
|---|---|
| Single pan analytical balance | Sartorius |
| Hot air oven | Biotechnis – India |
| Tablet punching machine | Karnavathi – 10 Station |
| Hardness tester | Pfizer tablet hardness tester |
| Roche friabilator | Electrolab |
| Dissolution apparatus | Campbell electronics –Mumbai |
| Disintegration apparatus | Campbell electronics –Mumbai |
| UV spectrophotometer | Elico-SL 159 UV-Visible spectrophotometer, Japan |
| Vernier caliper | Electro lab - Mumbai |

**Table no-3: Materials used**

| MATERIAL | SUPPLIER/ MANUFACTURER |
|---|---|
| Cinitapride | Chromo labs |
| Corbopol 940 | Lobachemie pvt. Ltd |
| Micro crystalline cellulose | SD fine chemicals |
| HPMC k4m | SD fine chemicals |
| HPMC e15m | Finar chemicals Ltd |
| HPMC k100m | Finar chemicals Ltd |
| Magnesium stearate | SD fine chemicals |
| Talc | SD Fine – Chem. ltd |

## METHODOLOGY

### PRELIMINARY STUDIES

**Determination of $_{max}$:**

**Stock solution of 1mg/ml Cinitapride was prepared by dissolving 100mg of a drug in water and diluted up to 100 ml with water . From this 1ml of solution is diluted with [0.1 N HCL] and make up to 100ml and $_{max}$ of the solution was found in the range from 200-400nm. The $_{max}$ of the solution was found to be 264nm.**

**Preparation of standard curve: pH1.2[28] .**

**Stock solution of 1mg/ml Cinitapride was prepared by dissolving 100mg of a drug in water and diluted up to 100 ml with water . From this 1ml of solution is diluted with [0.1 N HCL] and make up to 100ml to obtain concentration of 1µg/ml.From the standard stock solution of Cinitapride appropriate aliquots of 5,10,15,20,25and 30ml were pipetted out into 100ml volumetric flask and final volume was made with 0.1 N HCL,Absorbance spectra of each solution against 0.1 N HCl as blank were measured at 264 nm using Elico-SL 159 UV-Visible spectrophotometer.**

### FORMULATION OF FLOATING TABLETS:

### POLYMER SELECTION:

**Procedure: Trial batches of floating tablets were prepared using different polymers [HPMC k4m, HPMC k100m,HPMC e15m ]; different drug: polymer ratio was used. Tablets prepared by direct compression technique and evaluated for floating lag time in HCL buffer (pH 1.2) medium.**

**Inference: tablets prepared using polymers (HPMC k4m,HPMC k100m,HPMC e15m) showed best results in terms of floating lag time . Hence these polymers were selected for the development of Cinitapride floating tablets.**

**DRUG-EXCIPIENT COMPATABILITY STUDY BY FTIR:**

**IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymers. A physical mixture of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 6 tons pressure. It was then scanned from 4000 to 400 $cm^{-1}$ in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers; matching was done to detect any appearance or disappearance of peaks.**

**FORMULATION DESIGN:**

**Floating tablets of Cinitapride were prepared based on following design :**

- **Polymers : HPMC k4m,HPMC k100m and HPMC e15m.**
- **Swelling agent : Carbapol.**
- **Filler : Micro crystalline cellulose.**

**Tablets were prepared by direct compression method. A total of 9formulations (3 formulations based on HPMC k4m,3 formulation based on HPMC k100m& another 3 formulations based on HPMC e15m) were designed by varying the amounts of polymers at 3 levels (low, medium & high) using cross over design (as shown in Table-4).**

**Table no-4: Composition of floating tablets**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Cintapride | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| HPMC k4m | 40 | 60 | 80 | - | - | - | - | - | - |
| HPMC e15m | - | - | - | 40 | 60 | 80 | - | - | - |
| HPMC k100m | | | | | | | 40 | 60 | 80 |
| Carbopol940 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| MCC | 44 | 24 | 4 | 44 | 24 | 4 | 44 | 24 | 4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Mg.Stearete** | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **3** |
| **Talc** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** |

**F1: formulation with 40% hpmc k4m**

**F2: formulation with 60% hpmc k4m**

**F3: formulation with 80% hpmc k4m**

**F4: formulation with 40% hpmc e15m**

**F5: formulation with 60% hpmc e15m**

**F6: formulation with 80% hpmc e15m**

**F7: formulation with 40% hpmc k100m**

**F8: formulation with 60% hpmc k100m**

**F9: formulation with 80% hpmc k100m**

**PREPARATION OF POWDER BLEND:**

**The ingredients were accurately weighed and sifted through sieve #60, and then the materials except talc and magnesium stearate were blended using mortar and pestle for 10 min in an ascending order. Powder mixture then blended with talc and magnesium stearate for 5 min.**

**EVALUATION OF POWDER BLEND:**

**The prepared powder blends were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like Angle of repose, Bulk density, Tap density, Compressibility index & Hausner's ratio.**

**Angle of repose:**

**The angle of repose is the maximum angle formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample powder was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (r) and the height of the heap (h) were measured. The angle of repose is represented as ' ' and calculated using the following equation:**

$$\text{Tan} = h/r \qquad (1)$$

**Table no-5: Flow properties and corresponding Angles of repose**

| FLOW PROPERTY | ANGLE OF REPOSE (DEGREES) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |
| Very, very poor | >66 |

**Bulk Density:**

**The bulk densities of the powder blends were determined by transferring an accurately weighed 10 gm of sample powder to the graduated 50 ml measuring cylinder. The initial volume (bulk volume) was noted. The bulk density calculated using formula:**

**Bulk Density = Weight of Sample / Bulk Volume (2)**

**Tapped Density:**

**An accurately weighed 10 gm of sample powder was transferred to the graduated 50ml measuring cylinder and placed on the tap density test apparatus. The apparatus was operated for a fixed number of taps (500 taps). The final volume (tapped volume) of the powder mass was noted. The tapped density calculated using formula:**

**Tapped Density = Weight of Sample / Tapped Volume (3)**

**Compressibility Index:**

**The compressibility index is determined from the bulk volume and tapped volume of the powder. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after tapping until no change in volume occurs. It is represented in percentage.**

**% Compressibility = (Tapped density - Bulk density) / Tapped density X 100**

**(4)**

**Table no-6: Scale of Flowability based on Compressibility Index**

| COMPRESSIBILITY INDEX (%) | FLOW CHARACTER |
|---|---|
| • 10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| 32-37 | Very poor |
| >38 | Very, very poor |

**Hausner's Ratio:**

**Hausner's ratio is the ratio of bulk density to the tapped density of powder (or) initial volume of the powder mass to the final volume of the powder mass obtained after specified number of tapping.**

**Table no-7: Scale of Flowability based on Hausner's Ratio**

| HAUSNER'S RATIO | FLOW CHARACTER |
|---|---|
| 1-1.11 | Excellent |
| 1.12-1.18 | Good |
| 1.19-1.25 | Fair |
| 1.26-1.34 | Passable |
| 1.35-1.45 | Poor |
| 1.46-1.59 | Very poor |
| >1.60 | Very, very poor |

**Assay of Blend:**

**Powder blend equivalent to 10 mg of Cinitapride was weighed and transferred to 100ml volumetric flask. Added 20ml of HCL buffer (pH 1.2) and sonicated for 10min.Then solution was filtered through 0.45 µm whatmann filter paper and made up to 100ml with HCL buffer (pH 1.2). 1ml of resultant solution was taken and diluted to 100ml with HCL buffer (pH 1.2) and the absorbance was measured at 264nm using UV spectrophotometer.**

**COMPRESSION OF FLOATING TABLET:**

**Weighed accurately about 100mg of the mixture blend and fed in 10 station compression machine and compressed at 1.5N compression force using 6mm concave punches.**

**EVALUATION OF FLOATING TABLET:**

**Weight variation test:**

**20 tablets were selected randomly and weighed. Average weight was calculated. Each tablet was weighed individually. Weight of the individual tablets was compared with the average weight and reported with standard deviation. Since the tablets weighed 80mg – 250mg, Indian Pharmacopoeia specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%**

**Table no-8: Weight variation limit as per Indian Pharmacopoeia**

| Percentage deviation allowed under weight variation test | |
|---|---|
| **Average weight of tablet** | **Percentage deviation** |
| **• 80mg** | **10%** |
| **80-250mg** | **7.5%** |
| **• 250mg** | **5%** |

**Thickness and diameter:**

**Thickness and diameter were measured during tablet compression using Vernier calliper.**

**Hardness:**

**Hardness of the tablets was measured using Pfizer tablet hardness tester. A sample of 6 tablets was randomly taken from each batch. The tablets were held vertically in between the jaws which were pressed with hand until the tablet broken. The reading was noted from the needle of pressure dial which may be expressed in kilograms.**

**Friability:**

**Friability is performed to evaluate the ability of tablet to withstand abrasions. Ten tablets were weighed and placed in the tumbling chamber which was rotated for 100 revolutions. The tablets were dedusted and again weighed. The loss in weight indicated the friability.**

$$\% \text{ Friability} = \frac{A-B}{B} \qquad (5)$$

**Where A=Initial weight of tablet**

**B=Weight of tablet after 100 revolutions.**

**Assay of tablet:** [32]

**20 tablets were weighed and powdered. A quantity of the powder equivalent to 20 mg of Cinitapride was accurately weighed. Added 20 ml of water and shaken for 10 minutes. Then added 50 ml of methanol, shaken for a further 10 minutes, sufficient methanol was added to produce 100 ml and then filtered. 10 ml of the filtrate was diluted to 50 ml with methanol and the absorbance of the resulting solution was measured at the maximum at about 264nm. The content of Cinitapride was calculated.**

**I.P Limit: Tablets contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of Cinitapride.**

**COMPRESSION OF TABLETS**

**Accurately weighed powder blend equivalent to 2mg of Cinitapride is fed in 10 station compression machine , Round concave punches of 6mm diameter were used for compression. The tablets were compressed to a hardness of about 5 - 6kg/cm$^2$.**

***In-vitro Dissolution:***[29]

**Cinitapride release from different formulations was determined using a USP XXIII paddle apparatus 2 under sink condition. To simulate *in-vivo* condition the dissolution medium was selected as 900 ml HCL buffer (pH 1.2) samples were withdrawn at 1st,2$^{nd}$,3$^{rd}$,6$^{th}$,7$^{th}$,9$^{th}$ and 12$^{th}$ hour time interval at 37 ± 0.2 °C. All experiments were done in triplicate and average values were taken. The formulations prepared were subjected to dissolution tests for 12 hrs. Samples were withdrawn at predetermined time intervals, filtered through 0.45µm Whatmann filter paper and replaced by an equal volume of dissolution medium. Absorbance of the diluted dissolution samples were determined by UV spectrophotometer at 264nm and drug content was calculated using calibration curve method.**

**Dissolution test Conditions:**

| | |
|---|---|
| **Apparatus** | **: USP XXIII paddle apparatus 2.** |
| **RPM** | **: 100.** |
| **Temperature** | **: 37 ± 0.2 °C.** |
| **Medium** | **: HCL (pH 1.2)** |
| **Duration of test** | **: 12 hrs.** |
| **Sampling Interval** | **: 1$^{st}$,2$^{nd}$,3$^{rd}$,6$^{th}$,7$^{th}$,9$^{th}$ and 12$^{th}$** |
| **Sampling Volume** | **: 10ml.** |

**Floating Behaviours:** [30]

**Floating behaviour studies were carried out in a USP XXIII paddle apparatus 2 at a paddle speed of 100 rpm in 900 ml HCL buffer (pH 1.2) at 37 ±**

**0.2 °C. The parameters determined were; the time taken by the tablet to go upward and float on the surface (floating lag time), the time at which the tablet remained buoyant (floating duration) and were determined on the basis of visual inspection.**

**DRUG RELEASE KINETICS: [31]**

**To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models: zero order (Equation 6) as cumulative amount of drug released vs. time, first order (Equation 7)**

$$C = K_0 t \qquad (6)$$

**Where,**

**$K_0$: is the zero-order rate constant expressed in units of concentration/time**

**t: is the time in hours.**

**A graph of concentration vs. time would yield a straight line with a slope equal to $K_0$ and intercept the origin of the axes.**

$$LogC = LogCo \bullet kt/2.303 \qquad (7)$$

**Where,**

**$C_0$: is the initial concentration of drug,**

**K: is the first order constant, and t is the time.**

$$Q = Kt^{1/2} \qquad (8)$$

**Where,**

**K: is the constant reflecting the design variables of the system**

**t: is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.**

**To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law (Equation 9):**

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = kHC - t \qquad (9)$$

**Where,**

**$Q_t$ is the amount of drug released in time t,**

**$Q_0$ is the initial amount of the drug in the tablet, and**

**KHC is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs. time.**

**STABILITY STUDIES:**

**The prepared formulations which showed best *in vitro* results was selected and kept for stability testing for 90 days. The tablets were kept at 40± 2°C/ 75%±5%RH in a stability chamber and samples were withdrawn at initial, 30 $^{th}$, 60 $^{th}$ and 90$^{th}$ day and evaluated for drug content, dissolution study.**

# RESULTS

## PRELIMINARY STUDIES:

**Determination of $_{max}$ of Cinitapride:**

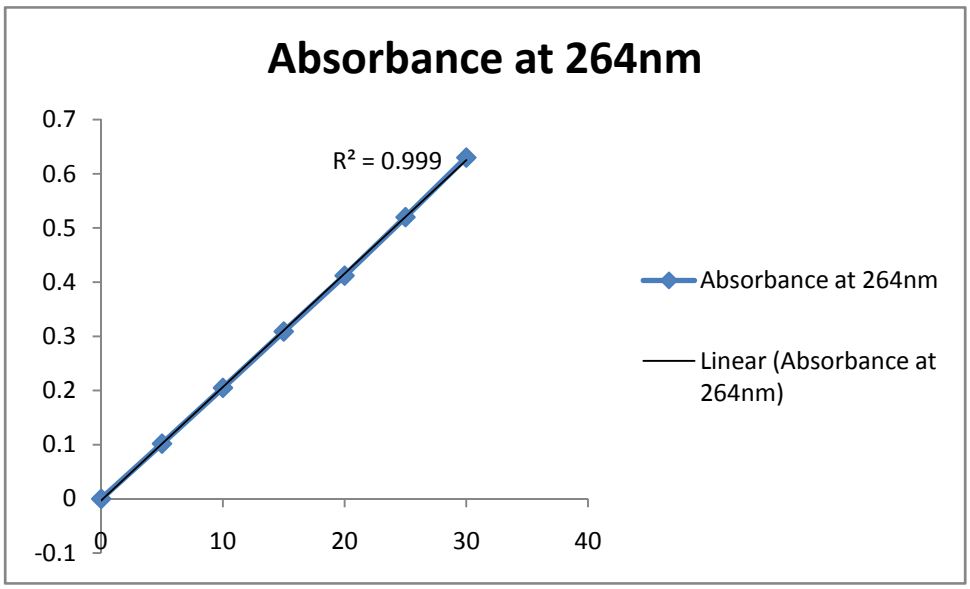
**Cinitapride showed absorption maxima at 264 nm.**

**Calibration curve of Cinitapride:**

**Table no-9: Standard Calibration Data of Cinitapride**

| Concentration (µg/ml) | Absorbance at 264nm |
|---|---|
| 5 | 0.102 |
| 10 | 0.205 |
| 15 | 0.309 |
| 20 | 0.412 |
| 25 | 0.520 |
| 30 | 0.630 |

**Fig.3: Standard Calibration curve of Cinitapride in 0.1N HCL at 264nm**




**PRE-COMPRESSION EVALUATION:**

**Evaluation of powder blend:**

**Table no-10: Pre-compression parameters of powder blend**

| Formulation | Bulk Density(gm\ml) | Tapped Density(gm\ml) | Compressability Index | Hausenr's Ratio | Angle Of Repose |
|---|---|---|---|---|---|
| F1 | 0.3 | 0.35 | 19 | 1.16 | 32.1 |
| F2 | 0.308 | 0.49 | 22.5 | 1.59 | 35.6 |
| F3 | 0.31 | 0.5 | 24.3 | 1.61 | 35 |
| F4 | 0.4 | 0.51 | 23.2 | 1.27 | 33.1 |
| F5 | 0.416 | 0.34 | 21.7 | 0.817 | 39.8 |
| F6 | 0.44 | 0.35 | 23.27 | 0.79 | 34 |
| F7 | 0.38 | 0.48 | 24.1 | 1.26 | 36.5 |
| F8 | 0.41 | 0.44 | 24.6 | 1.07 | 36 |
| F9 | 0.39 | 0.43 | 22.5 | 0.90 | 37.4 |

**Compatibility studies by FTIR:**

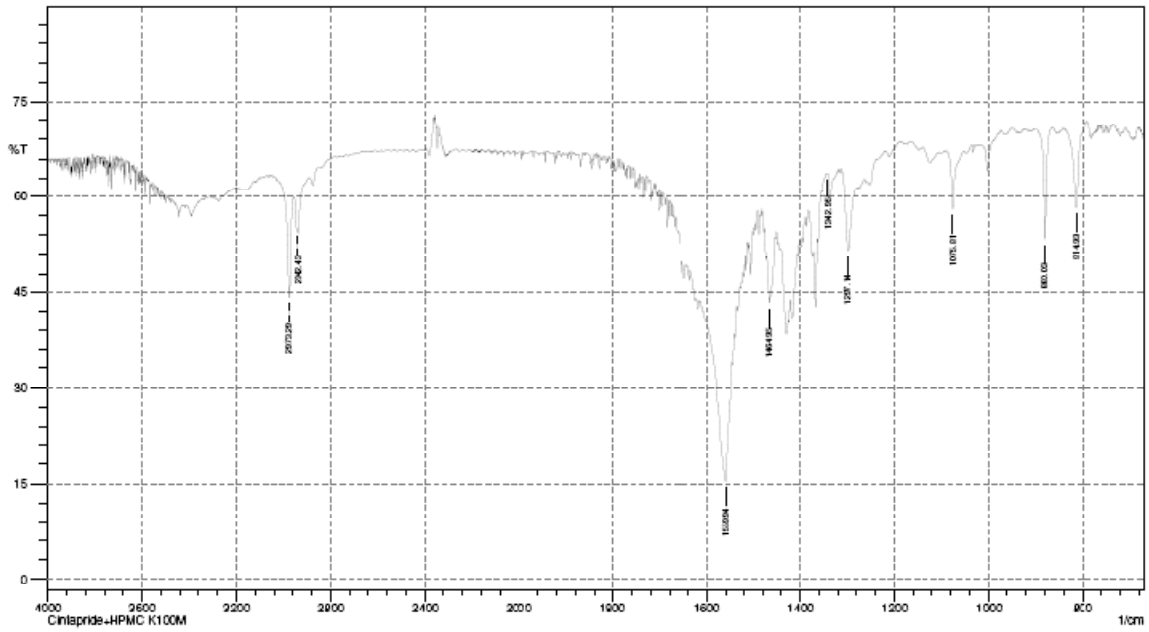



**Fig.4: IR Spectra of Drug + HPMCk100m**

**Table no-11: Characteristic peaks of IR spectra of Cinitapride**

| Frequency ($cm^{-1}$) | Functional group specification |
|---|---|
| 2973 | Aromatic –C-H- stretching |
| 1559 | Secondary amine –NH- bending |
| 1464 | CH- bending |
| 1368 | Primary alcohol –OH bending |
| 1296 | Secondary alcohol -O-H stretching |
| 1075 | C-O Stretching[ether] |

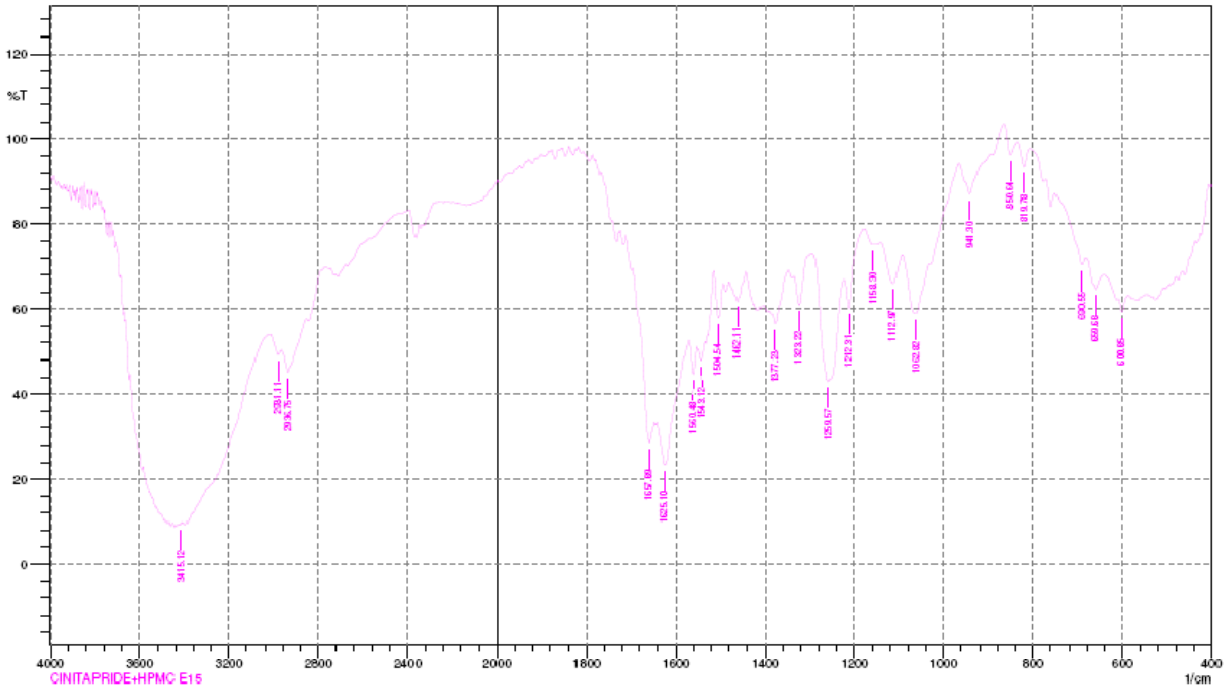



**Fig.5: IR Spectra of Drug + HPMC e15**

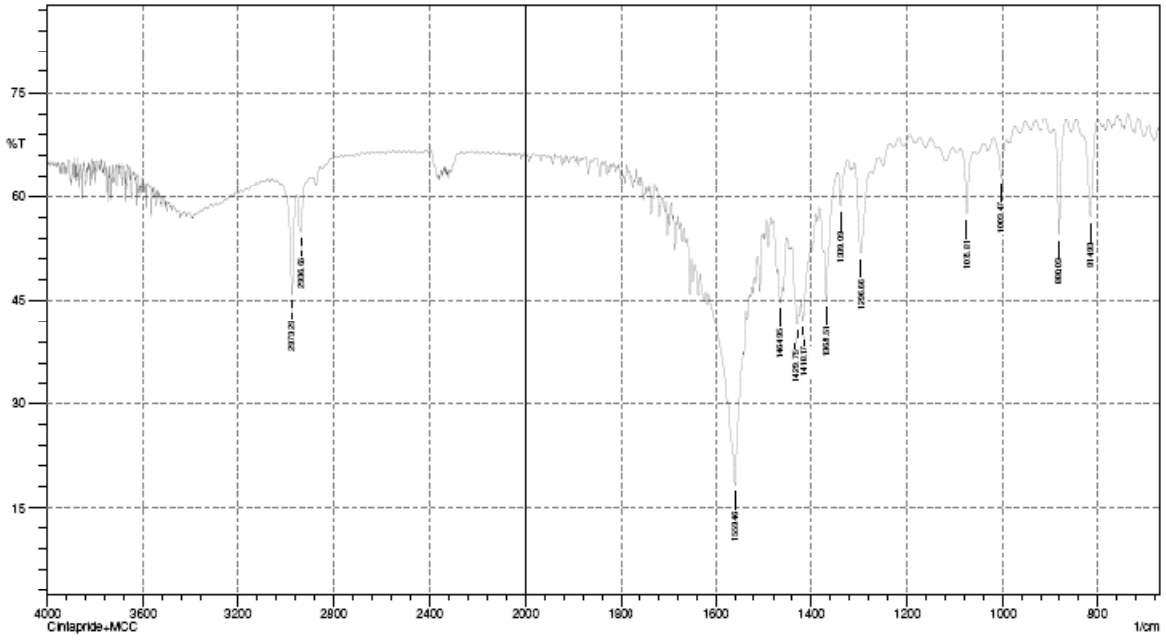



**Fig.6: IR Spectra of Drug + MCC**

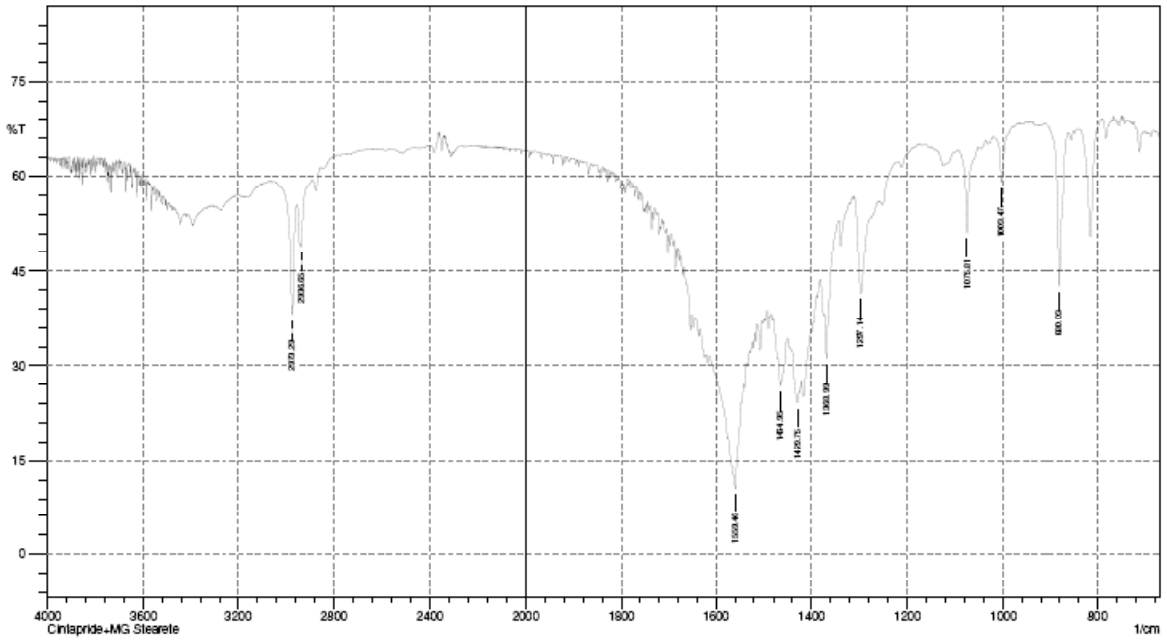



**Fig.7: IR Spectra of Drug + Magnesium Sterate**

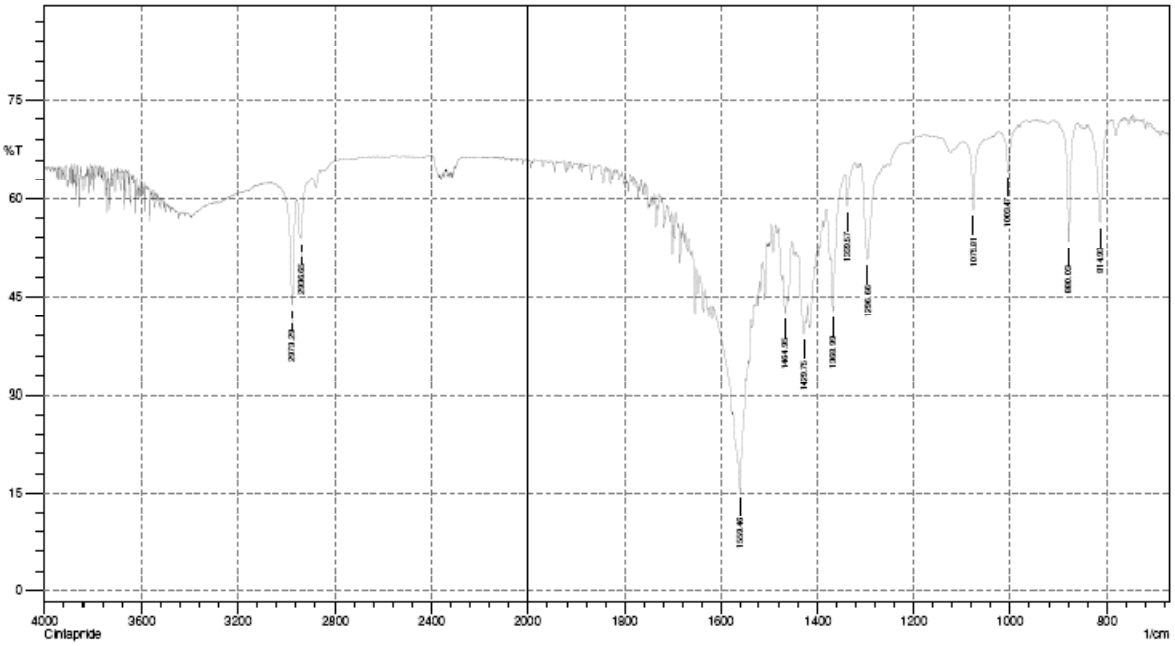



**Fig.8: IR Spectra of Pure Drug**

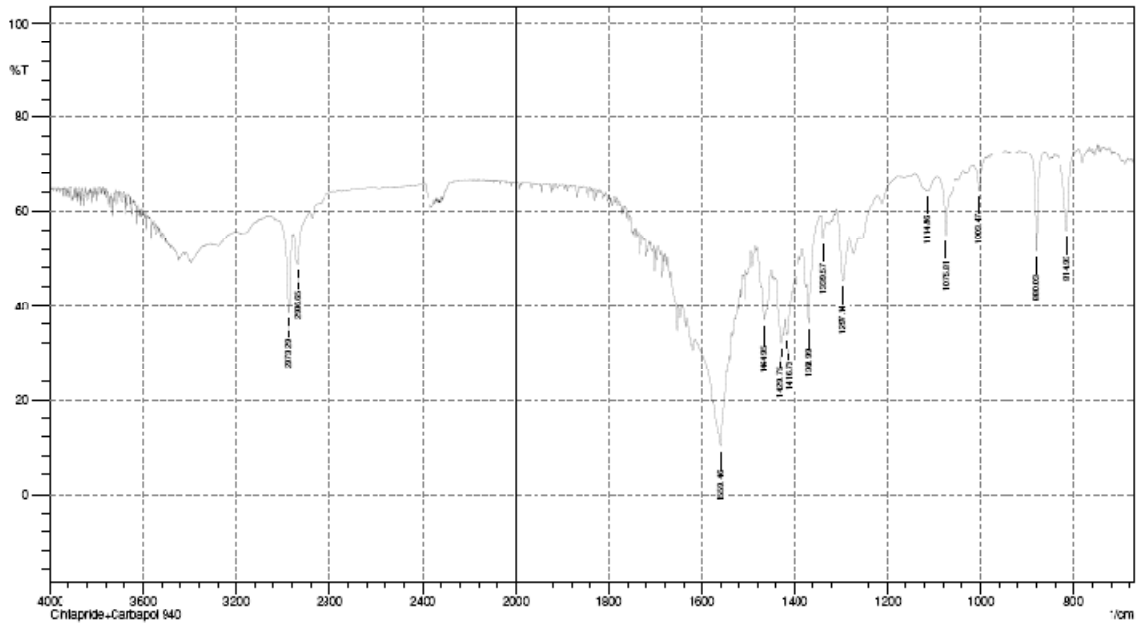



**Fig.9: IR Spectra of Drug + Carbapol 940**

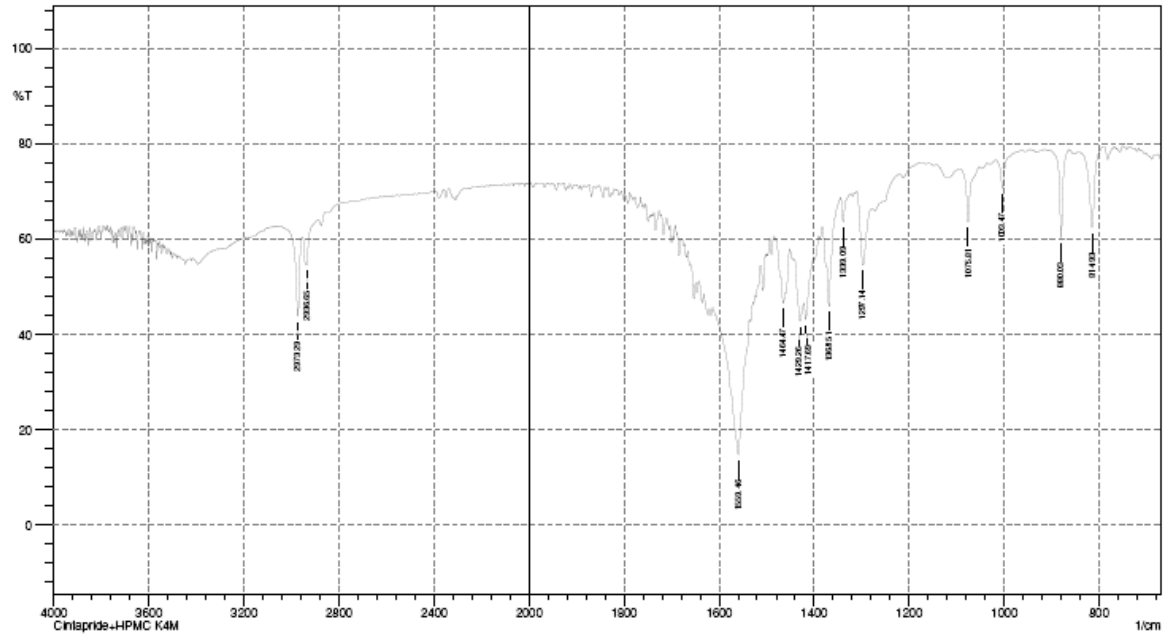



**Fig.10: IR Spectra of Drug + HPMC k4m**

**POST-COMPRESSION EVALUATION OF FLOATING TABLETS:**

**Evaluation of physical parameters:**

**Table no-12: Physical parameters of prepared tablets**

| Formulation | Avg.Wt (mg) | Thickness (mm) | Diameter(mm) | Hardness (Kg\cm$^2$) | Friability |
|---|---|---|---|---|---|
| F1 | 100.2 | 2.8 | 6 | 5.5 | 0.11 |
| F2 | 101.1 | 2.6 | 6 | 5.4 | 0.06 |
| F3 | 100.6 | 2.5 | 6 | 5.6 | 0.14 |
| F4 | 100.1 | 2.8 | 6 | 6 | 0.04 |
| F5 | 100.8 | 2.7 | 6 | 5.1 | 0.14 |
| F6 | 100.1 | 2.6 | 6 | 5.4 | 0.06 |
| F7 | 100.4 | 2.6 | 6 | 5.5 | 0.16 |
| F8 | 99.4 | 2.6 | 6 | 5.5 | 0.41 |
| F9 | 101.6 | 2.65 | 6 | 5.4 | 0.02 |

*** mean ± standard deviation (SD).**

**Evaluation of Floating Behaviours:**

**Table no-13: Results of *in-vitro* floating behaviours**

| Polymer | Formulation code | Floating lag time (sec) | Buoyancy (hrs) |
|---|---|---|---|
| HPMC k4m | F1 | 120 | Less than 12 |
| | F2 | 180 | More than12 |
| | F3 | 280 | Less than 12 |
| HPMC e15m | F4 | 110 | More than12 |
| | F5 | 90 | More than12 |
| | F6 | 67 | Less than 12 |
| HPMC k100m | F7 | 210 | Less than 12 |
| | F8 | 72 | Less than 12 |
| | F9 | 180 | Less than12 |

**Evaluation of *In-vitro* Drug Release:**

**Table no-14: Results of *in-vitro* drug release study of Cinitapride floating tablets**

| Formulation code | 1st hr | 2nd hr | 3rd hr | 6th hr | 7th hr | 9th hr | 12th hr |
|---|---|---|---|---|---|---|---|
| FI | 17.87 | 22.67 | 29.21 | 55.37 | 63.65 | 77.61 | 96.36 |
| F2 | 17 | 20.92 | 27.46 | 56.24 | 67.58 | 79.79 | 98.54 |
| F3 | 22.23 | 28.34 | 33.13 | 66.27 | 76.3 | 85.89 | 95.48 |
| F4 | 19.18 | 25.72 | 30.95 | 63.65 | 73.68 | 81.09 | 89.82 |
| F5 | 24.41 | 30.08 | 35.31 | 70.63 | 77.17 | 90.69 | 99.41 |
| F6 | 18.31 | 25.28 | 33.57 | 62.78 | 70.63 | 78.91 | 95.48 |
| F7 | 21.8 | 28.77 | 37.06 | 68.45 | 78.04 | 83.27 | 92.43 |
| F8 | 13.95 | 19.18 | 25.72 | 48.83 | 57.99 | 71.94 | 82.84 |
| F9 | 41.85 | 53.19 | 63.22 | 75.86 | 86.76 | 92 | 93.3 |

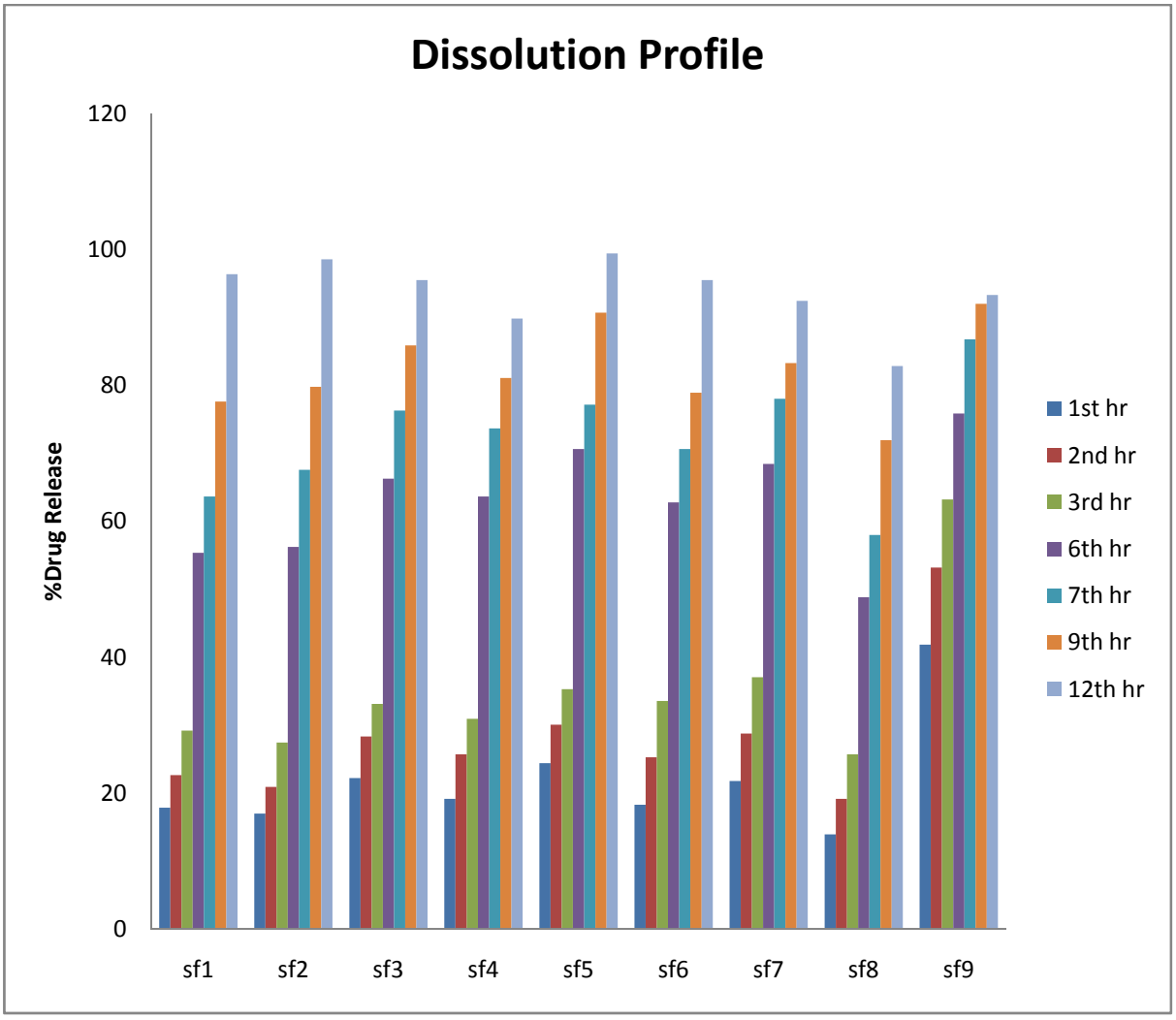



**Fig.11: Results of *in-vitro* drug release study of Cinitapride Floating Tablets**

**DRUG RELEASE KINETICS:**

**Table No-15: Results of drug release kinetics analysis**

| Formulation code | Zero-order | First –order |
|---|---|---|
| | $R^2$ | $R^2$ |
| F1 | 0.839 | 0.830 |
| F2 | 0.706 | 0.747 |
| F3 | 0.883 | 0.906 |
| F4 | 0.944 | 0.955 |
| F5 | 0.954 | 0.958 |
| F6 | 0.938 | 0.939 |
| F7 | 0.978 | 0.984 |
| F8 | 0.995 | 0.907 |
| F9 | 0.968 | 0.958 |

**STABILITY STUDIES:**

**Table no-16: Results of Parameters evaluated after 3 months stability study**

| Parameters evaluated | Formulation code | |
|---|---|---|
| | F5 | |
| | Initial | final |
| Physical appearance | - | No change |
| Assay (% drug content) | 99.89 | 97.73 |
| Floating lag time (sec) | 90 | 85 |
| Floating duration (hrs) | >12 | <12 |
| Cumulative % Drug Release (after 12hrs) | 99.41 | 98.56 |

## DISCUSSION

**PRELIMINARY STUDIES:**

**Determination of $_{max}$ of Cinitapride:**

**A solution containing (10µg/ml) of Cinitapride was scanned in the range of 200-400 nm. Cinitapride showed absorption maxima at 264 nm.**

**Calibration curve of Cinitapride:**

**Calibration curve of Cinitapride showed good linearity in the range of 5-30µg/ml with regression coefficient ($R^2$) value of 0.9998 as shown in (Fig.3).**

**PRE-COMPRESSION EVALUATION:**

**Evaluation of powder blend:**

**All the materials were properly mixed as per composition shown in (Table-4). For each designed formulation, blend of drug and excipients were prepared and subjected for pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The obtained results were shown in (Table10).**

**As a general guide, powders with angles of repose greater than 50° have unsatisfactory flow properties, whereas minimum angles close to 25° correspond to very good flow properties. The angle of repose ranged between 32.1° to 39.8°, which indicates good flow propriety of powders.**

**The bulk density and tapped density for all formulations were found to be in the range of 0.300 to 0.440 gm/cm$^3$ and 0.340 to 0.510 gm/cm$^3$ respectively, which indicates good packing character.**

**The powder has a good flowability, when the Hausner's ratio is lower than 1.2, and when the value exceeds 1.2 it indicates poor flow. Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. A compressible material will be less flowable, and powders with compressibility values greater than 20-21 % have been found to exhibit poor flow properties. The Hausner's ratio and % Compressibility index was found to be in the**

**range of 0.79 to 1.59 and 19 % to 24 % respectively, which supports the fact that the formulations have good flow and compaction properties.**

**All formulations exhibited good flow property and compressibility which is very essential for direct compression and hence tablets were prepared by using direct compression technology.**

**Compatibility studies by FTIR:**

**Drug polymer interaction was checked by comparing the IR spectra of pure drug with the IR spectra of physical mixtures of drug and excipients used. As shown in (Fig.4 to Fig.10).**

**IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. All the characteristic peaks of Cinitapride mentioned in (Table-11) were also found in the IR spectra of physical mixtures.**

**Frequencies of functional groups of pure drug remained intact in physical mixtures containing different polymers; hence, there was no major interaction between the drug and excipients used in this study.**

**COMPRESSION OF TABLETS:**

**The floating tablets were prepared by direct compression technique. The target weight of the prepared tablet was 100mg. The desired hardness is between 5 - 6 Kg/cm$^2$. All the tablets were found to be uniform in size and shape and no processing problems were encountered during compression process.**

**POST-COMPRESSION EVALUATION OF FLOATING TABLETS:**

**Evaluation of physical parameters:**

**The compressed tablets were evaluated for their weight variation, hardness, thickness, friability and content uniformity as per Indian pharmacopoeia [67] , and the results were shown in (Table-12).**

**All the compressed tablets passed the weight variation test. The mean thickness of the prepared tablets was found to be between 2.6 – 2.8mm. The mean hardness of the tablets ranged from 5.4 – 6.0 kg/cm$^2$. Percentage friability ranged from 0.02 % to 0.16%. The drug content in all the prepared tablets complied with the Indian pharmacopoeia requirements, which was found to lie within the range of 82.84to 99.41 %.**

**All values of the physical parameters were found to be within the pharmacopoeial limits.**

**Evaluation of Floating Behaviours:**

**The parameters determined were; Floating Lag Time- the time taken by the tablet to go upward and float on the surface, Floating Duration- the time at which the tablet remained buoyant (determined on the basis of visual inspection); and the results were shown in (Table-13).**

**Carbapol 940 was used as the Swelling agent. , the fluid permeated into the tablet, causing neutralization reaction to occur, which generates carbon dioxide ($CO_2$). The swelling polymer traps the $CO_2$ so generated and thus provides continued buoyancy.** [30]

**The floating lag time was found to be in the range of 67 to 280 seconds. Formulations containing varying concentration of polymers (F-1,2,3,4,5,6,7,8 and 9) showed buoyancy time of 12 hrs.**

**Evaluation of *In-vitro* Drug Release:**

**Cinitapride release from different formulations was determined in 900ml HCL buffer (pH 1.2) at 37 ± 0.2 °C. All experiments were done in triplicate and average values were taken. The dissolution data of formulations were shown in (Table-14).**

**It was observed that the particular concentration of polymer HPMC e15m shows release of drug over an extended period of time. Hence formulation (F5) were able to efficiently control Cinitapride release over a time period of 12 hrs.**

**Carbopol-940 being highly swellable agent were able to swell to forms a thick viscous layer around the tablet. Since increases the diffusion path length and the drug diffusion tends to slow down and hence a reduction in drug release was observed.** [65]

**DRUG RELEASE KINETICS:**

**The *in vitro* drug dissolution data was analyzed for establishing kinetics of drug release. Model fitting was done [zero-order, first-order] . Interpretations of data were based on regression coefficient. The kinetic analysis data of all the formulations were shown in (Table-15).**

**The $R^2$ values obtained from zero order plot was found to be higher in comparison to first order plot which suggest that the drug release rate from the prepared tablets were in constant and controlled manner.**

**STABILITY STUDIES:**

**Accelerated stability studies were carried out according to ICH guidelines. Optimized formulations (F5) were sealed in aluminium packaging coated inside with polyethylene, and kept in a stability chamber at 40°C± 2°C and 75%±5% RH for 3 months. At the end of the period, samples were analyzed for drug content, floating characteristics and *in-vitro* drug release as shown in (Table-16).**

**Stability study of optimized formulations revealed no significant change in physical appearance, drug content, floating lag time, floating duration as well as *in-vitro* drug release. And hence formulations were found to be stable at 40°C± 2°C and 75%±5% RH for 3 months.**

# SUMMARY

**The present study was aimed to formulate and evaluvate the tablets containing Cinitapride based on floating technique in order to increase gastric retention time for enhancing site-specific absorption in the stomach or upper parts of the small intestine as well as to produce controlled release of the drug for a longer time. Cinitapride shows pH dependent solubility and stability. It is more soluble & stable in acidic than alkaline pH. Hence, it will be beneficial to increase its gastric residence time.**

**FORMULATION DESIGN:**

**In this study; Cinitapride were prepared based on floating technique using: 3 different polymers, HPMC k4m, HPMC e15m and HPMC k100m, Carbapol 940 as (Swelling agent) and Microcrystalline cellulose as (filler). A total of 9 formulations (3 formulations in each polymer) were designed by varying the amounts of polymer at 3 levels (low, medium & high) using cross over design.**

**PRE-COMPRESSION STUDIES:**

**The prepared powder blends of all the 9 formulations were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results obtained from these studies showed that the prepared blends were having satisfactory fluidity and compressibility; hence tablets can be prepared by direct compression method.**

**IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymers. This study revealed that there was no major interaction between the drug and excipients used.**

**COMPRESSION OF TABLETS:**

**The floating tablets were prepared by direct compression technique at a compression force (1.5N) in a concave punches (6mm size). The target weight of the prepared tablet was 100mg. The desired hardness is between 5-6Kg/cm$^2$. All the**

**tablets were found to be uniform in size and shape and no processing problems were encountered during compression process.**

**POST-COMPRESSION STUDIES:**

**The compressed tablets were evaluated for their weight variation, hardness, thickness, friability and content uniformity as per Indian pharmacopoeia and the results were found to be within the prescribed limits.**

**Floating behaviour studies were carried out in a USP XXIII paddle apparatus 2 at a paddle speed of 100 rpm in 900 ml HCL buffer (pH 1.2) at 37 ± 0.2 °C. The parameters determined were; (Floating Lag Time, Floating Duration ). Floating lag time for all formulations were found to be less than 5min. Formulations containing varying concentration of polymer showed buoyancy time of 12hrs.**

**Cinitapride release from different formulations was determined using a USP XXIII paddle apparatus 2 at a paddle speed of 100 rpm in 900 ml HCL buffer (pH 1.2) at 37 ± 0.2 °C under sink condition for 12 hrs. In this study, it was observed that the medium concentration of polymer [HPMC e15m] in Formulation (F5) were able to efficiently control Cinitapride release over a time period of 12 hrs.**

**The *in vitro* drug dissolution data obtained were plotted in various kinetic models for establishing kinetics of drug release. Zero order plot suggest that the drug release rate from the prepared tablets were in constant and controlled manner, for formulation (F5).**

**Accelerated stability studies were carried out for optimized formulation (F5) in a stability chamber at 40°C±2°C and 75%±5% RH for 3 months. The study revealed no significant change in physical appearance, drug content, floating lag time, floating duration as well as *in-vitro* drug release. And hence formulations were found to be stable.**

# CONCLUSION

**Drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of drugs that exhibit absorption window, low bioavailability and extensive first pass metabolism.**

**In the present work floating tablets have been prepared incorporating a highly soluble anti-ulcer drug Cinitapride using polymers like (HPMC k4m,HPMC e15m and HPMC k100m). swelling agent (Carbapol 940) was used to keep the tablets floating over the simulated gastric fluid (pH 1.2) for more than 12 hrs. All the formulations showed floating lag time less than 5 min. Microcrystalline cellulose is used as a filler. The drug release mechanisms for these formulations were confirmed as zero-order release. The formulations (F5) were selected as an optimized formulations because it gave the best results in terms of the required *in-vitro* buoyancy as well as drug release in a sustained release manner and also were found to be stable under the stability conditions.**

**Thus the results of the current study clearly indicate, a promising potential of the floating tablet as an alternative to conventional dosage form, further clinical studies are needed to assess the utility of this system for patients suffering from Gastro-esophageal reflux disease, Non-ulcer dyspepsia.**

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