FORMULATION AND INVITRO EVALUATION OF NORFLOXACIN GASTRIC FLOATING DRUG DELIVERY SYSTEM.

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: GOVINDARAJ.S

REG.No.261710260

Under the Guidance of

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled "***FORMULATION AND INVITRO EVALUATION OF NORFLOXACIN GASTRI FLOATING DRUG DELIVERY SYSTEM***", submitted by the student bearing **REG.No.261710260** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

CERTIFICATE

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DECLARATON

I do hereby declared that the dissertation **"*FORMULATION AND INVITRO EVALUATION OF NORFLOXACIN GASTRIC FLOATING DRUG DELIVERY SYSTEM* ",** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2018-2019, under the guidance and supervision of **Mr. K. Jaganathan, M.Pharm.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **GOVINDARAJ.S**

Date: **REG.No.261710260**

Dedicated to Parents,

Teachers&

My Family

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1.INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the Ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time(GRT).Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs),will provide us with new and important therapeutic options. GRDFs extend significantly the period of time over which the drug may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs are carried out frequently, often several times perday.

As a mechanism to override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of these drugs at the absorption site. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid, microspheres and pharmacosomes, etc. compared with other applications, the frequency of dosing may be the same, but the gastro retentive dosage forms will

alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhancedbioavailability.[1]

One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

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

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified sap system or by the simultaneous administration of pharmacological agent that delay

gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. *In vivo/in vitro* evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems.[2] Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems. Pharmaceutical dosage form (DF) with gastro retentive properties would enable an extended absorption phase of these drugs with narrow absorption window. After oral administration, DF would be retained in stomach and release drug there, in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in upper GIT. Another interesting importance for the DF with prolonged residence time in the stomach is, drugs that are required to be formulated into gastro retentive dosage forms include:

1. Drugs acting locally in thestomach.
2. Drugs that are primarily absorbed in thestomach.
3. Drugs that are poorly soluble at alkalinepH.
4. Drugs with a narrow window ofabsorption.
5. Drugs rapidly absorbed from the GI tractand
6. Drugs that degrade in thecolon.

MECHANISTIC ASPECTS OF FLOATING DRUG DELIVERY SYSTEM

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co administration of gastric-emptying delaying drugs.

Among these, the floating dosage forms have been used most commonly. However, most of these approaches are influenced by a number of factors that affect their efficacy as a gastro retentive system.[1,4]

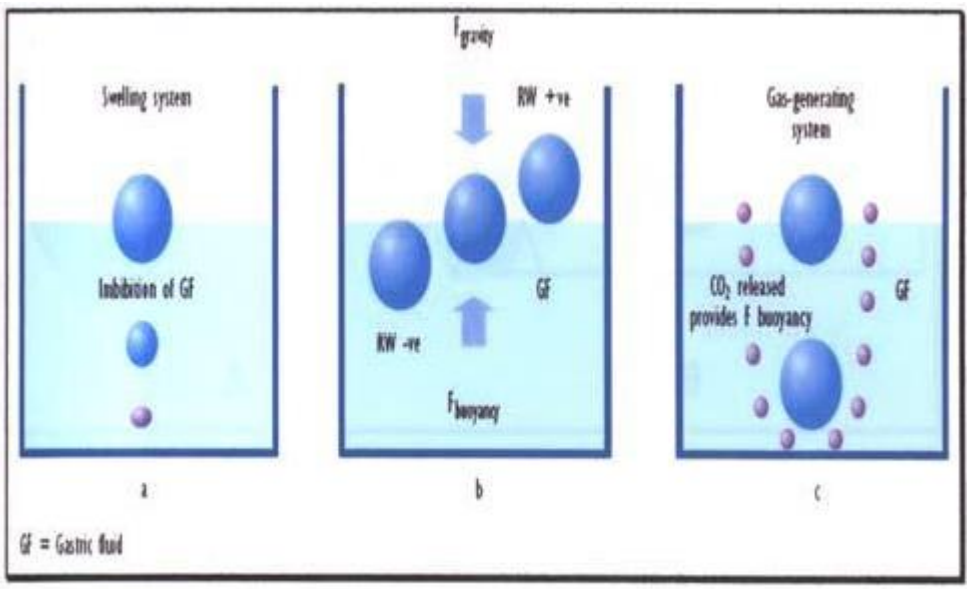


Figure *1*. Mechanism of Floating Systems

Incorporation of the drug in a controlled release gastro retentive dosage form(CR-GRDF) Can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.

Pharmacokinetic aspects:- Absorption window-validation that the drug is within the category of narrow window

Enhanced bioavailability

- Enhanced first pass biotransformation
- Improved bioavailability due to reduced P-glycoprotein (P-gp)activity in the duodenum.
- Reduced frequency of dosing.

- Targeted therapy for local ailments in the upper GI tract.

Pharmacodynamic Aspects:-

- Reduced fluctuation of drug concentration
- Improved selectivity in receptor activation.
- Reduced counter-activity of the body.
- Extended time over critical (effective) concentration.
- Minimum adverse activity at thecolon.[11]

Gastric emptying

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. Gastric emptying occurs during fasting as well as fed states.

The pattern of motility is however distinct in the 2 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 inter digestive myoelectric cycle or migrating mylo electric cycle (MMC), which is further divided into following 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 potential and 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 contractionsforShortperiod.Itisduetothiswavethatalltheundigestedmaterialis

4. swept out of the stomach down to the small intestine. It is also known as the house keeper wave.
5. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Table-1. The transit time of different dosage forms across the segment of G.I tract.

Dosage Form	Transit Time (h)		
	Gastric	Small intestine	Total
Tablets	2.7-1.5	3.1-0.4	5.8
Pellets	1.2-1.3	3.4-1.0	4.6
Capsules	0.8-1.2	3.2-0.8	4.0
Oral Solution	0.3-0.07	4.1-0.5	4.4

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 empty ingrate.

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 emptyingrate.[35]

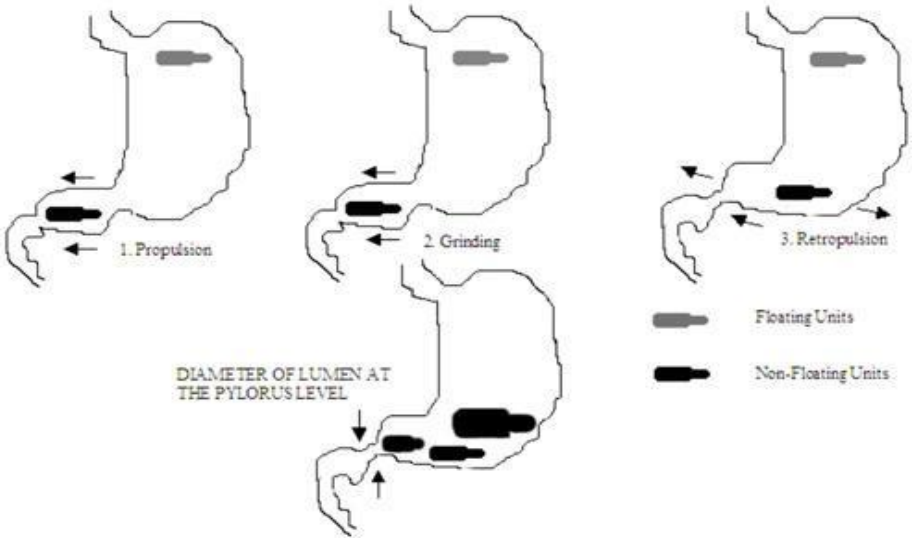


Fig. 2 Intragastric residence positions of floating and non floating units[2]

Factors Affecting Gastric Retention

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

- Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
- Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- 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; can affect floating time.
- Biological factors – diabetes and Crohn's disease, etc.

APPROACHES TO GASTRIC RETENTION

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid, In such a situation, there is nothing to float on. Floating systems can be based on the following

- Hydro dynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float.
- Effervescent systems- gas generating materials such as carbonates are incorporated. These materials react with gastric acid and produce carbon dioxide, which allows them to float.
- Low-density systems have a density lower than that of the gastric fluid so they are buoyant.
- Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles for min the gel, enabling floating.
- Bio adhesive or muco adhesive systems – these systems permit a given delivery system (DDS) to be incorporated with bio/muco adhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastricemptying.However,themucusonthewallsofthestomachisinastate of constant renewal, resulting in unpredictable adherence. The stomach is a size-filtering system and so it would seem ideally suited to retaining a DDS is not small enough to be taken orally if sizes larger than the pylorus are required. Several systems have been investigated to encourage gastric retention using increasing size of DDS. Systems have been based on expansion due to gases and swelling due to intake of externalliquids.[1,36]

TYPES OF GASTRORETENTIVE DOSAGE FORMS

A.Floating drug delivery systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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 the fluctuations in plasma drug concentration. FDDS can be divided into non effervescent and gas-generating(effervescent)system.

(a)Non-effervescentsystems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier18. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types:

(i) Colloidal gel barriersystem:

Sheth and Tossounian first designated this hydrodynamic ally balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxyl propyl cellulose, hydoxyethyl cellulose, hydroxyl propyl methyl cellulose (HPMC),polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

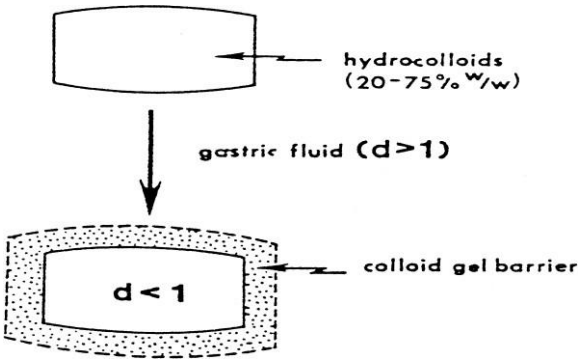


Fig.3.Intragastric floating tablet

(ii) Micro porous compartment system:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls20. The peripheral walls of the drug reservoir compartment are completely sealed to prevent anydirectcontactofgastricsurfacewiththeundissolveddrug.Inthestomach,the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the

dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate leading to formation of a porous system, when compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5hr.

(iv)Hollow microspheres /Microballons:

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for More than 24 hr.

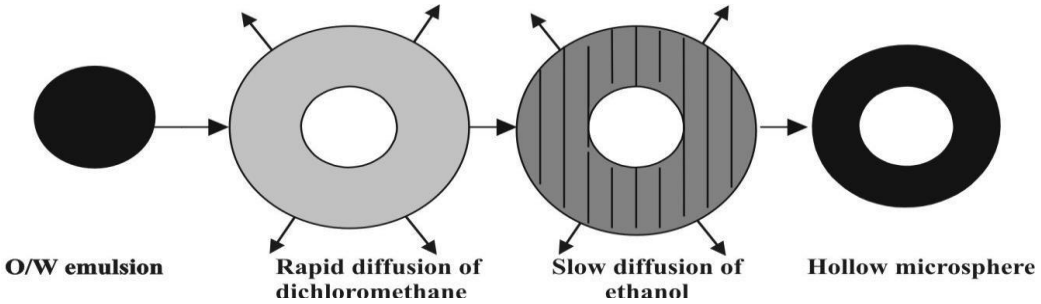


Fig. 4 Formulation of floating microspheres

(a) Gas-generating (Effervescent)systems:

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and poly vinyl pyrrolidone coated with hydroxypropyl methyl cellulose (HPMC), and floating system based on ion exchange resin system.

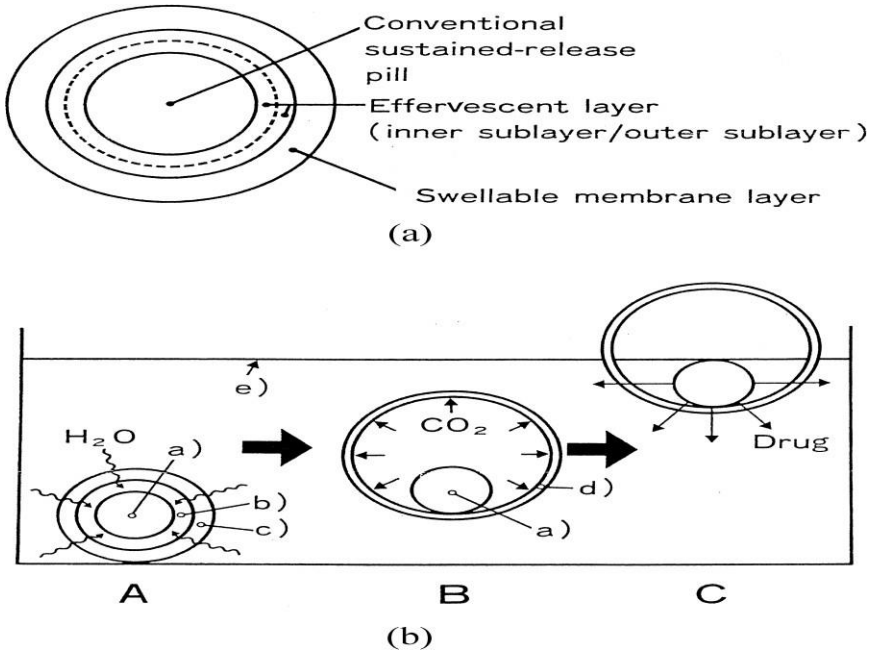


Fig.5 (a) A multiple-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (378C)

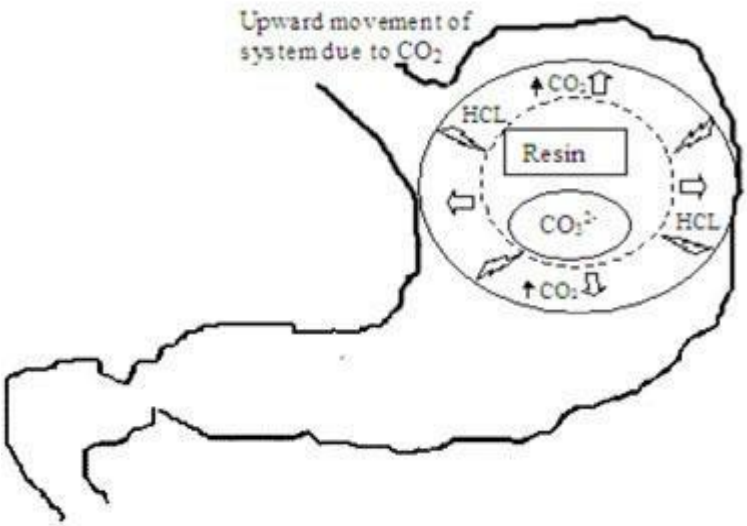


Fig:-6 Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin.

A.Expandable systems

Expandable gastro retentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro retentively is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved *in vivo* absorption properties.

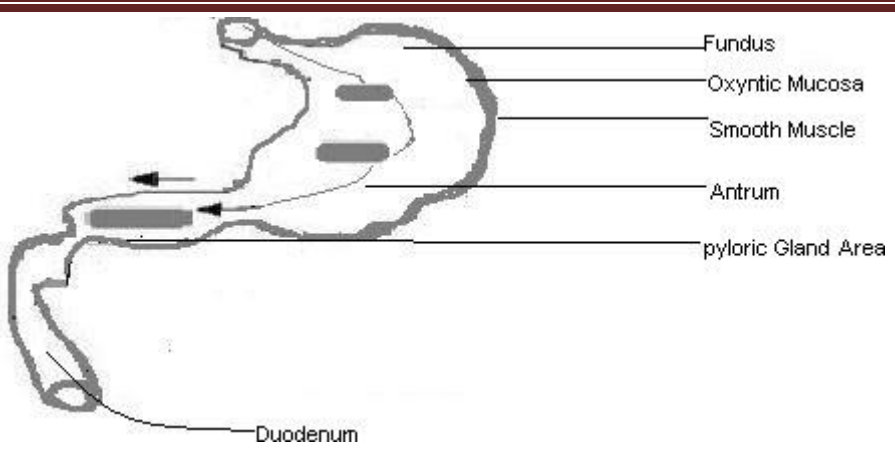


Fig.No.7. Swelling and Expanding Systems

A. Bio/Muco-adhesivesystems

Bio adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin,etc.

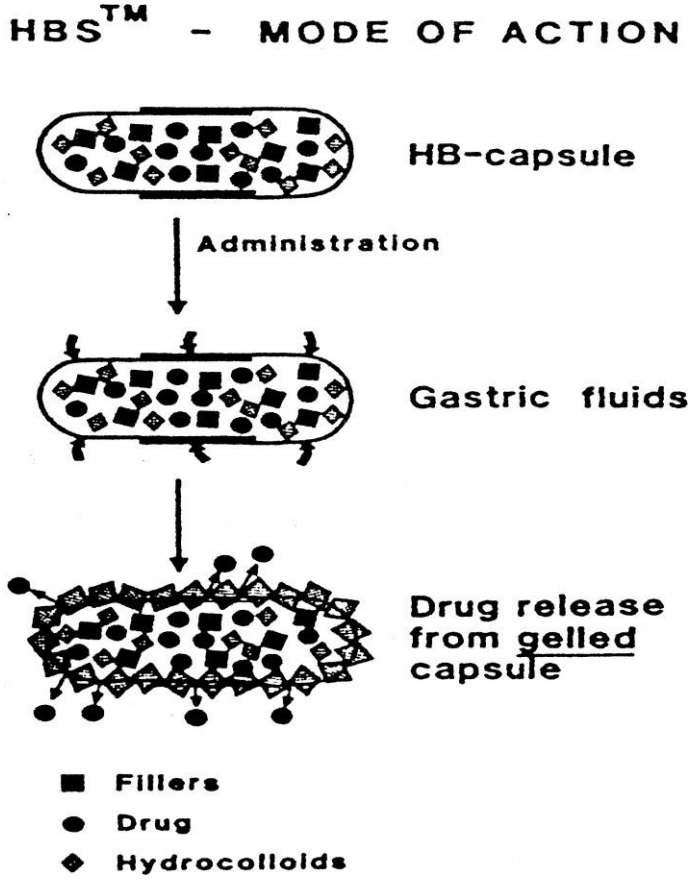


Fig.8 Working principle of the hydro dynamically balanced system within the gel structure.

B. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc

oxide,titanium dioxide and iron powder, etc. These materials increase density by up to 1.5– 2.4g/cm-3.[2,3,24,34].

Brand name	**Drug (dose)**
Madopar	Levodopa (100 mg) Benserazide (25 mg)
Valrelease	Diazepam (15 mg)
Liquid Gaviscon	Al-hydroxide (95 mg) Mg carbonate (385 mg)
Topalkin	Al-Mg antacid
AlgamateFlatcoat	Al-Mg antacid
Conviron	Ferrous sulfate
Cifran OD	Ciprofloxacin (1 g)
Cytotec	Misoprostal(100 mcg/200 mcg)

TableNo.2 Marketed products of FDDS

Advantages of Floating drug delivery system

1. The gastro retentive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circ-umstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I.tract.
2. These systems require a high level of fluid in the stomach for drug deliveryto float and work efficiently-coat,water.
3. The drugs that are significantly absorbed through out gastro intestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.
5. The dosage form should be administered with a glass of water(2oo-250ml).[4]

Applications of Floating Drug Delivery Systems:-

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 forms at the site of absorption and thus enhances the Bioavailability. These are summarized as follows.

1.Sustained Drug Delivery: Sustained drug absorption from oral controlled release dosage form is often limited due to short gastric retention time. However, GFDDS remain in the stomach for several hours to their increased GRT (table 1.2). it has been suggested that due to their low density than their gastric contents and relatively large size they do

not pass through the pylorus that has an opening of approximately 0.9- 1.9cm54-57. It has been observed that major portion of drug releases in the colon rather than the stomach in case of modified release capsule. However, prolongation in the GRT may sustain the drug –releasebehavior.

2.Site Specific Drug Delivery: Drugs having absorption sites in the upper small intestine like furosemide and riboflavin are typically formulated In the floating dosage forms. It has been reported that absorption of furosemide takes place mainly through stomach followed by duodenum. This characteristics of furosemide prompted scientists to develop a monolithic floating system, which could prolong the GRT and thereby increase the Bioavailability. GFDDS serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted. A bilayer-floating capsule has been developed for local delivery of misoprostol to their gastric mucosa for prevention of gastric ulcers caused by non- steroidal anti-inflammatory drugs (NSAIDs.). Mechanistically, the drug replenishes the GI-protective prostaglandins that are depleted by NSAIDs. Therefore, sustained ad controlled delivery of misoprostol to the stomach provides sufficient local therapeutic levels vis-a-via exposure to the drug. This in turn reduces the side effects caused by the presence of the drug in systematic circulation (uterotonic activity) and also retards diarrhea. Which is the result of combination of intestinal and systematic exposure of drug. Moreover, the prolonged gastric availability of the miso prostol from FDDS also reduces the dosing frequency. 5-

Fluorouracil bearing floating tablets have be successfully evaluated in four patients with stomach neoplasms.

3.Absorption or Bioavailability Enhancement:- Drugs that have poor Bioavailability because of site-specific absorption from the upper part of the gastrointestinaltractarepotentialcandidatestobeformulatedasfloatingdrug delivery systems, thereby maximizing their absorption. A significant increase in the Bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%).[4]

Evaluation of FDDS

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37 C. in practice, floating time is determined by using the USP disintegration apparatus containing 900 ml of 0.1 N HCL as a testing medium maintained at 37 C. The time required to float the DF is noted as floatation time. Burns et al developed and validated an *in vitro* dissolution method for a floating dosage form, which had both rapid release and S R properties. The method, although based on the standard BP (1993)/ USP (1990) apparatus 2 methods, was modified such that paddle blades were positioned at the surface of the dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic release dissolution profiles when paddle speeds were increased form 70 to 100 rpm and the dissolution medium pH was varied (6.0-8.0). The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased form 7 to 14 mm. The specific gravity of FDDS can be determined by the displacement method using analytical grade benzene as a displacing medium.

The system to check continuous floating behavior contains a stainless steel basket connected to a metal string and suspended from Sartorius electronic balance. The floating object is immersed at affixed depth into a water bath, which is covered to

prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an online PC through RS232^{0}C inter phase using a sarto wedge program. A lotus spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37 C, data was collected at 30 sec interval; baseline was recorded and subtracted form each measurement. Dissolution basket had a holder at the bottom to measure the downward force.

γ-Scintigraphy

γ-Emitting radioisotopes compounded into CR-DFs has become the state of art for evaluation of gastro retentive formulation in healthy volunteers. A small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of γ-Scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique then the complicated and expensive preparation of radiopharmaceuticals.

Radiology

This method if the state of art in preclinical evaluation of gastro retentivity. Its major advantages as compared to γ-Scintigraphy are simplicity and cost. However, use of X-ray is declined due to strict limitations, regarding the amount of exposure and its often requirement in high quantity. A commonly used contrast agent is barium sulphate.

Gastroscopy

It comprises of perusal endoscopy, used with a fibrotic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.

Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs do not sharp acoustic mismatches across their interface with the physiological milieu. Therefore, ultra sonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intra gastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

Magnetic resonance imaging (MRI)

In the last couple of years, MRI was shown to be valuable tool in gastrointestinal research for the analysis of gastric emptying, motility and intra gastric distribution of macronutrients and drug models. The advantages of MRI include high soft tissue contrast, high temporal and spatial resolution, as well as the lack of ionizing irradiation. Also, harmless paramagnetic and supra magnetic MR imaging contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study oforgans.[9]

2. AIM AND OBJECTIVES

The aim of the proposed research work is to formulation and evaluation of Norfloxacin gastric floating drug delivery system.

There are different types of dosage forms, which are being administered through different routes. However oral route is the most preferred route of administration because of its patient compliance. Now a days oral controlled systems are designed offering a number of advantages including improvement in patient compliance, therapeutic efficacy and safety. Decreased side effects and reduced dosing frequency. Majority of the drugs are having site-specific absorption In the G.I. tract and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I. tract. Influence such absorption. Gastric retention time is one of the important factors, which adversely affect the performance of these drugs when administered simply by an oral controlled drug delivery system.

Norfloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops DNA and protein synthesis. it is a potential drug in treating various serious G.I diseases like gastritis, urinary tract infections, prostatitis and gonorrhea etc.

The half-life following a single oral dose is 4 hrs. The success of a therapy depends on selection of the appropriate delivery system and the drug. Controlled release dosage forms are designed to complement the pharmaceutical activity of a medicament in order to achieve better selectivity and longer duration of action. Thus, Norofloxacin is chosen as a suitable candidate for controlled release drug delivery system.

The aim of the study was to design and evaluate floating drug delivery system of Norfloxacin which may facilitate the following expectations.

- Improve the bioavailability of the drug.
- To increase the effectiveness in therapy.
- Reduction of dosing frequency.
- To improve patient compliance.
- To maintain plasma concentration of drug in therapeutic range for longer time.

3. REVIEW OFLITERATURE

C. Sauzet, et al.[10]developed an innovative floating gastro retentive dosage form (GRDF). The developed technology induces a low-density dosage form containing high active pharmaceutical ingredient (API) concentration by using a hydrophobic dusty powder excipient under specific conditions. The new dosage form was obtained by state of the art wet granulation manufacturing process. An experimental design using a discrete variable and four mixture variables was conducted in order to optimize API concentration and buoyancy of the new dosage form. An apparatus was developed to measure the apparent density of floating tablet. The GRDF was characterized for apparent density, buoyancy, porosity and dissolution using in vitro experimentations.

Ammon Hoffman, et al**.**[11]reported the studies on pharmacokinetic and pharmaco-dynamic aspects of gastro retentive dosage forms. These dosage forms provided continuous input of the drug to the upper parts of the gastro intestinal tract and improved the bio-availability of the drugs with narrow absorption window. They found that a controlled release gastro retentive dosage form (CR-GRDF) formulations was superior to the other models of administration for the studied drugs, levodopa and riboflavin but not formetformin.

Baumgartnar, et al.[12] developed a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to becomebuoyant.

Rameshbomma,etal.[13]developedfloatingmatrixtabletsofnorfloxacintoprolong gastric residence time, leading to an increase in drug bioavailability. Tablets were preparedbythewetgranulationtechnique,usingpolymerssuchashydroxypropyl

methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum. Tablets were evaluated for their physical characteristics, *viz*., hardness, thickness, friability, and mass variation, drug content and floating properties. Further, tablets were studied for *in vitro* drug release characteristics for 9 hours. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. The best formulation (F4) was selected based on *in vitro* characteristics and was used *in vivo* radiographic studies by incorporating BaSO4. These studies revealed that the tablets remained in the stomach for 180 ± 30 min in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs.

Talwar, et al.[14] developed a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The viscolysing agent initially and the gel-forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporaldelivery).

JaleshVarshosaz, et al. [15] prepared floating-bioadhesive tablets to lengthen the stay of drug in its absorption area. Effervescent tablets were made using sodium carboxy methyl cellulose,(CMC), HPMC, polyacrylic acid (AA), polymetacrylic acid (MAA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had longer lag time than 10%. The type of polymer had no significant effect on the floating lag time. All tablets floated atop the medium for 23-24 hr. Increasing CMC caused higher mucoadhesion that AA ($p < 0.05$). All formulations showed a Higuchi, non-

fickian release mechanism. Tablets with 10% effervescent base, 80% CMC/20% HPMC, or 80% AA /20% MAA seemed desirable

ZiyaurRahman, et al.[16] developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and *in vitro* dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h *in vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45°C/75% RH for three months. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for *in vivo* X-ray studies showed that BFT had significantly increased the gastric residencetime.

Whitehead L., et al.[17] performed an *in vivo* study demonstrating prolonged gastric retention of floating dosage forms. They compared *in vivo* behaviour of multiple unit dosage form (FDF) to a multiple unit non-floating dosage from manufactured from identical material. The result suggests that, in the fed state, this FDF has potential for sustained drug delivery for either local or systemic purposes.

Mahesh Chavanpatil, et al.[18] Reported that psyllium husk with HPMC K100M increases the dimensional stability of the formulations, which is necessary in case of once daily formulations. Sodium bicarbonate acts as a gas-generating agent, which is necessary in case of gastroretentive dosage forms. Crosspovidone improved the drug

release profile and swelling factor of psyllium husk based formulations, they also concluded that channeling agents, such as betacyclodextrin are useful to increase the initial burst release from psyllium husk based formulations. The optimized formulation was found to be stable at all the stability conditions. Based on the *in vivo* performance in a parallel study design in healthy subjects, the developed formulation shows promise to be bioequivalent to the marketed product of ofloxacin (Zanocin) **Brijesh S. Dave,** et al.[19] prepared a gastro retentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxyl propyl methylcellulose were evaluated 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 3^2 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 variables. The times required for 50% (t50) and 80% drug dissolution (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 gastro retentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. **Shoufeng Li,** et al.[20] reported the effect of HPMC and carbopol 934 on the calcium release and floating properties of Gastric Floating Drug Delivery system using 2 x 3 factorial design. A decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K 100 LV) was shown to be beneficial than higher viscosity polymer (K4M) in improving floating properties

ofGFDDS.

Srivastava AK, et al.[21] worked on the design and *in vitro* evaluation of atenolol floating drug delivery system. Floating matrix tablets of atenolol were formulated using different polymers like HPMC (K4M and K15M), guar gum and sodium carboxy methylcellulose (CMC) alone and in combination. The effect of gas generating agent, on floating capacities and drug release pattern was also studied. They found gas generating agent decrease lag time but increased the drug release rate. **Sanford Bolton** et al.[22] formulated novel floating controlled release drug delivery system with an effort to increase the gastric retention time of dosage form and to control the drug release. Theophylline (300 mg) floating tablets were formulated using a mineral oil and agar and radiolabeled floating tablets were prepared by adding radiolabeled indium III with the same constituents and only the radiolabeled tablets were dip coated to retain the marker within the tablet and the *in vitro- in vivo* release rate were compared with Theodur (Key Pharma). The buoyancy was attributed to air and oil entrapped in the agar gel network. The *in vitro* release rate of the floating tablet was slower. Bio availability studies in human volunteers under both fasting and non-fasting conditions showed results comparable to those with Theodur. The floating controlled release theophylline tablet maintained constant theophylline levels of about 2 mg/ml for 24 hours, which may be attributable to the release from the agar gel matrix and the buoyancy of the tablet in thestomach.

Gan Lin Chen et al.[23] have formulated floating sustained release capsules of verapamil using HPMC and HPMC-K15M. The effect of weight filled in the capsules, amount of HPMC, addition of effervescent on the dissolution kinetics were studied. The conventional capsules were filled with verpamil, HPC and effervescent. The release of verapamil from the capsules followed the Higuchi release model.

However, when effervescent was added, a zero -order drug release was observed after a burst phase, entrapped air was considered as a barrier to diffusion and matrix relaxation in drug release.

Rajeev Garg, et al. [24]preparaed and evaluated floating tablets of Silymarin as model drug for prolongation of gastric residence time. Floating effervescent tablets were formulated by various materials like hydroxypropyl methylcellulose (HPMC) K 4M, K 15M, psyllium husk, swelling agent as crospovidone and microcrystalline cellulose and gas generating agent like sodium bicarbonate and citric acid and evaluated for floating properties, swelling characteristics and *in vitro* drug release studies. Floating noneffervescent tablets were prepared by polypropylene foam powder and different matrix forming polymers like HPMC K 4M, Carbopol 934P, xanthan gum and sodium alginate. *In vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsemeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations. The developed floating tablets of Silymarin may be used in clinic for prolonged drug release for at least 24 h, thereby improving the bioavailability and patientcompliance.

Rajendrajangde, et al.[25]developed a oral delivery of NSAID nimesulide by using a non-disintegrating floating dosage form which can increases its absorption in the stomach by increases in the drugs gastric residence time. The polymer used were HPMC (low and High viscosity), gaur gum, carbapol along with sodium bicarbonate as the gas generating agents. The prepared tablets were evaluated for physicochemical properties and drug release. *In vitro* release studies indicated that the nimesulide release form the floating dosage form was uniform and followed zero order release. The incorporation of guargum helps to maintain the devices integrity

due toits viscosity property also affect the drugs release profile. Sodium bicarbonate which was used as the gas generating agents causes the tablets to floats the required time>24hr.

Yang, et al.[26] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (Tetracycline, Metronidazole, and Clarithromycin) in *Helicobacter pylori*–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The floating feature aided in prolonging the gastric residence time.

Patel VF, et al.[27] developed Ranitidine floating tablets; in which they optimized types of filler, different viscosity grades of HPMC and its concentration. Two fillers namely Avicel pH 102 and Tablet tose 80 were used. Study revealed that type of filler had significant effect on release of drug from hydrophilic matrix tablets (f2 value 41.30) and floating properties. Three different viscosity grades of HPMC namely K100 LV, K4M and K15M were used. Viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties. The drug release from hydrophilic matrices occurred via diffusion mechanism following square root of time profile (Higuchi equation). Hardness of tablets had greater influence on floating lag time which might be due to decreased porosity. Position of paddle and types of dissolution medium had no significant effect on drug release

Amin AF, et al.[28] developed a gastro retentive drug delivery system of ranitidine hydrochloride was designed using guar gum, xanthan gum, and HPMC. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A

3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine HCl from a gastro retentive formulation.

Nur, et al.[29] developed floating tablets of Captopril using HPMC (4000 and 15000 cps) and carbopol 934P. *In vitro* buoyancy studies revealed that tablets of 2 kg/cm^2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm^2 sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm^2 hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of Captopril was achieved.

Ingani, et al.[30]published works have shown that hydro dynamically balanced systems (HBS) i.e. sustained release oral dosage forms with a specific gravity lower than 1 and remaining buoyant on the gastric juice of the stomach can have an enhanced gastrointestinal transit time. For this investigation, a double-layer sustained release compressed hydrophilic matrix was formulated in order to achieve a foreseeable and reproducible flotation of the tablet. A CO_2 generating blend was, for this purpose, added to one of the layers, this gas being entrapped in the gelified hydrocolloid as liberated by the action of the gastric medium. The *in vivo* behaviour of this floating tablet was then compared to a classical HBS capsule and to a similar but non-floating double-layer hydrophilic matrix on subjects alternatively in fasted or fed state. As these three dosage forms contain a riboflavin (RF) soluble derivative, it was possible

to measure the RF urinary excretion rates and, consequently, to conclude that *in vivo* buoyancy is preponderant over bio adhesion for both floating capsules and tablets. These dosage forms also significantly increase the gastric residence time when compared to the non-floating dosage form. Compared to the classical HBS capsule, the floating tablet is showing *in vivo* equivalent floating properties when administered after a light meal and higher RF urinary excretion rates when administered to fasted subjects.

Sheth, et al**.**[31] developed hydro dynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastricfluids.

Patel VF, et al.[32]developed an intra-gastric drug-delivery system for Cefuroxime axetil. The 3^2 full factorial design was employed to evaluate contribution of hydroxyl propyl methyl cellulose (HPMC) K4M/HPMC K100 LV ratio (polymer blend) and sodium lauryl sulfate (SLS) on drug release from HPMC matrices. Multiple regression analysis was performed for factorial design batches to evaluate the response. All formulations had floating lag times below 2 minutes and constantly floated on dissolution medium for more than 8 hours. It was found that polymer blend and SLS significantly affect the time required for 50% of drug release, percentage drug release at 12 hours, release rate constant, and diffusion exponent (P G .05). Also linear relationships were obtained between the amount of HPMC K100 LV and diffusion exponent as well as release rate constant. Kinetic treatment to dissolution profiles revealed drug release ranges from anomalous transport to case 1

transport, which was mainly dependent on both the independentvariables.

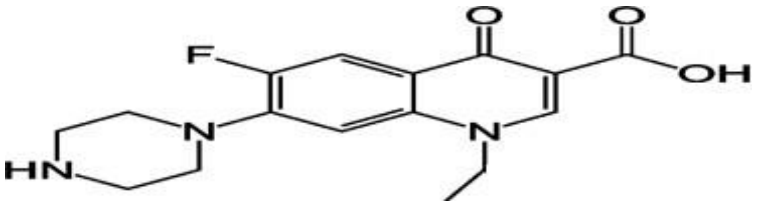
3.1 DRUGPROFILE

3.1.1 NORFLOXACIN[56]

Generic name: Norfloxacin.

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

Structure:



Chemical name: 1-ethyl- 6-fluoro- 4-oxo- 7-piperazin- 1-yl-1-H quinoline-3-carboxylic acid.

Melting point **:** 221.0 ^{0}C. **Molecular**

Formula **:** $C_{16}H_{18}FN_3O_3$

Molecular mass **:** 319.331g/mol.

Physical state: Norfloxacin is a white to pale yellow crystalline powder. Its empirical formula is$C_{16}H_{18}FN_3O_3$.

Dose **:** Orally 200-800mg twice daily.

Solubility: It is freely soluble in 0.1N Hcl and glacial acetic acid and very slightly soluble in ethanol and methanol and water.

Storage: Norfloxacin store at $25^{0}(77^{0}F)$ in a tightly closed container.

Category: Antibacterial (Fluroquinolones)

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

This mechanism can also affect mammalian cell replication. In particular, some congeners of this drug family (for example those that contain the C-8 fluorine) display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and *in vivo* tumor models. Although quinolones are highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is not known. Quinolone induced DNA damage was first reported in1986.

Recent studies have demonstrated a correlation between mammalian cell cytotoxicity of the quinolones and the induction of micronuclei. As such some fluoroquinolones may cause injury to the chromosome of eukaryotic cells. There continues to be debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe adverse reactions experienced by some patients following fluoroquinolone therapy.

Pharmacokinetics

Norfloxacin is rapidly absorbed orally, but food delays absorption, and first pass metabolism occurs. It is excreted primarily in urine, both by glomerular filtration and tubular secretion

TABLE NO: 3

1.	C max(mg/lit)	0.44
2.	T_{max}	0.15(h)
3.	Oral bioavailability	30 to 40
4.	Plasma protein binding is	10-15%
5.	Volume of distribution (L/kg)is	3-4
6.	Percent metabolized is about	20
7.	Elimination half-life	3-4hrs
8.	Routesofadministration	oral and iv

Contraindications

- Norfloxacin is also now considered to be contraindicated for the treatment of certain sexually transmitted diseases by some experts due to bacterial resistance. There are only three contraindications found within the 2008 package insert. Co administration of norfloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co administered drug.
- Concomitant administration with tizanidine is contraindicated.
- Norfloxacin is contraindicated in persons with a history of hypersensitivity to tendinitis, any member of the quinolone class of antimicrobial agents, or any of the product component.

Pregnancy

The fluoroquinolones rapidly cross the blood-placenta and blood-milk barriers,andareextensivelydistributedintothefetaltissues.Forthisreason,the

fluoroquinolones are contraindicated during pregnancy due to the risk of spontaneous abortions and birth defects. The fluoroquinolones have also been reported as being present in the mother's milk and are passed on to the nursing child, which may increases the risk of the child suffering from this syndrome as well, even though the child had never been prescribed or taken any of the drugs found within this class.

Pediatric population

Fluoroquinolones are not licensed by the U.S. FDA for use in children due to the risk of fatalities as well as permanent injury to the musculoskeletal system, with two exceptions. Norfloxacin is being licensed for the treatment of complicated urinary tract infections and pyelonephritis due to Escherichia coli, and inhalational anthrax (post exposure), and levofloxacin was recently licensed for the treatment of inhalational anthrax (post exposure). However, the fluoroquinolones are licensed to treat lower respiratory infections in children with cystic fibrosis in the UK.

Adverse effects

Serious adverse events occur more commonly with fluoroquinolones than With any other antibiotic drug classes. In most, adverse reactions are mild to moderate; however, occasionally serious adverse effects occur, regarding peripheral neuropathy (irreversible nerve damage), tendon damage, heart problems (prolonged QT Interval /torsades de pointes), pseudo membranous colitis, rhabdomyolysis (musle break down),Stevens Johnson syndrome, as well as concurrent usage of NSAIDs contributing to the severity of these reactions.

Significant drug interactions

Norfloxacin can alter and be altered by the metabolism and effects of other drugs, resulting in some significant drug-drug interactions that may affect the musculoskeletal, central nervous, renal, and other systems. Current or past treatment

with oral corticosteroids is associated with an increased risk of achilles tendon rupture, especially in elderly patients who are also taking the fluoroquinolones, the central nervous system adverse effects, including seizure risk, may be increased when NSAIDs are combined with quinolones. The interaction between quinolones and NSAIDs is important, because it has the potential for considerable CNS toxicity. The mechanism for this interaction is believed to be due to a synergistic increased antagonism of GABA neurotransmission.

Norfloxacin renal clearance may affect other drugs subject to renal clearance or otherwise affecting the kidney. The use of Norfloxacin concomitantly with cyclosporine has also been associated with transient elevations in serum creatinine. Renal tubular transport of methotrexate may be inhibited by concomitant administration of Norfloxacin, potentially leading to increased plasma levels of methotrexate and risk of methotrexate toxicity. Probenecid interferes with renal tubular secretion of Norfloxacin and produces an increase in the level of Norfloxacin in serum.Some quinolones, including Norfloxacin, exert an inhibitory effect on the cytochrome P-450 enzyme CYP1A2, thereby reducing clearance, and thus increasing blood levels of tizanidine and methylxanthines (e.g., theophylline and caffeine). The quinolones have also been reported to enhance the effects of warfarin or its derivatives. Such interactions can augment the effects of the co-administered drug,including adverse effects. Norfloxacin can reduce effects of other drugs; for example, it has been shown to interact with thyroid medications (levothyroxine), resulting in unexplained hypothyroidism. Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant Norfloxacin.

Overdose

Overdose of Norfloxacin may result in reversible renal toxicity. Treatment of overdose includes emptying of the stomach via induced vomiting or by gastric lavage. Careful monitoring and supportive treatment, monitoring of renal function and maintaining adequate hydration is recommended by the manufacturer. Administr ation of magnesium, aluminum, or calcium containing antacids can reduce the absorption of Norfloxacin.

3.1 POLYMER REVIEW

3.1.1 Guar Gum Non proprietary names:

BP: Guar galactomannanPhEur: Guar galactomannanum USPNF: Guar gum.[57]**Regulatorystatus**

GRAS listed. Accepted as a food additive in Europe.Included in the FDA. Inactive ingredients guide (oral suspensions, syrups, and tablets; topical preparation, vaginal tablets). Included in nonparental medicines licensed in UK.

Synonyms

E412; Galactosol; guar flour; jaguar gum; Meyprogat; Meyprodor; Meyprofin.

Chemical name and CAS number

Galactomannan polysaccharide [9000-30-0]

Molecular formula:

$(C_6H_{12}O_6)_n$ _220 000

.

Structure formula:

Guar gum consists of linear chains of (1!4)-b-D-mannopyranosyl units with a D-galactopyranosyl units attached by (1!6) linkages. The ratio of D-galactose to D-mannose is between 1 : 1.4 and 1 : 2

Description: Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

Typical Properties

- Sulphated ash:<1.5%
- Density : 1.492g/cm3
- Solubility: practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol
- Viscosity: 4.86 Pa s (4860 cP) for a 1% w/v dispersion.
- Solubility and storage condition: Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.
- Guar gum powder should be stored in a well-closed container in a cool, dry place.
- The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methyl paraben and 0.02% propyl paraben as a preservative

Safety

Guar gum is widely used in foods and oral and topical pharmaceutical formulations.

LD_{50} (hamster, oral): 6.0 g/kg LD_{50} (mouse, oral): 8.1 g/kg

LD_{50} (rabbit, oral): 7.0 g/kg LD_{50} (rat, oral): 6.77 g/kg

Functional category

Suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent

Application in pharmaceutical formulation or technology .

- Guar gum is widely used in oral and topical pharmaceutical formulations. 2). In pharmaceuticals, guar gum is used in solid-dosage forms as a binderand
- Disintegrant
- Concentration up to 10 %w/w is used as tablet binder.
- Guar gum is used as a suspending and thickening and stabilizing agent in inoral and topicalformulations.
- Guar gum is commonly used in cosmetics, food products, and pharmaceutical Formulations
- It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose.
- Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus.

3.1.2 Carboxy Methyl Cellulose Sodium[57] Nonproprietary Names

BP: Carmellose sodium JP: Carmellose sodium PhEur: Carmellosumnatricum USP: Carboxymethylcellulose sodium

Synonyms

Akucell ; Aquasorb ; Blanose ; cellulose gum; CMC sodium; E466; Finnfix ; Nymcel; SCMC; sodium carboxymethylcellu- lose; sodium cellulose glycolate; sodium CMC; Tylose CB .

Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt

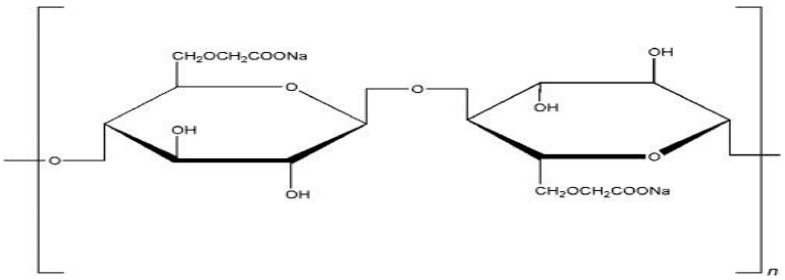
Empirical Formula and Molecular Weight

The USP 28 describes carboxy methyl cellulose sodium as the sodium salt of a poly carboxy methyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Functional Category

Coating agen; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbingagent.

Structural formula



Description

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder.

Solubility:

Practically insoluble in acetone, ethanol (95%), ether, and toluene.Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution

Viscosity:

Various grades of carboxy methyl cellulose sodium are commercially available that have differing aqueous viscosities; see Table III. Aqueous 1% w/v solutions with viscosities of 5–13 000 mPa s (5–13 000 cP) may be obtained.An

increase in concentration results in an increase in aqueous solution viscosity. Prolonged heating at high temperatures will de polymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxy- methylcellulose solutions is fairly stable over a p H range of 4–10. The optimum pH range is neutral.

Applications in Pharmaceutical Formulation or Technology

Carboxy methyl cellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration. Carboxy methyl cellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions. Higher concentrations, usually 3–6%, of the medium viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxy methyl cellulose sodium is additionally one of the main ingredients of self- adhesive ostomy, wound care, and dermatological patches, where it is used as a muco adhesive and to absorb wound exudate or trans epidermal water and sweat. This muco adhesive property is used in products designed to prevent post-surgical tissue adhesions; and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxy methylcellulose sodium can affect drug protection and delivery. There have also been reports of its use as a cyto-protective agent. Carboxy methyl cellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

Stability and Storage Conditions

Carboxy methyl cellulose sodium is a stable, though hygroscopic material. Under high-humidity conditions, carboxy methyl- cellulose sodium can absorb a large quantity (>50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time. Aqueous solutions are stable at pH 2– 10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9. Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative. The bulk material should be stored in a well-closed container in a cool, dry place.

3.1.3 Hydroxy Propyl Methyl Cellulose Non proprietary Names

- BP:Hypromellose
- JP:Hydroxypropylmethylcellulose[57]
- PhEur:Hypromellosum
- USP:Hypromellose

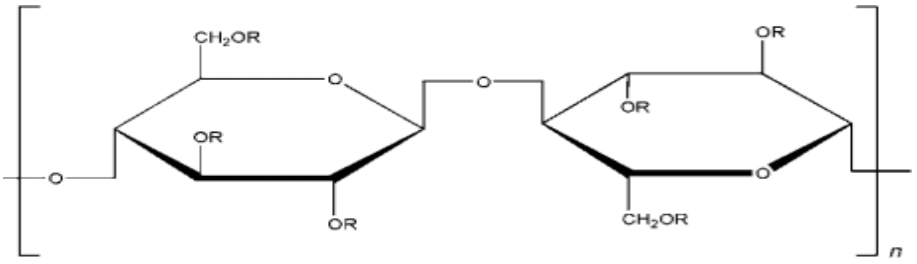
Synonyms

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

Chemical Name and CAS Registry Number:

Cellulose hydroxypropyl methyl ether [9004-65-3]

Structure



Empirical Formula and Molecular Weigh

The PhEur 2005 describes hypromellose as a partly O methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 208^0C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types ofhypromellose.

Molecular weight is approximately 10 000–1 500 000 daltons.

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; 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 a matrix for use in extended-release tablet formulations.
- Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to

retard

- The release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.
- ower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include Any Coat C, Spectracel, andPharmacoat.
- Hypromellose is also used as a suspending and thickening agent in topical formulations.Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity,
- With fewer un dispersed fibers present, and is therefore preferred in formulations for ophthalmic use.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Hypro mellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
- As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.
- It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or

granular powder.

Typical Properties

Acidity/alkalinity : pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash : 1.5–3.0%, depending upon the grade and viscosity. Auto ignition temp :3608^{0}C

Density(bulk) : 0.341 g/cm3

Density(tapped) : 0.557 g/cm3

Density(true) : 1.326g/cm3

Melting point : browns at 190–200^{0}C;

chars at 225–230^{8}C.

Glass transition temp :170–180^{0}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 soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and 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.

Specific gravity: 1.26

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.

- Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.
- To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90^{0}C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.
- When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

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^{0}C, depending upon the grade and concentration of material.
- Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.
- However, aqueous solutions are liable to microbial spoilage and should be

preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chlorideis commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

- Hypromellose powder should be stored in a well-closed container, in a cool, dryplace.

Incompatibilities

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

Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard tohealth.

LD_{50} (mouse, IP): 5g/kg LD_{50} (rat, IP): 5.2g/kg

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended.

Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combust

4.MATERIAL AND METHODS

4.1.MATERIALS

Table 4.LIST OF MATERIALS USED

S.No	Material
1	Norfloxacin (Gift sample of M/s. Micro Labs, Bangalore)
2	Guar gum, HPMC K15M, (Ontop pharmaceuticals, Bangalore)
3	Sodium CMC (Ontop pharmaceuticals, Bangalore)
4	Sodium bicarbonate (S.D fine chemicals, Mumbai)
5.	Lactose, PVP K30 (S.D fine chemicals, Mumbai)
6.	Magnesium stearate (S.D fine chemicals, Mumbai)
7.	Hydrochloric acid Qualigens Fine Chemicals
8.	Talc (S.D fine chemicals, Mumbai)
9	Distilled water

Table 5. LIST OF INSTRUMENTS USED

S.No	Instrument
1	Electronic Weighing Balance (A W 120, Shimadzu Corporation, Japan)
2	Tablet compression machine (Cadmach, Ahmedabad, India)
3	Tablet Dissolution Tester (Electro lab TDT- 08L, Mumbai, India)
4	UV/visible double beam Spectrophotometer (Systronics, Ahmedabad, India)
5	Friability test apparatus (INCO Instruments and chemicals Pvt Ltd, Ambala city, India)
6	pH meter L I 120 (Elico India Pvt Ltd, Hyderabad, India)
7	Monsanto Tablet Hardness Tester
8	Screw guage
9	FTIR spectrophotometer(Shimadzu corporation),Japan.

4.1.METHODS:

4.2.1. a) Analysis of Excipients used in the formulation:

The following excipients, guar gum, sodium CMC, HPMC K15M as polymers and PVP K30 as binder and co-polymer, Sodium bicarbonate as effervescent mixture, Magnesium Stearate as lubricant, Talc as glidant are selected for formulating GFDDS and these have been evaluated and analyzed for the physico- chemical characters.

b) Analysis of the Model Drug

a) Description: Drug was observed for its general appearance.

b) Melting point: Melting point was determined using melting point apparatus.

c) UV Spectroscopy: A stock solution of Norfloxacin (100 µg/ml) was prepared in 0.1N HCl. Then UV spectrum was scanned in the range of 278 nm using Shimadzu1700.

d) IR Spectroscopy: IR spectroscopy study was carried to assess the compatibility between Norfloxacin and polymer guar gum, sodium CMC, HPMC K15 M. The pure drug and drug with excipients were separately scanned. The pellets were prepared on potassium bromide press. Both the spectra were compared for confirmation of peaks. The Norfloxacin spectra and spectra data were shown in the **Figure.no10-12**.

C) Standard curve of Norfloxacin:

A stock solution of Norfloxacin (100 µg/ml) was prepared in 0.1N HCL. The UV spectrum was recorded in the range of 278 nm. The solutions of 2 to10 µg/ml were prepared from stock solution by appropriate dilution with 0.1 N HCL. The absorbance of each of solution was recorded using Shimadzu 1700 at wavelength of maximum absorption.

Preparation of pH 1.2 buffer solution (Simulated gastric fluid)

8.5 ml of hydrochloric acid solution was added and made up to the volume to 1000ml.

Primary stock solution

100mg of Norfloxacin was accurately weighed and dissolved in pH 1.2 buffer and then made up to 100ml a concentration of1000µ/ml.

Secondary stock solution

10ml of primary stock solution was diluted with buffer 1.2 pH to get a concentration of100µ/ml.

Sample solution

From the secondary stock solution aliquots ranging from 0.2 to 1ml were pippet out and diluted to 10ml with buffer to get the concentration of 2 to 10µ/ml. The absorbance was measured at 278 nm against blank. A standard graph was plotted by keeping the known concentration on x-axis and obtained absorbance on y-axis.

4.3 FORMULATION:

Preparation: In this work, direct compression method[16] has been employed to prepare HBS of Norfloxacin with guar gum, sodium CMC, hydroxyl propyl methyl cellulose (HPMC)K15M.

Procedure: All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then PVP K 30, Lactose and sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh. Tablets were compressed on a single punch tablet machine (Cadmach, India) using 8 mm flat round punches.

FORMULATION TABLE

Table 6. Composition of Norfloxacin Floating Tablets(mg)

EXCEPIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Norfloxacin	400	400	400	400	400	400	400	400	400
Guar gum	-	-	120	60	-	60	-	80	-
SCMC	-	120	-	-	60	60	80	40	80
HPMC K15M	120	-	-	60	60	-	40	-	40
$NaHCO_3$	100	100	100	100	100	100	100	100	100
PVP-K-30	10	10	10	10	10	10	10	10	10
Lactose	40	40	40	40	40	40	40	40	40
FLT (sec.)	220	165	130	175	420	180	240	180	140
TFT (hrs)	>24	>24	>24	>24	>24	>24	>24	>24	>24

4.4 EVALUATION:

Evaluation of tablets:

Tablets are evaluated for both pre-compression parameters like Angle of repose, flow rate, bulk density, tapped density, Carr's index as well as their post compression parameters like various quality control tests such as tablet thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for GFDDS like floating lag time and total floating time & release rate of drug.

4.4.1. Pre compression Parameters

i). Angle ofRepose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Performed to determine the flow rate of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation: **$\theta = \tan^{-1} (h / r)$**

ii)BulkDensity:

Bulk density was obtained by dividing the mass of powder by the bulk volume in cm ^{3}.The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2- second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by

dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$Df = M / Vp$

Where, Df = bulkdensity

M = weight of sample in grams

Vp = final volume of powder in $cm^{3.}$

ii) Tapped density:

The tapped density was obtained by dividing the mass of powder by tapped volume in cm^3.The sample of about 50 cm^3 of powder, previously been passed through a standard

sieve no.20, is carefully introduced in to a 100 ml graduated cylinder. The cylinder was dropped at 2- second intervals on to hard wood surface three times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

Do = M/Vp

Where, Do = bulk density

M = weight of sample in grams

Vp = final tapped volume of powder in cm^3

iii) Carr's index:

Carr's developed an indirect method of measuring powder flow from bulk densities. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated to equation given below

$$\% \text{ Compressibility} = \frac{Do - Df}{Do} 100$$

Where, Df = Fluff of poured bulk or bulk density Do =

Tapped or consolidated bulk density

4.4.1 Post compression parameters

i) Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Venire calipers.

ii) Hardness:

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at

random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2. The mean values are given in **Table no.11,15&19.**

iii) Friability:

The friability test was carried out to evaluate the hardness and stability instantly. In Roche friabilator in which twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). The percent loss in weight or friability (f) was calculated by the formula given below and the results are given in **Table no.11,15&19**.

$$f = (1-W/Wo) \times 100$$

where f= friability

Wo= initial weight W= final weight

iv) Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the **Table no.2** and none deviate by more than twice the percentage The mean and standard deviation were determined. The results are given **Table no. 11,15&19**.

Table no. 7. IP Standard for Uniformity of weight

Sr no.	**Avg. Wt. Of tablet**	**%of deviation**
1	80 mg or <80	10
2	>80 to <250 mg	7.5
3	>250 or more	5

v) Content Uniformity:

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia .The content uniformity test is mandatory for tablets whose average weight is below 50mg. This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 100 mg of Norfloxacin was dissolved in 0.1 N HCL in 100ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 278 nm using 0.1 N HCL as blank and the % drug content were estimated using the followingformula.

Note: the regression equation for Norfloxacin from standard graph is-

$Y = 0.118x+0.000$

$R^2 = 0.998$

$$\text{Concentration (mcg/ml)} = \frac{\text{Absorbance} - \text{Intercept}}{\text{Slope}}$$

Drug content(mg) = concentration x dilution factor

$$\text{\% Drug content} = \frac{\text{drug content (mg)}}{\text{label claim (-mg)}} \times 100$$

vi) *In vitro* buoyancy determination:

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter'scomplication

4.4.2.vi.1) Floating Lag Time:

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37+_0.5^{o}C, paddle rotation at 50 rpm and 900ml as volume,it is measured using stopwatch. The results are given in **Table no 6.**

vi. 2) Total Floating Time:

The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37+_0.5^{o}C,paddle rotation at 50 rpm ,it is measured using stopwatch.

4.4.3.i) *In vitro* dissolution studies:

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus 2). The stirring rate was 50rpm. 0.1 N hydrochloric acid was used as dissolution medium 900ml and was maintained at 37±0.5^{0}C. Samples of 5ml were withdrawn at predetermined time intervals, filtered

and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Norfloxacin at 278 nm by using a double beam UV spectrophotometer (Shimadzu- 2000). Each dissolution study was performed for three times and the mean values were taken.

4.4.4) Drug Release kinetics:

The analysis of drug release mechanism from the pharmaceutical dosage form is an important but complicated process and it is practically evident in the case of matrix systems. as model-dependent approach, the dissolution data are fitted to four popular release model such as a zero-order, first order, Higuchi and andpeppasequations,which have been described in the literature .The order of drug release from matrix systems was studied by using Higuchi equation and Erosion equation.

1.ZERO ORDER RELEASE KINETICS: It defines a linear relationship between the fractions of drug release vs.times

$$\mathbf{Q=K_0t}$$

Where Q is the fraction of drug release at time t & K0 is the Zero order release rate constant.A plot of fraction of drug release against time will be linear, if the release obeys Zero order release kinetics.

2.FIRST ORDER RELEASE KINETICS:

Assuming that the exposed surface area of a tablet decrease exponentially with time during dissolution process. Suggested that drug release from most of the slow release tablets could be described adequately by apparent first orderkinetics.

The equation that describes First Order Kinetics is **In (1-Q) = -K1t**

Where, Q is the fraction of drug released at time t. And K 1

is the First Order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys First order release kinetics

3.HIGUCHI EQUATION:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the surface root oftime.

$$Q = K^2 \ t^{1/2}$$

Where, K^2 is release rateconstant.

A plot of the fraction of drug released against root of time will the linear if the release obeys Higuchi Equation.This equation describes drug release as a diffusion process based on the Flick's Law. Square root timedependent.

4.EROSION EQUATION:

This equationde fines the drug release based on tablet erosion alone.

$$Q= 1-(1-K3\ t)^3$$

Where, Q is the fraction of drug released at time t,

k3 is the release rate constant. Thus, a plot between [1-(1-Q) 1/3] against time will be linear if the release obeys erosionequation.

5.POWER LAW: (PEPPAS & KORSEMEYER EQUATION):

In order to define a model, which would represent a better fit for the formulation dissolution data was further analyzed by Peppas & Korsem eyer equation **Mt \ M α= K.tn**

Where, Mt is the amount of drug released at time t and M α is the amount released at Time α, thus the Mt \ Mα is the fraction of drug released at time t, K is the kinetic constant and n is the diffusional exponent.

To characterize the mechanism for both solvent penetration and drug

Release n can be used as abstracted .A plot between log of Mt\M α against log of time will be linear if the release obeys Peppas & Korsemeyer equation and the slope of this plot represents n value.

Interpretation of diffusion exponent and solute release mechanism for cylindrical shape release mechanisms from polymeric film.

Table No. 8. Releases kinetics

DIFFUSIONEXPONENT (Release exponent (n))	Overall solute diffusion mechanism (Drug transport mechanism)
0.45 0.5	Fickian diffusionSLAB/CYLINDER
0.45 < n < 0.89 0.5 < n < 1.0	Anomalous(non-fickian)transport SLAB/CYLINDER
0.89 1.0	Case-II SLAB/CYLINDER
n>0.89 n> 1.0	Supercase-IItransport SLAB/CYLINDER

The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n = 1.0 indicate non-fickian mechanism. In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0.This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

4.5 STABILITY STUDIES

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and *in vitro* release rates, that they claim to have at the time of use. A controlled release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the controlled release product useless. The *in vitro* and *in vivo* release rates

of controlled release product may be altered by atmospheric or accelerated conditions such as temperature and humidity.

Definition: Stability is defined as "The capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity" (FDA 1987).

Objective and Purpose:

Most recently a guideline issued by the International Conference on Harmonization (ICH, 1993) indicates that the purpose of stability testing is to provide evidence on how the quality of a drug substance or the drug product varies with time under the influence of variety of environmental factors, such as temperature, humidity and light, and enables recommended storage conditions, retest periods, and shelf life to be established. The purpose of stability study is not only to characterize the degradation of a drug product but also to establish an expiration-dating period or shelf life applicable to all future batches of drugproduct.

Types of stability studies:

Basically, there are two types of stability studies:

- Short –term stabilitystudies
- Long - term stabilitystudies

A typical short-term stability study is an accelerated stability testing study under stressed storage conditions. The purpose of it is not only to determine the rate of chemical and physical reactions but also predict a tentative expiration-dating period under ambient marketing conditions.

The accelerated stability study is useful in following ways:

1. The results provide estimate of the kinetic parameters for the rate of

reactions.

2. The results can be used to characterize the relationship between degradation and storage condition.
3. The results supply critical information in the design and analysis of long-term stability studies under ambient conditions at the planning stage.
4. Long term studies, which include both preapproval and post approval stability studies, are usually conducted under ambient condition.
5. A pre-approval stability study is also known as NDA stability study, the purpose of it is to determine (estimate) a drug expiration dating applicable to all future batches.
6. A post approval stability study is usually referred to as a marketing stability study; the purpose of it is to make sure that the drug product currently on market can meet the USP/NF specifications up to the end of expiration dating period.

Table 9. Conditions according to ICH guidelines

Types	**Conditions**		**Minimum time period at submission (month)**
	Temperature C) (⁰	**Relative humidity (%)**	
Short-term testing	40^0 C $\pm$ 2^0 C	75% $\pm$ 5%RH	6
Long-term testing	25^0 C $\pm$ 2^0 C	60% $\pm$ 5%RH	12

5. Results for Drug Analysis:

The present analytical method obeyed Beer's law in the concentration range 2-10 µg/ml and is suitable for the estimation of Norfloxacin from different solutions. The correlation coefficient (r) was found to be 0.999, indicating a positive correlation between the concentration of Norfloxacin and the corresponding absorbance values.

Table no.10 STANDARD CURVE – IN BUFFER PH 1.2

S.NO	Concentration (µg/ml)	Absorbance at 278 nm	
1.	2	0.242	
2.	4	0.473	
3.	6	0.711	
4.	8	0.946	
5.	10	1.193	

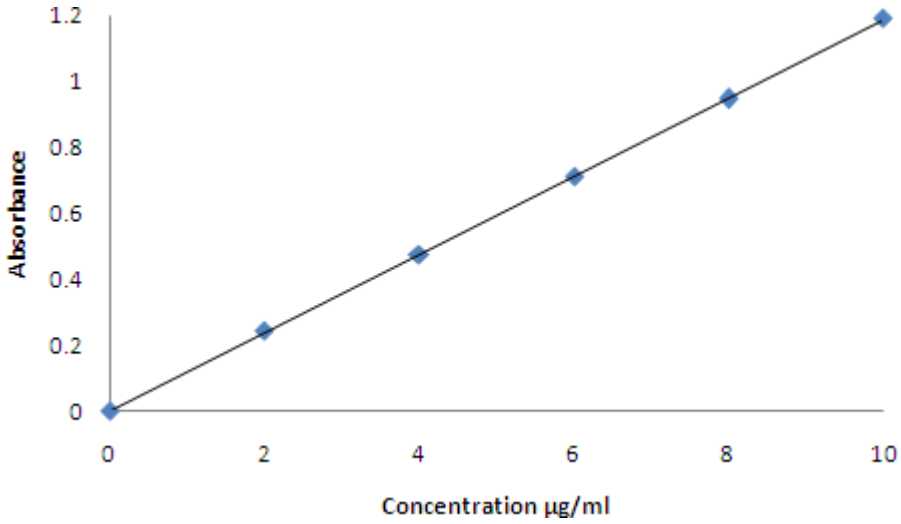


Fig. 9: Standard Calibration curve for Norfloxacin.

5.1 DRUG POLYMER INTERACTION STUDY:

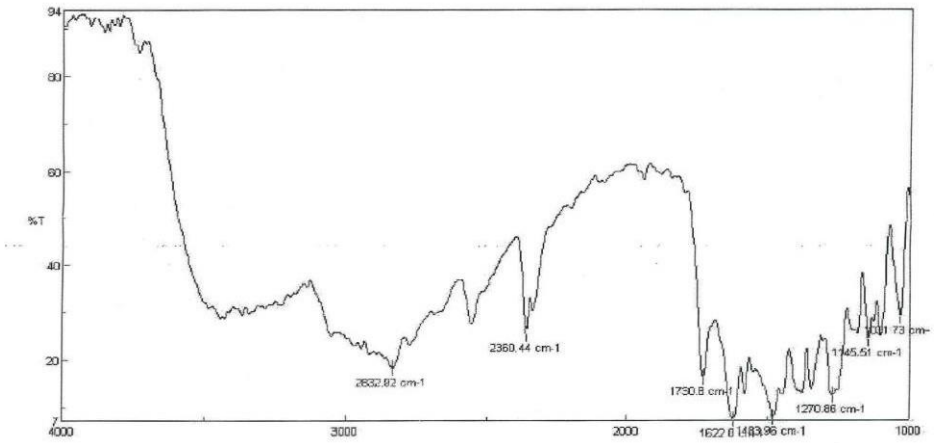


Fig.10: FTIR spctra of Norfloxacin

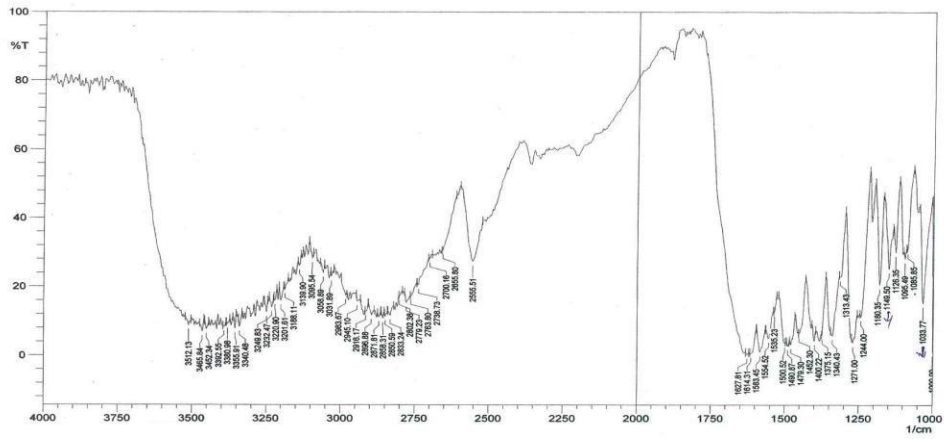


Fig.11: FTIR spctra of Norfloxacin with Guar gum

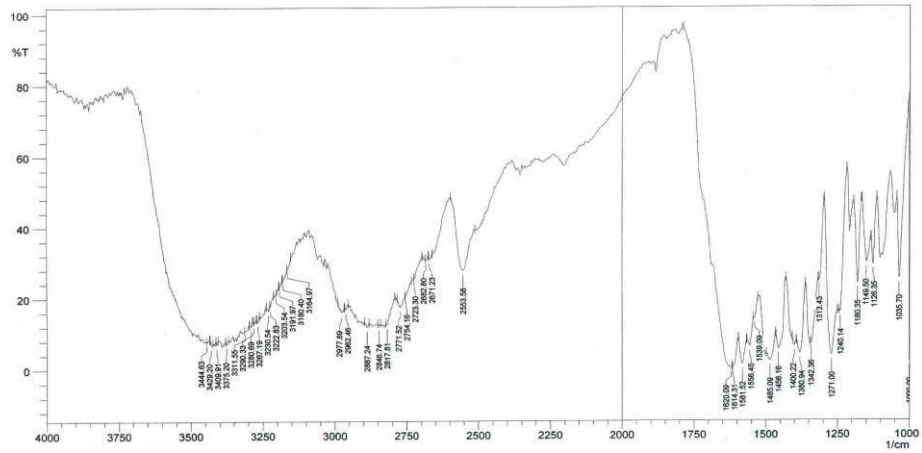


Fig.12: FTIR spctraof Norfloxacin with HPMC K15M

5.3. Formulation F1 to F3 results

Table.no.11. Tabletting Characteristics

Formulation	**Weight[a] (mg)**	**Drugcontent[a](%)**	**Hardness[a] (Kg/cm^2)**	**Friability[b] (%)**
MARKETED	513.00+1.36	98.62+0.18	10.2+0.32	0.06
F1	670.00+1.46	99.24+1.54	5.82+0.49	0.45
F2	670.00+1.28	99.74+0.97	5.14+0.24	0.32
F3	670.00+1.37	99.94+0.48	5.06+0.56	0.26

a: Mean +S.D., n=10tablets **,** **b:** n=10tablets

Table.no.12. Cumulative percent

Time (hrs)	**Cumulative percent (+ S.D.) drug released**			
	MARKETED	**F1**	**F2**	**F3**
1.	19.22±0.48	18.57±0.27	20.02±1.64	14.65±0.10
2.	40.23±1.62	31.75±1.74	26.08±0.53	25.67±0.85
3.	53.8±0.07	50.56±0.87	39.53±0.66	36.75±1.29
4.	66.02±1.67	64.64±0.08	48.58±0.38	45.67±0.17
5.	84.71±1.86	73.3±1.72	59.38±0.45	57.84±0.10
6.	99.72±0.87	84.4±1.55	67.96±0.78	64.65±0.16
7.	--	90.05±2.4	83.42±0.05	69.96±0.94
8.	--	98.31±0.52	89.53±0.75	77.76±1.64
9.	--	--	95.23±0.19	84.48±0.08
10.	--	--	99.12±0.75	91.24±0.71
11.	--	--	--	95.16±0.08
12.	--	--	--	99.37±0.54

Fig.13: *In vitro* release profile of Norfloxacin formulation F1, F2 & F3, with marketed product

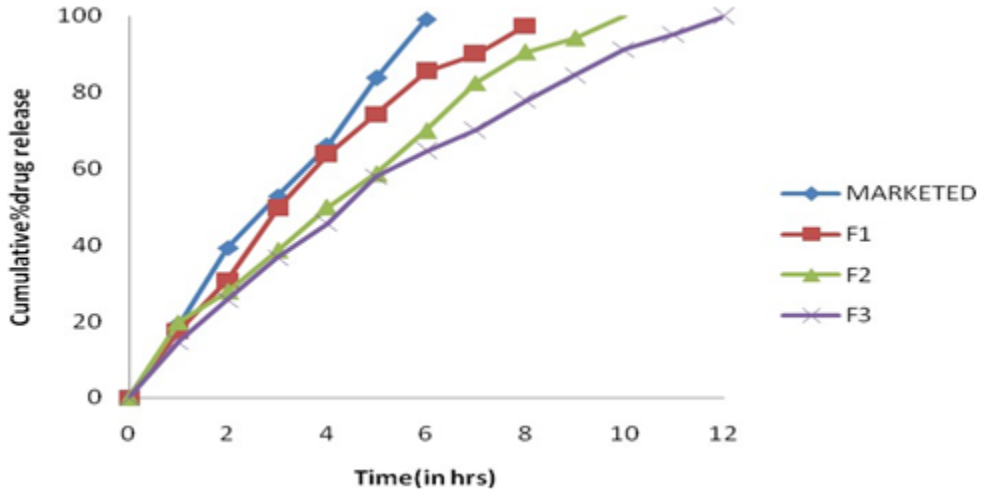


Fig.14: Cumulative percent drug released Vs time plot (Zero Order) for Norfloxacin formulations F1,F2& F3 with marketed product

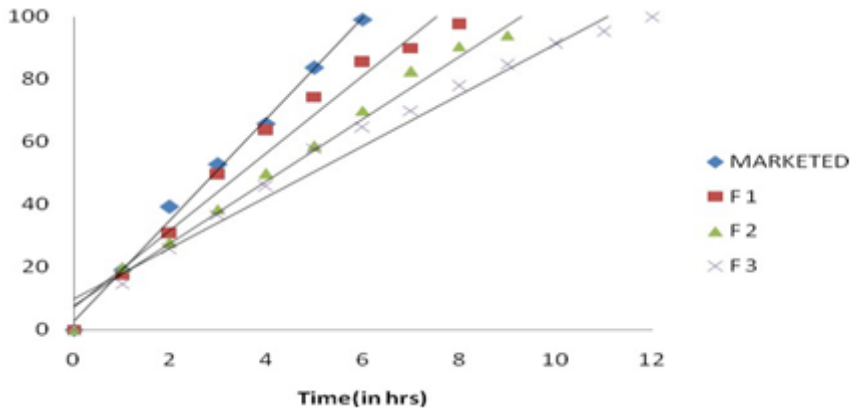


Fig.15: Log Cumulative Percent Drug Remaining Vs Time Plots (First order) for Norfloxacin formulations F1,F2&F3 with marketed product

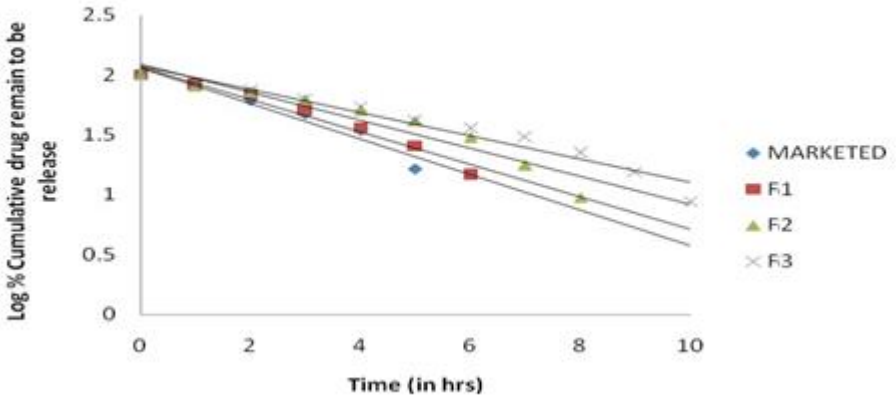


Fig.16: Cumulative percent drug released Vs square root of time (Higuchi's Plot) for formulations F1,F2& F3 with marketed product

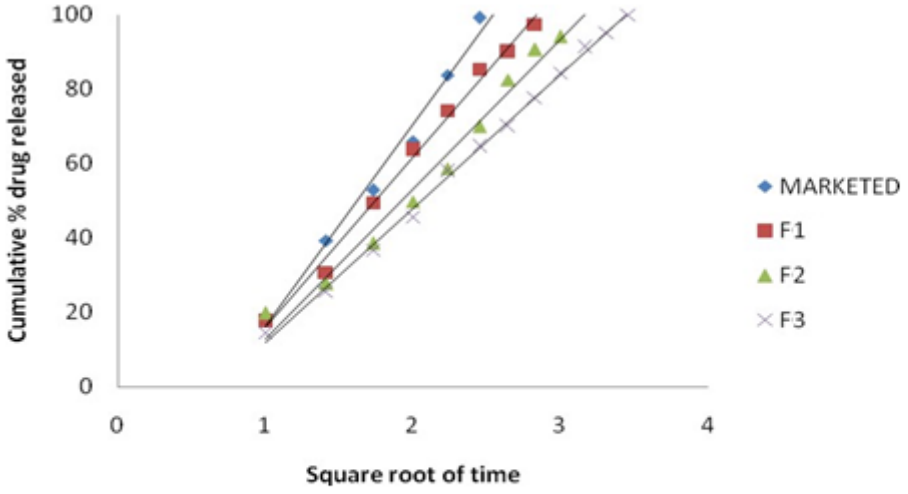


Fig.17: Log Cumulative percent drug released Vs Log time (Peppa's Plot) for formulations F1,F2& F3, with marketed product

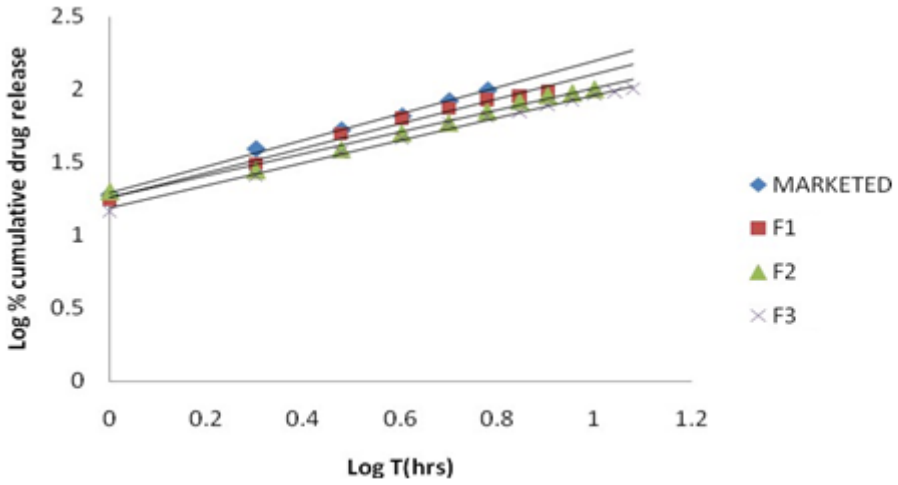


Table.no.13 Correlation coefficients (r values) of release kinetics of F1 to F3

FORMULATION	Zero order	First order	Higuchi Matrix	Peppas	
				r	N
MARKETED	0.996	0.929	0.986	0.996	0.900
F1	0.971	0.911	0.992	0.988	0.751
F2	0.984	0.921	0.983	0.989	0.678
F3	0.975	0.932	0.997	0.995	0.778

Table.no.14 Kinetic parameters

FORMULATION	T_{50}(hrs)
MARKETED	3.18±0.54
F1	3.81±0.125
F2	4.01±0.186
F3	4.56±0.168

$T_{50\%}$: time taken to dissolve 50% of thedrug.

5.4 Formulation F4 to F6 results

Table.no.15. Tabletting Characteristics

Formulation	Weight[a] (mg)	Drugcontent[a](%)	Hardness[a] (Kg/cm^2)	Friability[b] (%)
MARKETED	515.00+1.36	98.62+0.18	10.2+0.32	0.06
F4	670.00+0.56	99.34+0.54	6.02+0.49	0.38
F5	670.00+0.18	99.66+0.86	5.94+0.24	0.30
F6	670.00+0.47	98.25+0.68	5.30+0.56	0.27

a: Mean +S.D., n=10tablets **,** **b:** n=10tablets

Table.no.16 Cumulative percent

Time (hrs)	Cumulative percent (+ S.D.) drug released			
	MARKETED	**F4**	**F5**	**F6**
1.	19.02±0.48	18.7±2.17	17.37±1.64	16.2±2.10
2.	39.23±1.62	36.52±1.74	29.1±0.53	29.6±0.85
3.	52.8±0.07	47.9±0.87	37.09±0.56	35.4±1.09
4.	65.92±1.67	59.67±0.16	48.6±0.28	43.64±0.77
5.	83.71±1.86	72.71±0.22	61.24±0.25	58.4±2.74
6.	99.72±0.87	87.63±0.55	78.24±0.28	65.74±2.16
7.	--	98.54±0.48	83.36±0.98	79.8±1.04
8.	--	--	93.13±0.35	87.26±0.54
9.	--	--	99.15±0.76	92.12±0.83
10.	--	--	--	99.76±0.89

Fig.18: *In vitro* release profile of Norfloxacin formulations F4,F5& F6 With marketed product

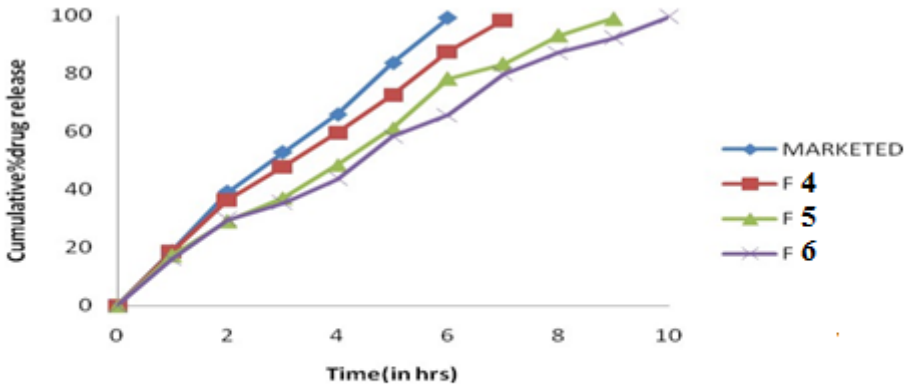


Fig.19: Cumulative percent drug released Vs time plot (Zero Order) for Norfloxacin formulations F4,F5 ,F6 with marketed product

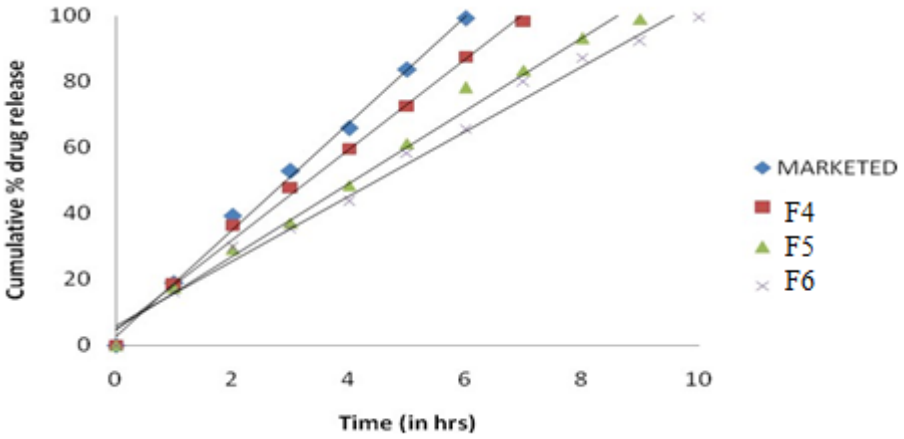


Fig.20: Log Cumulative Percent Drug Remaining Vs Time Plots (First order) for Norfloxacin formulations F4,F5,F6 with marketed product

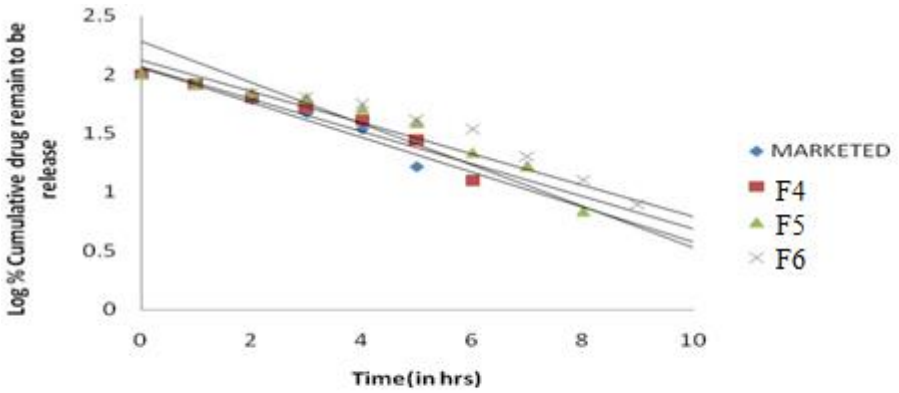


Fig.21: Cumulative percent drug released Vs square root of time (Higuchi's Plot) for formulations F4, F5, F6 with marketed product

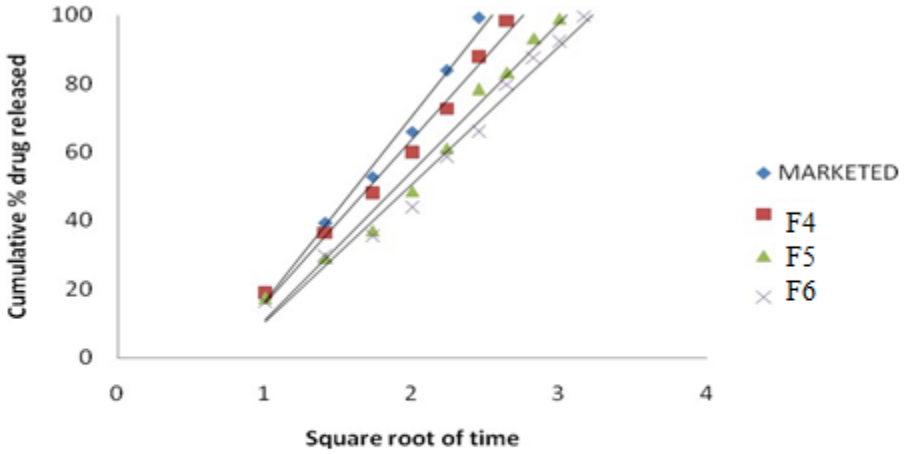


Fig.22: Log Cumulative percent drug released Vs Log time (Peppa's Plot) for formulations F4,F5 ,F6 with marketed product

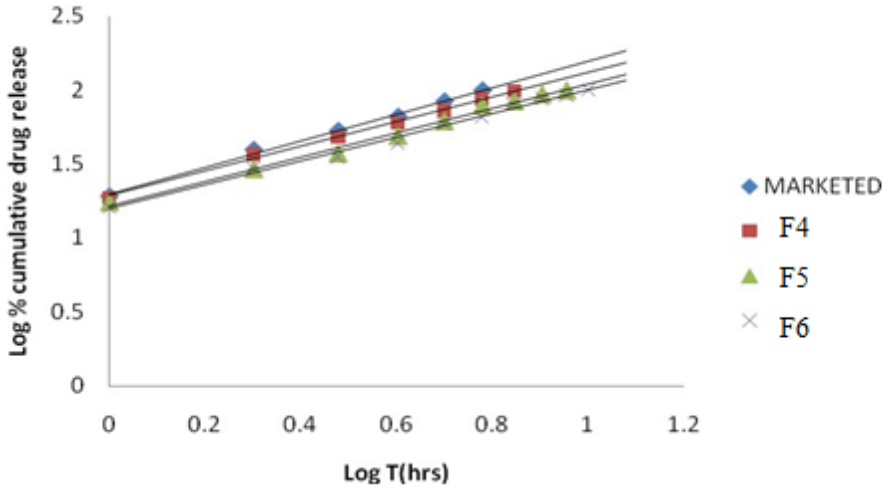


Table.no.17. Correlation coefficients (r values) of release kinetics

FORMULATION	Zero order	First order	Higuchi Matrix	Peppas	
				r	n
MARKETED	0.996	0.929	0.986	0.996	0.900
F4	0.993	0.926	0.987	0.997	0.838
F5	0.989	0.908	0.978	0.991	0.822
F6	0.988	0.735	0.980	0.991	0.799

Table.no.18. Kinetic parameters

FORMULATION	T_{50}(hrs)
MARKETED	3.18±0.54
F4	3.23±0.104
F5	4.23±0.066
F6	4.5±0.168

$T_{50\%}$: time taken to dissolve 50% of thedrug.

5.5. Formulation F7 to F9Results

Table.no.19. Tabletting Characteristics

Formulation	**Weight[a] (mg)**	**Drugcontent[a] (%)**	**Hardness[a] (Kg/cm^2)**	**Friability[b] (%)**
MARKETED	515.00+1.36	98.62+0.18	10.2+0.32	0.06
F7	670.00+1.46	98.67+0.54	6.82+0.49	0.22
F8	670.00+1.28	99.65+0.97	5.14+0.54	0.26
F9	670.00+1.37	98.25+0.58	6.06+0.36	0.31

a: Mean +S.D., n=10tablets **,** **b:** n=10tablets

Table.no.20 Cumulative percent drug release of formulation F7 to F9

Time (hrs)	**Cumulative percent (+ S.D.) drug released**			
	MARKETED	**F7**	**F8**	**F9**
1.	19.02±0.48	18.78±1.29	10.08±1.09	12.45±0.86
2.	39.23±1.62	27.39±0.84	18.37±0.54	19.65±0.43
3.	52.8±0.07	32.61±1.47	27.56±1.45	24.47±0.78
4.	65.92±1.67	41.67±0.98	34.81±0.98	29.69±0.87
5.	83.71±1.86	56.32±0.79	43.95±1.25	36.78±0.19
6.	99.62±0.87	64.98±0.58	55.89±0.78	43.14±2.69
7.	--	72.26±0.4	62.92±0.13	51.74±0.48
8.	--	84.11±0.52	71.13±0.45	63.21±0.94
9.	--	91.35±0.23	80.32±0.19	70.28±0.45
10.	--	99.82±0.45	88.67±2.75	77.93±0.53
11.	--	--	93.73±0.78	83.76±0.17
12.	--	--	99.35±0.01	90.55±0.44

Fig.22: *In vitro* release profile of Norfloxacin formulations F7,F8,F9 with marketed product

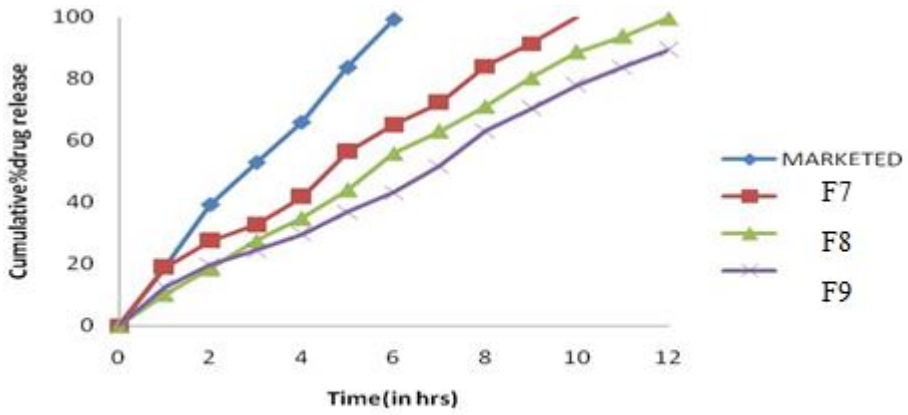


Fig.23: Cumulative percent drug released Vs time plot (Zero Order) for Norfloxacin formulations F7,F8,F9 with marketed product.

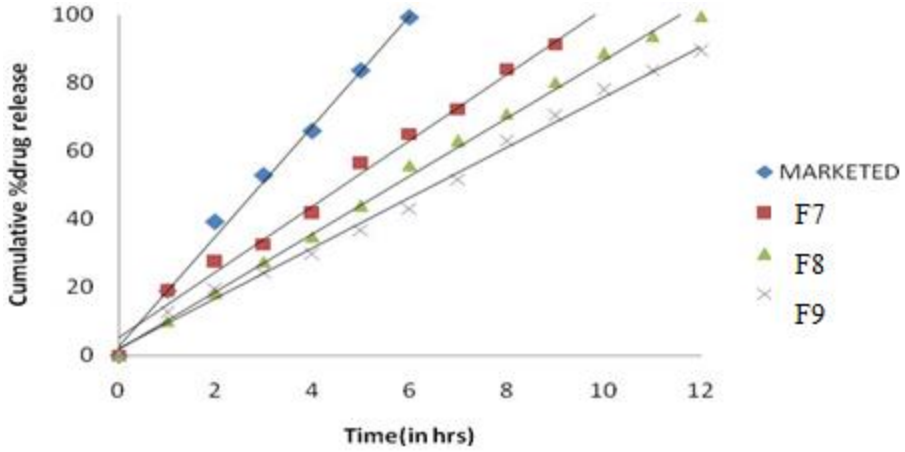


Fig.24: Log Cumulative Percent Drug Remaining Vs Time Plots (First order) for Norfloxacin formulations F7,F8,F9 with marketed product.

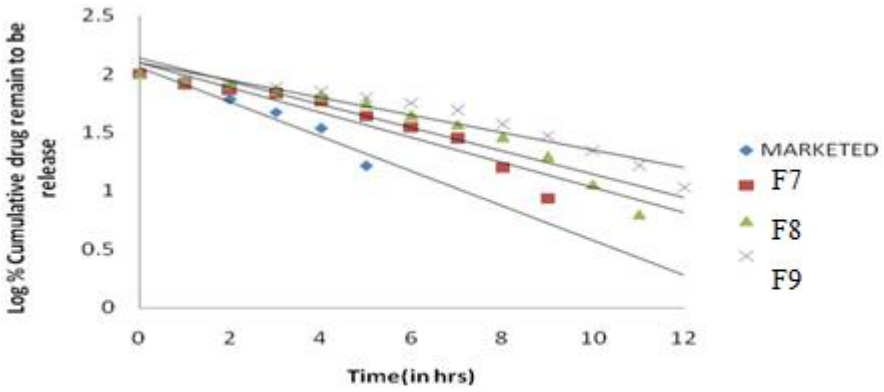


Fig.25: Cumulative percent drug released Vs square root of time (Higuchi's Plot) for formulations F7,F8,F9 with marketed product.

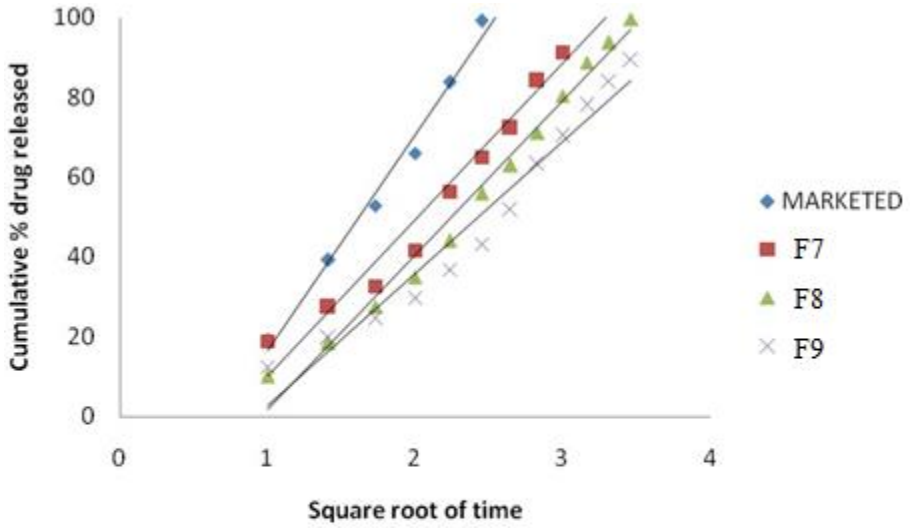


Fig.26: Log Cumulative percent drug released Vs Log time (Peppa's Plot) for formulations F7,F8,F9 with marketed product .

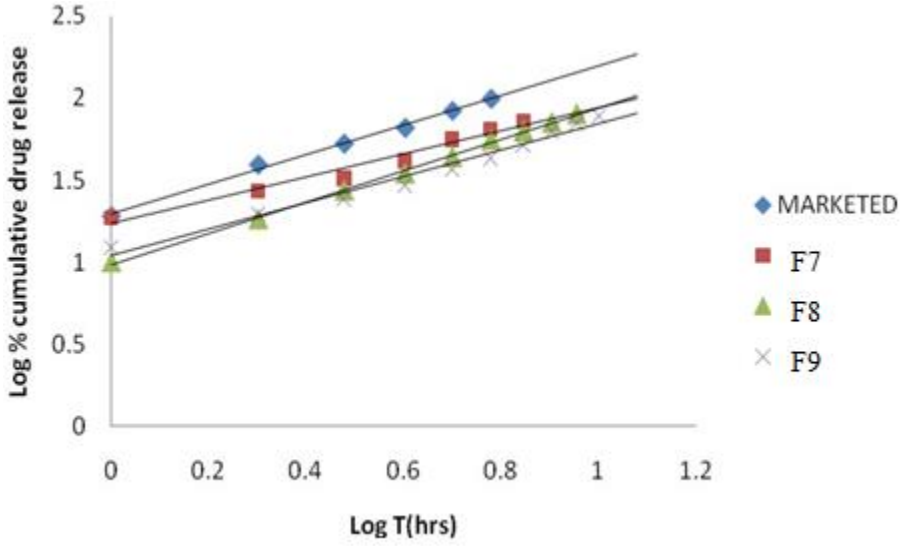


Table.no.21. Correlation coefficients (r values) of release kinetics

FORMULATION	Zero order	First order	Higuchi Matrix	Peppas	
				r	N
MARKETED	0.996	0.929	0.986	0.996	0.900
F7	0.992	0.910	0.968	0.968	0.708
F8	0.996	0.900	0.982	0.998	0.954
F9	0.994	0.919	0.955	0.976	0.803

Table.no.22. Kinetic parameters F7 to F9

FORMULATION	T_{50}(hrs)
MARKETED	3.18±0.035
F7	4.53±0.104
F8	5.59±0.46
F9	7.05±0.168

$T_{50\%}$: time taken to dissolve 50% of thedrug

7.SUMMARY

The purpose of this investigation study was to design a Gastric floating drug delivery system of Norfloxacin by using easily available inexpensive natural and semi synthetic polymers. Norfloxacin has favorable characters to be formulated as Controlled GFDDS, it is well absorbed throughout the whole gastrointestinal tract, Norfloxacin is least absorbed from the lower part of the gastrointestinal tract and is better absorbed from the stomach. This drug has a repetitive dose schedule (400 mg twice daily), short biological half-life (3–4 h) and reduced bioavailability(30–40%) . Hence selected as model drug, such as optimum $t^{1/2}$, multiple doses per day are required for the treatment it is a potential drug in treating various serious G.I diseases like gastritis, urinary tract infections, prostatitis and gonorrhea etc, it has comparatively less side effects shown by other fluoroquinolene drugs , etc , single dose is enough compared to overall multiple doses given in a day to maintain the peak plasma level and therapeutic concentration in blood.

Floating tablets of Norfloxacin were prepared by using various natural and semi synthetic polymers such as guar gum, sodium CMC, HPMC K15M. These polymers were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies.

Guar Gum is a potential excepient which is available easily and is inexpensive, this excipient has very good swelling and binding properties when comes

in contact with fluids like water and gastric fluids. Hence selected as a binder in the present study.

Sodium CMC is another polymer easily available, it possess good potential in pharmaceutical preparations as it has good swelling index and it is also used as a binding agent, so it can be safely taken in orally and not toxic in nature, it is from natural source and used prefearbly.

HPMC K15M is a Semi Synthetic controlled release polymer, and hence selected to compare with natural polymers.

Formulations were prepared by using natural and semi synthetic polymer and optimized by using direct compression method. The prepared tablets exhibited satisfactory physico- chemical characteristics. All the prepared batches shown good *in vitro* buoyancy studies and continuous till 24 hours.

8.CONCLUSION

From the present study, the following conclusions were observed:

- Gastric Floating Drug Delivery (GFDD) systems of Norfloxacin with shorter lag time can be prepared by direct compression method using guar gum, HPMC K15M, sodium CMC individual and mixed polymers and NaHCO3 as gas generating agent.
- All the prepared tablet formulations were found to be good without capping and chipping.
- The *in vitro* dissolution profiles of all the prepared GFDDS formulations of Norfloxacin were found to extend the drug release over a period of 7 to 12 hours .
- Release of Norfloxacin from the GFDDS formulations follows zero order kinetics (0.97 to 0.99).When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.678 to 0.900) indicated that the drug release was by non-fickian mechanism.
- IR spectroscopic studies indicates no drug-excipient interaction in the prepared formulations.
- Comparing the all formulations, GFDDS formulation of F3 was considered as an ideal formulation which exhibited 99.37% of drug release in 12 hours, and floating lag time of 130 seconds with a floating time of 24 hours.

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