FORMULATION AND *INVITRO*EVALUATION OF LEVOFLOXACIN LOADED FLOATING MICROSPHERE

.

A Dissertation submitted to

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

CHENNAI - 600 032

In partial fulfillment of the award of the degree of

MASTER OF PHARMACY

in

Branch-I - PHARMACEUTICS

Submitted by

Name: VIJAYARAGHAVAN A

REG.No.261610264

Under the Guidance of

Dr. S. BHAMA, M.Pharm, Ph.D.,

PROFESSOR

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

MAY-2019

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *INVITRO* EVALUATION OF LEVOFLOXACIN LOADED FLOATING MICROSPHERE",**submitted by the student bearing **Reg. No: 261610264** 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**

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Dr. S. Bhama, M.Pharm, Ph.D.,
Professor& Head,
Department of Pharmaceutics,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

Dr. R. Sambathkumar, M. Pharm., PhD.,
Professor &Principal,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

CERTIFICATE

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Place: Kumarapalayam

Date:

Dr. S. Bhama, M.Pharm, Ph.D.,
Professor& Head,
Department of Pharmaceutics,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

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Date:

Dr. R. Sambathkumar, M. Pharm., PhD.,
Professor &Principal,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

DECLARATON

I do hereby declared that the dissertation **"FORMULATION AND *INVITRO* EVALUATION OF LEVOFLOXACIN LOADED FLOATING MICROSPHERE"**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 2017-2018, under the guidance and supervision of **Dr. S. Bhama, M.Pharm, Ph.D.,**Professor& Head,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 **Mr.VIJAYARAGHAVAN A**

Date: **Reg. No.261610264**

DEDICATED TO PARENTS, TEACHERS& MY FAMILY

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Mr. A. VIJAYARAGHAVAN

Reg. No.26161024

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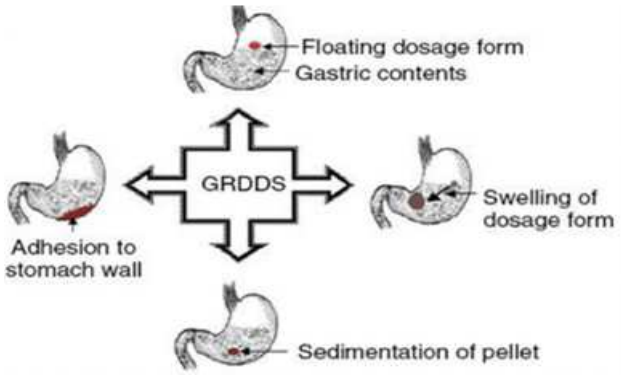
1. INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *invivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances.

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., gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options. Gastroretentive 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 various applications. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. [1-2]

Fig No: 1.1 Gastroretentive drug delivery



Gastroretentive Techniques

Several techniques including floating, swelling inflation and adhesion have been explored to increase the gastro retention of dosage forms.

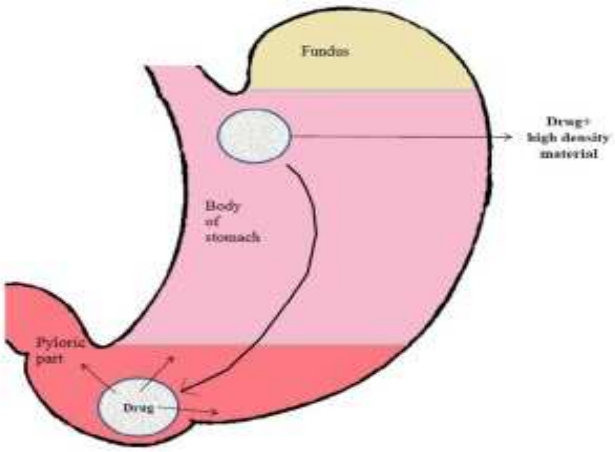
1.1.1 Approaches to Gastroretention

Several techniques are reported in the literature to increase the gastric retention of drugs.

a) High density systems

These systems, which have a density of ~3g/cm^3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm^3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide and iron powder must be used to manufacture such high-density formulation. [3]

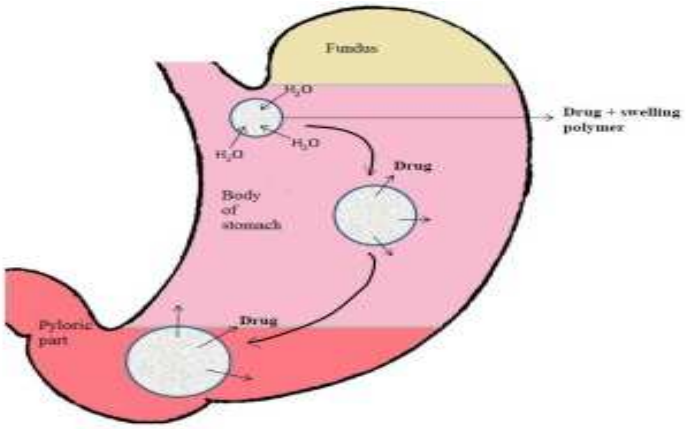
Fig No: 2



b) Swelling and expanding systems

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.[4-5]

Fig no: 3



c) Incorporating delaying excipients

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting

considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like triethanolaminemyristate in a delivery system. [6]

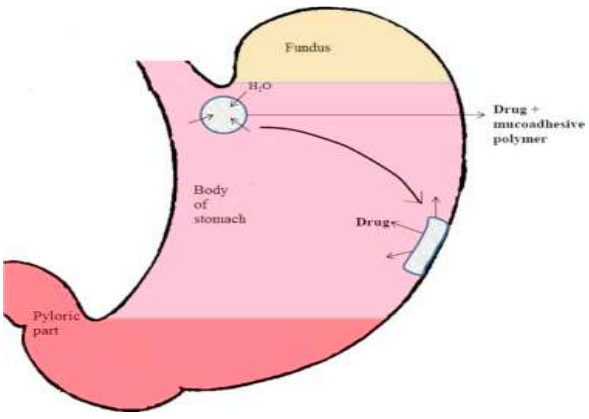
d) Modified systems

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device. [7]

e) Mucoadhesive&bioadhesive systems

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. [8-9]

Fig no: 4



f) Floating systems [10-13]

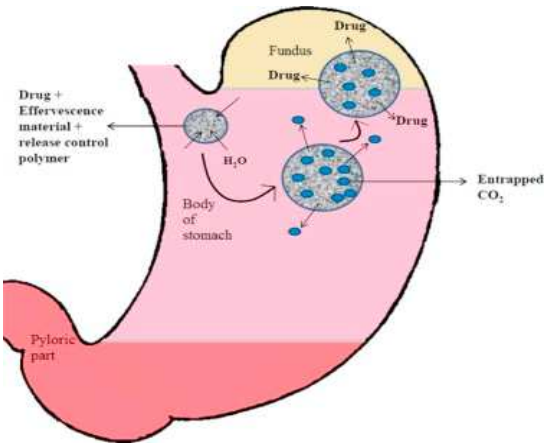
Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.

While the system floats over the gastric contents, the drug is released slowly at the desiredratewhich results in increased GRT and reduces fluctuation in plasma drug concentration. The floating drug deliverysystem andbioadhesive drugdeliveryare widely used technique for gastroretention and floating systems in particular has been extensively researched, mainly because the floating system does not adversely effect the motility of GI tract. Floating systems can also be classified as effervescent and non-effervescent systems.

- **Effervescent systems**

Floatation of a drug delivery system in thestomach can be achieved by incorporating a floating chamber filled with vacuum, air or an inert gas. Gas can be introducedinto the floating chamber by the volatilization of an organicsolvent (e.g., ether or cyclopentane) or by the CO_2producedas a result of an effervescent reaction. These devices containa hollow deformable unit that converts from a collapsed toan expanded position and returns to the collapsed position aftera predetermined amount of time to permit the spontaneousejection of the inflatable system from the stomach.

Fig No: 5



- **Non-effervescent systems**

Non-effervescent systems incorporate a high level (20–75 % w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form. The following approaches used in designing intra- gastric floating systems.

1.1.2 Factors affecting gastric retention time of the dosage form

- Density- The density of the dosage form should be less than that of the gastric contents (1.004g/ml)
- Size- The size of the dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.
- Shapeof the dosage form- the tetra hedron resided in the stomach for longer period than other devices of similar size. Single or multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units., allow co-administration of units with different release profile or containing incompatible substances and permit larger

margin of safety against dosage form failure compared with single unit dosage form.

- Fed or unfed state- under fasting conditions, the GI motility is characterized by periods of strong motor activity that occurs every 1.5-2 hrs. The migrating motor complex (MMC) sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.
- Nature of meal- feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release.
- Caloric content-GRT can be increased by 4-10 with a meal that is high in protein and fat.
- Frequency of feed- The GRT can be increasing over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.
- Gender- mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.
- Age- people with age more than 70 have a significant longer GRT.
- Concomitant drug administration- anticholinergic like atropine and propetheline, opiates like codeine can prolong GRT. [14-19]

1.1.3 Potential drug candidates for gastro retention[20-21]

Delivery of the drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing

or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates forcontrolledreleasegastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Narrow absorption window in GI tract, e.g., Riboflavin and Levodopa

2. Basically absorbed from stomach and upper part of GIT, e.g., Chlordiazepoxide.

3. Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

4. Locally active in the stomach, e.g.,Aantacids and Misoprostol.

5. Drugs that degrade in the colon, e.g., Ranitidine HCL and Metronidazole.

1.1.4 Advantages of gastro-retentive drug delivery systems

- The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
- For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

- Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

- The controlled, slow delivery of drug form Gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site specific drug delivery reduces undesirable effects of side effects.

- Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index. Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency. Reduction of fluctuation in drug concentration makes it possible to obtain improved selective receptor activation.

- The sustained mode of drug release from gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes. [22-24]

1.1.5 Disadvantages of gastro-retentive drug delivery systems[25]

- Unsuitable for drugs with limited acidsolubility. E.g. Phenytoin.
- Unsuitable for drugs those are unstable inacidic environment. E.g. Erythromycin.
- Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin &NSAID's.
- Drugs that absorb selectively in colon E.g. Corticosteroid

1.2 Microspheres

Microspheres are solid, free flowing powders approximately spherical particles ranging from 1-1000µm in size. They are made up of polymeric or protein substances in which the drug is dispersed throughout the microspheres matrix. Microspheres have been widely accepted as a means to achieve oral and parenteral controlled release drug delivery system.[26] The microspheres requires a polymeric substance as a carrier (natural and synthetic polymer) and a core material.Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout matrix that have the potential for controlled release of drugs. Microspheres are small in size and therefore have large surface to volume ratios. The potential uses of microspheres in the pharmaceutical have been considered since the 1960's and have a number of applications [27]

1.2.1 Ideal characteristics microspheres (microparticle carriers)[28]

- Longer duration of action and control in content release
- Increase of therapeutic efficiency and reduction of toxicity
- Sterility, relative stability, biocompatibility and bioresorbability of drug
- Target ability in drug action.

1.2.2 Application of microspheres

- Production of sustained release, controlled release and targeted medications.
- Reduced dose dumping of drugs.
- They facilitate accurate delivery of small quantities of potent drugs and reduced concentration of the drug at sites other than the target organ of tissues.
- They provide the ability to manipulate the *in vivo* action of the drugs, pharmacokinetic profile, tissue distribution and cellular interactions of the drug.
- Protection of the drugs from the environment.
- Conversion of oil and other liquids, facilitating ease of handling.
- Delay of volatilization, taste and odour masking.
- Freedom from incompatibility between drugs and excipients especially the buffers.
- Improvement of flow properties and safe handling of toxic substances.
- Dispersion of water insoluble substance on aqueous media.

1.2.3 Classification of microspheres

- Bio-adhesive microspheres
- Magnetic microspheres
- Therapeutic magnetic microspheres
- Diagnostic microspheres
- Radioactive microspheres

- Biodegradable polymeric microspheres
- Synthetic polymeric microspheres
- Floating microspheres.

1.2.4 Method of Preparation [29-30]

Production of sustained release, controlled release and targeted medications re-duce the dose dumping potential compared to large implantable devices. Different methods of preparation of microspheres are as follows

- Wax coating and hot melt
- Spray coating and pan coating
- Coacervation
- Spray drying
- Solvent Evaporation
- Precipitation
- Freeze drying
- Chemical and thermal cross– linking

a. Wax coating and hot melt

Wax may be used to coat the core particles, encapsulating the drug by dissolution or dispersion in molten wax. The waxy solution or suspension is dispersed by high speed mixing into cold solution, such as cold liquid paraffin. The mixture is agitated for at least one hour. The external phase (liquid paraffin) is then decanted and the microspheres are suspended in a non- miscible solvent and allowed to air dry. Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

b. Spray coating and pan coating spray

Coating and pan coating employ heat- jacketed coating pans in which the solid drug core particles are rotated and the coating material is sprayed. The core particles are in size range of micrometers up to few millimeters. The coating material is usually sprayed at angle from the side into the pan. The process is continued until an even coating is completed. In addition, several batches of microspheres cab be prepared with different coating thickness and mixed to achieve specific controlled release pattern.

c. Coacervation

This process is a simple separation of macromolecular solution into two immiscible liquid phases, a dense coacervate phase, which is relatively concentrated in macromolecules and a dilute equilibrium phase. In presence of only one macro-molecule, this process is referred to as simple coacervation. When two or more macromolecules of opposite charge are present, it is referred to as complex coacervation. Former one is induced by various parameters like change in temperature, addition of non-solvent or micro ions, which results in dehydration of macromolecules because they promote polymer-polymer interactions over polymer solvent interaction. These can be manipulated to produce microspheres with specific properties.

d. Spray drying

It is single step, closed- system process applicable to wide variety of materials, including heat-sensitive materials. The drug and polymer coating materials are dissolved in suitable solvent (aqueous or non-aqueous) or the drug may be present as a suspension in the polymer solution. Alternatively, it may be

dissolved or suspended within an emulsion or coacervate system. For example, biodegradable polylactide microspheres can be prepared by dissolving the drug and the polymer in methylene chloride. The microsphere size is controlled by the rate of spraying, the feed rate of the polymer drug solution, the nozzle size, the temperature in drying and collecting chambers, and the size of the two chambers. The quality of the spray dried products are improved by the addition of plasticizers that promote the polymer coalescence and film formation and enhance the formation of smooth surfaced and spherical microspheres.

e. Solvent evaporation

In this method, the drug and the polymer must be soluble in organic solvent, frequently ethylene chloride. The solution containing polymer and drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvents and leave the solid polymer-drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension.

f. Precipitation

It is a variation on the evaporation method. The emulsion consists of polar droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a co-solvent. The resulting increase in the polymer concentration causes precipitation forming a suspension of microspheres.

g. Freeze Drying

This technique involves the freezing of the emulsion and the relative freezing points of the continuous and dispersed phases are important. The continuous phase

solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer- drug particles.

h. Chemical and thermal cross - linking

Microspheres made from natural polymers are prepared by a cross-linking process, polymer includes gelatin, albumin, starch and dextrin. A water-oil emulsion is prepared, where the water phase is a solution of polymer that contains drug to be incorporated. The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil soluble emulsifier. Once the desired water-oil emulsion is formed, the water soluble polymer is solidified by thermal treatment or addition of a chemical cross-linking agent such as glutaraldehyde to form a stable chemical cross link.

1.3 Floating microspheres

In floating types the bulk density of the microspheres is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and decreases fluctuation in plasma concentration. Moreover it also reduces chances of dose dumping reduces dosing frequencies and produces prolonged therapeutic effect.

1.3.1 Advantages of floating microspheres

- Improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

- Gastric retention time is increased because of buoyancy.
- Enhanced absorption of drugs which solubilize only in stomach.
- Drug release is in controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.
- Improved receptor activation selectivity.
- Extended time over critical (effective) concentration.
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.

1.3.2 Mechanism of floating systems[31-33]

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement

of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations,

F = F buoyancy - F gravity

= (Df - Ds) gv

Where,

F = total vertical force,

D_f= fluid density,

Ds = object density,

v = volume and

g = acceleration due to gravity.

1.3.3 Components are used in preparation of floating drugs[35-36]

Materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Bees wax, fatty acids, long chain fatty alcohols etc.,

Polymers: The following polymers are used in the preparations of floating drugs delivery systems like Hydroxymethyl cellulose, Carbapol, Xanthum gum, Guar gum etc.

Inert fatty materials: Edible oils.

Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid.

Low density material: Polypropylene foam powder (Accurel MP 1000®), Calcium silicate etc.

1.3.4 Application of floating drug delivery system [37-39]

a. Sustained Drug Delivery

HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents. Recently sustained release floating capsules of nicardipine were developed and evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD cap (8 hours).

b. Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine eg riboflavin, furosemide and misoprostal. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E, used as protectant of gastric ulcer caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

c. Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavalibiling of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablet (33.4%) and enteric coated LASIX-long product (29.5%).

d. Maintenance of Constant Blood Level

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

Table No: 1 Drugs used in the formulations of floating dosage forms

S.No.	Dosage forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Nifedipine, Cholestyramine, Theophylline, Nicardipine, Flavoxate,Dipyridamol, Terfinadine and Tranilast
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3.	Films	Cinnarizine and Albendazole.
4.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid, Pepstatin and Propranolol.
5.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillintrihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbidemononitrate, Para-aminobenzoic acid, Piretamide, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline, Theophylline and Verapamil hydrochloride.

Table No: 2 List of floating microspheres

Dosage form	Drug
Floating microspheres	Ketoprofen
	Stavudine
	Verapamil Hydrochloride
	Boswellic Acid
	Captopril
	Metformin Hydrochloride
	Famotidine
	Ranitidine Hydrochloride
	Ofloxacin Hydrochloride
	Glipizide
	Acyclovir
	Silymarin
	Gabapentin

2. LITERATURE REVIEW

DeveshKapoor*et al* (2012) [40] developed floating microspheres of captopril in order to achieve an extended retention in the upper GIT which may enhance the absorption and improve the bioavailability. The microspheres were prepared by solvent evaporation method using different ratio of hydroxyl propyl methyl cellulose (HPMC K4M) with drug in the mixture dichloromethane and ethanol at ratio of (1:1), with tween80 as the surfactant.

RamyaShivani B *et al* (2015)[41]formulated omeprazole loaded floating microspheres by solvent evaporation technique. Total ten formulations were prepared by altering the concentration of drug to polymer concentrations. Process parameters such as stirring speed, stirring time and organic to aqueous phase ratio were optimized. Trials were made at 1:5 and 1:10 organic to aqueous phase ratio by altering drug to polymer concentration. Floating Microspheres were prepared by non-effervescent system. The obtained formulations were evaluated for drug content, entrapment efficiency, Buoyancy time and In vitro dissolution studies.

Amul Mishra *et al* (2018) [42] prepared the controlled release drug delivery system possessing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drug having “absorption window” continually releasing the drug prior to absorption window for prolong period of time, thus ensuring optimal bioavailability. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drug that are poorly soluble or unstable in intestinal fluids.

Hitesh Kumar *et al* (2012) [43] prepared and evaluated ethyl cellulose floating microspheres containing Ranitidine hydrochloride. Microspheres were prepared by non-aqueous solvent evaporation method using ethanol/ liquid paraffin system. The influence of formulation factors (drug: polymer, stirring speed, concentration of surfactant) on particle size, encapsulation efficiency and in vitro release characteristics of the microspheres were investigated.

Nagesh C *et al* (2011) [44] developed new intra-gastric floating microspheres for controlled delivery of levofloxacin for the treatment of peptic ulcer caused by Helicobacter pylori (H. pylori). Floating microspheres of levofloxacin were prepared by emulsion solvent evaporation technique. The drug was encapsulated with HPMC and eudragit S 100 in different polymers ratios. i.e. 1:1,1:2,1:3.prepared microspheres were evaluated for % entrapment, particle size, Buoyancy, dissolution study and drug release kinetics.

KeerthiSumanaMurathoti *et al* (2016) [45]developed and evaluated a new oral drug delivery system utilizing both the concepts of controlled release and mucoadhesiveness, which could remain in stomach and control the drug release for longer period of time and thus to improve the bioavailability of the drug and reducing its dose related side effects. Gelatin/Acrypol 934P mucoadhesive microspheres of Levofloxacin were prepared by emulsification cross- linking method.

ChaudharyAmitet al(2012)[46] prepared and evaluated levofloxacin microspheres with mucoadhesivepolymers like Sodium Alginate, sodium carboxymethyl Cellulose and Carbopol-940.Microspheres were prepared by w/o emulsification solvent evaporation method and evaluated. Drug release was

controlled by the diffusion mechanism. Stability studies were performed at three different temperatures for six weeks. All the formulation showed satisfactory stability profile.

Ninan Ma *et al* (2012) [47] prepared floating alginate (Alg) microspheres was prepared by the ionotropic gelation method with calcium carbonate (CaCO3) being used as gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding chitosan (Cs) into the gelation medium and by coating with eudragit, respectively. The gastrointestinal transit of optimized floating sustained release microspheres was compared with that of the non-floating system manufactured from identical material using the technique of gamma-scintigraphy in healthy human volunteers.

HarriHeiskanen a *et al* (2012) [48] formulated and evaluated methylaluminoaxane (MAO) microspheres of average size smaller than 100µm were prepared using a solvent extraction process; excess of perfluorocarbon (PFC) was added to the hydrocarbon-in-perfluorocarbon emulsion to solidify the MAO droplets. The main reason for the increased size of the MAO microspheres was the increased coalescence with increasing preparation temperature. In addition the porosity of the MAO microspheres increased with increasing preparation temperature.

DeveshKapoor*et al* (2012)[49] developed and evaluated floatingmicrospheres of captopril in order to achieve an extended retention in the upper GIT which may enhance the absorption and improve the bioavailability. The microspheres were prepared by solvent evaporation method using different ratio of hydroxyl propyl methyl cellulose (HPMC K4M) with drug in the mixture dichloromethane and

ethanol at ratio of (1:1), with tween80 as the surfactant. The effects of polymers concentration on drug release profile were investigated. A 32 full factorial design was applied to systemically optimize the drug release profile.

Shiv Shankar Hardenia*et al* (2012) [50] worked on ethylcellulose microspheres containing ciprofloxacin were prepared and evaluated for in-vitro performance of ciprofloxacin. Ciprofloxacin microspheres containing ethylcellulose were prepared by emulsion solvent diffusion evaporation method. It was found that drug release from the formulations was different at different concentrations of polymers and different RPM and temperature. The mucoadhesive property of the ethylcellulose microspheres was evaluated by in-vitro wash off test. By the results it was concluded that ethylcellulose microspheres showed reproducible results, with good mucoadhesive properties and good surface morphology.

KameswararaoSankula *et al* (2012)[51] prepared and evaluated the mucoadhesive microspheres of rosvastatin. Rosvastatin microspheres were prepared by orifice- ionotropic gelation method using polymers such as HPMC (K 100 M), carbopol 940P, sodium CMC, guar gum, sodium alginate, ethyl cellulose, methyl cellulose and xanthan gum. Totally 15 different formulations of rosvastatin were prepared by using the above polymers. The microspheres were characterized for drug content, entrapment efficiency, mucoadhesive property by *in vitro* wash-off test and *in-vitro* drug release.

Pankaj Pant *et al* (2012) [52] developed gastroretentivemucoadhesive microspheres of clarithromycin to combat Helicobacter pyroli infection in ulcer patients. Clarithromycin is used for the treatment of H. pyroli. Its dosing schedule is 8 to 12 hour but the level of drug use to drop below its Minimum Inhibitory

Concentration (MIC) well before administration of the subsequent dosing. Retaining the drug at a site above its absorption site i.e. in the stomach would allow the drug to be absorbed effectively from its site of absorption and gives time for healing of peptic ulcer caused by H. pyroli infection by increasing time for local action of drug.

Purushothaman et al (2017) [53] formulated sustained release system for metoprolol succinate designed to increase its residence time in the stomach without contact with the tablets was achieved through the preparation of floating tablets by the direct compression method. In the present study attempt has been made to develop sustained released drug delivery system by formulating the floating tablets of metoprolol succinate using peanut husk powder as a natural polymer and it was concluded that the combination of peanut husk powder, HPMC and carbopol shows better Gastric retention.

KeziaKereen *et al* (2017) [54] prepared floating microspheres of an anti-hypertensive drug trandolapril as a model drug for prolongation of gastric residence time using both gas forming agents like sodium bicarbonate and low density polymers like eudragit of various grades and HPMC. The effervescent microspheres were prepared by ionotropic gelation technique using polymer sodium alginate along with guar gum and xanthan gum and non-effervescent microspheres were prepared by solvent evaporation emulsification technique using HPMC, ethylcellulose and eudragit RLPO and RSPO. The optimised formulation (F6) showed good percent yield, drug entrapment and drug release.

3. AIM AND OBJECTIVES

- The aim of the present work was to formulate and evaluate levofloxacin loaded floating microspheres.
- Levofloxacin is used to treat *Helicobacter Pyroli* infection after failure of first line treatment.
- Existing marketed products of the formulation more dosing frequency of two to three times a day.
- The main reason for treatment failure is the short residence time of antimicrobial agents in the stomach and availability of insufficient antimicrobial concentration in the mucus layer of the stomach.
- Therefore it is essential to develop suitable dosage forms that not only solve the limitations of conventional delivery systems but also deliver the antibiotics to the site of action.
- Floating microspheres of levofloxacin is formulated for improving the drug bioavailability by prolongation of gastric residence time.
- Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

- Solubility of the selected drug decrease with increase in pH making stomach better site of absorption. Hence an attempt has been made to formulate a GI levofloxacin floating microsphere. Floating microspheres helps in retaining the microspheres in stomach fluids for longer duration and better absorption with site specificity.

- Hence levofloxacin floating microsphere prepared by emulsion solvent evaporation method for better drug delivery.

4. PLAN OF WORK

I. Pre formulation studies

a) Organoleptic properties

b) Melting point

c) pH of the solution

d) Solubility

e) Flow properties

Angle of repose

Bulk density

Tapped density

Measurement of powder compressibility

Hausner ratio

f) Drug excipient compatibility studies

g) Calibration curve of Levofloxacin

II. Formulation of Levofloxacin floating microspheres

III. Evaluation of Levofloxacin floating microspheres

a) Micromeritics properties

i) Determination of bulk density tapped density

ii) Angle of repose

iii) Measurement of compressibility index and Hausner ratio

b) Percentage yield of microspheres

c) Drug entrapment efficiency

d) Buoyancy studies

e) *Invitro* dissolution studies

f) Kinetics of drug release

g) IR spectroscopy

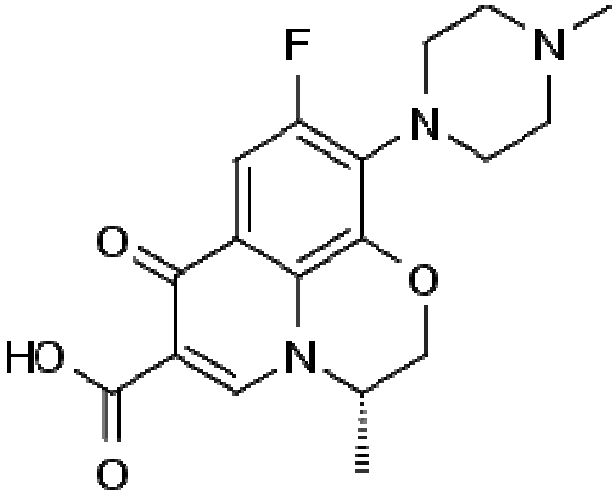
h) Scanning Electron Microscopy

i) Stability study

5.DRUG PROFILE

LEVOFLOXACIN HEMIHYDRATE [55]

Levofloxain is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.



Description: A synthetic fluoroquinolone (fluoroquinolones) antibacterial agent that inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replication.

Molecular weight: 361.3675 g/mol

Molecular formula: $C_{18}H_{20}FN_3O_4$

Indication : For the treatment of bacterial conjunctivitis caused by susceptible strains of the following .

Organisms: Corynebacterium species, Staphylococusaureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus (Groups C/F/G), Viridans groupstreptococci,Acinetobacterlwoffii,Haemophilusinfluenzae,Serratiamarcescens.

Pharmacodynamics: Levofloxacin, a fluoroquinoloneantiinfective, is the optically active L-isomer of ofloxacin. Levofloxacin is used to treat bacterial conjunctivitis, sinusitis, chronic bronchitis, community-acquired pneumonia and pneumonia caused by penicillin-resistant strains of *Streptococcus pneumoniae*, skin and skin structure infections, complicated urinary tract infections and acute pyelonephritis.

Mechanism of action : Levofloxacin inhibits bacterial type II topoisomerases, topoisomerase IV and DNA gyrase. Levofloxacin, like other fluoroquinolones, inhibits the A subunits of DNA gyrase, two subunits encoded by the gyrA gene. This results in strand breakage on a bacterial chromosome, supercoiling, and resealing; DNA replication and transcription is inhibited.

Absorption : Absorption after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose.

Protein binding : 24-38% (to plasma proteins)

Metabolism: Mainly excreted as unchanged drug (87%); undergoes limited metabolism in humans.

Route of elimination: Mainly excreted as unchanged drug in the urine

Half life : 6-8 hours

Toxicity : Side effects include disorientation, dizziness, drowsiness, hot and cold flashes, nausea, slurring of speech, swelling and numbness in the face.

Adverse effects: Adverse effects are typically mild to moderate. However, severe, disabling, and potentially irreversible adverse effects sometimes occur, and for this reason use it is recommended that use of fluoroquinolones be limited.

Prominent among these are adverse effects that became the subject of a black box warning by the FDA in 2016.[1]The FDA wrote: "An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious adverse effects that can occur together. These adverse effects can involve the tendons, muscles, joints, nerves, and central nervous system Rarely, tendinitis or tendon rupture may occur due to fluoroquinolone antibiotics, including levofloxacin. Such injuries, including tendon rupture, has been observed up to 6 months after cessation of treatment; higher doses of fluoroquinolones, being elderly, transplant patients, and those with a current or historical corticosteroid use are at elevated risk.The U.S. label for levofloxacin also contains a black box warning for the exacerbation of the symptoms of the neurological disease myasthenia gravis. Similarly, the UK Medicines and Healthcare Products Regulatory Agency recommendations warn of rare but disabling and potentially irreversible adverse effects, and to recommend limiting use of these drugs.Increasing age and corticosteroid use appears to increase the risk of musculoskeletal complications.

Overdose : Overdosing experiments in animals showed loss of body control and drooping, difficulty breathing, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

In the event of an acute overdosage, authorities recommend unspecific standard procedures such as emptying the stomach, observing the patient and maintaining

appropriate hydration.Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

POLYMER PROFILE

SODIUM ALGINATE[56]

Nonproprietary Names

Sodium alginate (BP)

Natriialginas (PhEur)

Sodium alginate (USPNF)

Synonyms

Algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.

Chemical Name and CAS Registry Number

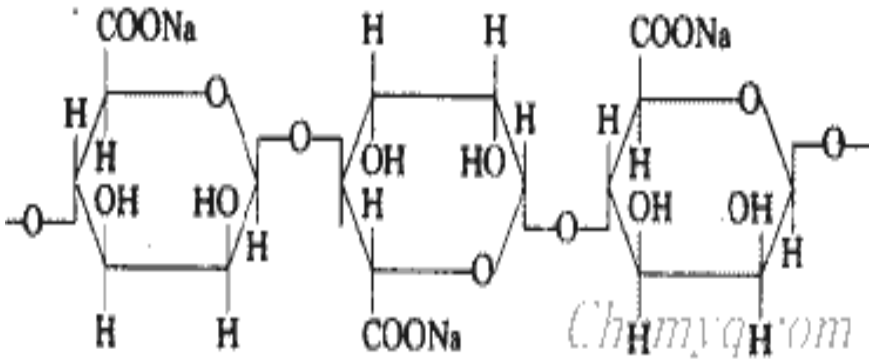
Sodium alginate [9005-38-3]

Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture ofpolyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

The block structure and molecular weight of sodium alginate samples has been investigated.

Structural Formula



Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility

Practicallyinsoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents andaqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming aviscous colloidal solution.

Viscosity: 20–400 mPas.

Loss on drying ≤15.0%

Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stable if stored at low relativehumidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at ph 4–10. The bulk material should be stored in an airtight container in a cool, dry place.

Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

Safety

It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

HYDROXY PROPYLMETHYL CELLULOSE [56]

Nonproprietary Names

Hypromellose (BP)

Methylhydroxypropylcellulosum (pheur)

Hydroxypropylmethyl cellulose (USP)

Synonyms

Cellulose, Methocel; methylcellulose propylene glycol ether, hydroxylpropyl methyl ester, E464, HPMC, methyl hydroxylpropylcellulose; Metolose; Tylopur,pharmacoat,culminalMHPC.

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight

The Pheur 2005 describes hydroxyl propylmethylcelluloseas a partly OmethylatedandO-(2-hydroxypropylated) cellulose.Molecular weight varies from 10 000–1 500 000.

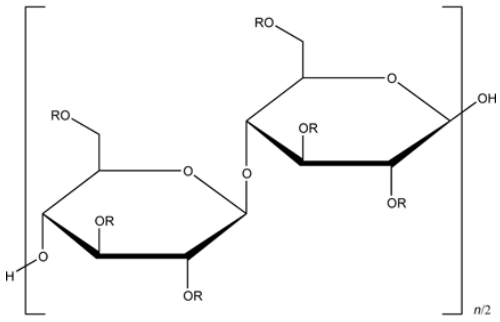
Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy white coloured fibrous or granular powder**.**

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.

Structural Formula



Where R is H, CH3, or CH3CH (OH) CH2

Moisture content

Hydroxypropyl methyl cellulose 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.

Viscosity content-51000000mPas (2%w/w solution at 20°C)

The different commercial grades are available according to the viscosities

Methocel K4M Premium 2208 4000

Methocel K100M Premium 2208

Density: Density (bulk) 0.341g/cm3

Density (Tapped) 0.557g/cm3

Density (true) 1.326g/cm3

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

Melting point: Browns at 190–200°C; chars at 225–230°C

Loss on drying:≤ 5.0%

Burnt residue:≥1.0%

Specific gravity: 1.26

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

Hydroxypropyl methyl cellulose is widely used in oral, ophthalmic and topicalpharmaceutical formulations.

In oral products, hydroxypropyl methyl cellulose 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.

Hydroxypropyl methyl cellulose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, it gives greater clarity, compared to methyl cellulose so it is preferred in ophthalmic formulation in conc. of 0.45-1.0%w/w used.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

In addition, hydroxypropyl methyl cellulose is used in the manufacture of capsules, as an adhesive in plastic bandages.

Incompatibilities

Hydroxypropyl methyl cellulose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Stability and Storage Conditions

It is a stable although slightly hygroscopic. Bulk material should be stored in air tight container, in a cool and dry place.

Safety

It is widely used in oral and topical pharmaceutical formulations. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

SODIUM CARBOXY METHYL CELLULOSE[57]

Nonproprietary Names

Carmellose sodium (BP)

Carmellose sodium (JP)

Carmellosumnatricum (PhEur)

Carboxymethylcellulose sodium (USP)

Synonyms

Akucell**,**Aquasorb, Blanose, cellulose gum, E466, Finnfix, Nymcel, SCMC, sodium cellulose glycolate,Tylose CB.

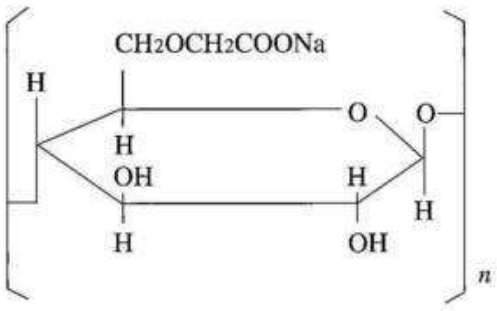
Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

Empirical Formula and Molecular Weight

Carboxymethyl cellulose sodium as the sodium salt of polycarboxy methyl ether of cellulose. Molecular weight is 90 000–700 000.

Structural Formula



n: degree of polymerization

Description

Sodium carboxymethylcellulose 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.

Moisture content

It contains less than 10% water. Sodium carboxymethyl cellulose is hygroscopicand absorbs significant amounts of water at temperatures up to 378°C at relative humidity's of about 80%.

Viscosities : 5–13 000 mPas

Density **:** Density (bulk): 0.52 g/cm3

Density (tapped): 0.78 g/cm3

Melting point: Browns at approximately 2278°C, and chars at approximately 2528°C.

Loss on drying: ≤10.0%

Functional Category

Coating agent, stabilizing agent, suspending agent, tablet and capsule disintegrate, tablet binder, viscosity-increasing agent, water-absorbing agent.

Applications in Pharmaceutical Formulation or Technology

Sodium carboxymethyl cellulose is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing properties.

Sodium carboxymethyl cellulose is additionally one of the main ingredients of self adhesiveostomy, wound care, and dermatological patches, where it is used as a mucoadhesiveandto absorb wound exudates or transepidermal water and sweat. Encapsulation with sodium carboxymethylcellulose can affect drug protection and delivery. It is used as a cytoprotective agent.

Sodium carboxymethyl cellulose is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

Incompatibilities

Sodium carboxymethyl cellulose is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%).

Stability and Storage Conditions

Sodium carboxymethyl cellulose is a stable, although it is slightly hygroscopic.The bulk material should be stored in a well-closed container in a cool, dry place.

Safety

Sodium carboxymethyl cellulose is used in oral, topical, and some parenteral formulations. It is generally regarded as a nontoxic and nonirritant material althoughexcessive consumption may have laxative effect.

6. MATERIALS AND METHODS

Table No 3 : Materials and instruments used in the formulation

S. No.	MATERIALS	SUPPLIERS/MANUFACTURERS
1	Levofloxacin	Spectrum Pharma Labs
2	Sodium alginate	S.D.fine chem. Ltd. Mumbai
3	Sodium carboxy methyl cellulose	S.D.fine chem. Ltd Mumbai
4	Hydroxy propyl methyl cellulose K4M	Otto chem. Laboratories Pvt.Ltd
5	Hydroxy propyl methyl cellulose K100M	Otto chem. Laboratories Pvt.Ltd
6	Sodium chloride	Rankem,RFCL Ltd, New Delhi
7	Polysorbate 80 (tween 80)	Sisco Research laboratories Pvt.Ltd.
8	Dichloromethane	Rankem,RFCL Ltd, New Delhi
9	Methanol	Merck SpecialitiesPvt.Ltd, Mumbai

Table No 4 : Instruments used in the formulation

S. No	INSTRUMENTS	SUPPLIERS/MANUFACTURERS
1	Weighing balance	WinsarPvt Ltd
2	Homogenizer	Remi EQP Ltd
3	Mechanical stirrer	Remi EQP Ltd
4	Magnetic stirrer	Remi EQP ltd
5	Hot plate	Krishna Pvt Ltd
6	Optical microscope	AlmicroPvt Ltd
7	UV spectrophotometer	Eleiko Ltd
8	FT-IR spectrophotometer	Bruker alpha
9	Dissolution apparatus (USP-VIII)	Labindia PVT Ltd
10	Scanning Electron Microscope (SEM)	Hitachi S3400N

6.1 Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Preformulation studies relate to pharmaceutical and analytical investigation carried out in supporting formulation development efforts of the dosage forms.The following preformulation studies were performed to obtain purity of drug.

6.1.1 Organoleptic properties [58]

a) Color and nature

Transferred small quantity of the sample on a white piece of paper spreaded the powder and examined visually.

b) Taste and odour

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

6.1.2 Melting point

It is one of the parameters to judge the purity of crude drug. In case of pure chemicals, melting points are very sharp and constant**.**

Procedure

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

6.1.3 pH of the solution

Weighed and transferred accurately about 1.0 g of sample in a 200ml clean and dried beaker, dissolved in carbondioxide free water and made up the volume to 100ml with same solvent, mixed. Read the pH of freshly prepared solution by using precalibrated pH meter.

6.1.4 Solubility

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

6.1.5 Physical characteristics [59]

a) Angle of repose

The flow properties of powder are critical for an efficient microsphere preparing. If the drug is identified at pre formulation stage to be "poorly flowable" the problem can be solved by selecting appropriate excipients. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Procedure

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10gm of sample powder was filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in a different directions.

The height of the heap was measured by using scale. The values of angle of repose were calculated by using the following formula.

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

Where,

θ = Angle of the repose

h = Height of the heap

r = Radius of the heap

Table No 5 : Angle of repose limits

Angle of Repose	**Flowability**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends on particular shape as the particle become more spherical in shape, bulk density increases.

Bulk density was determined by measuring the volume of a known mass of a powder sample that has been passed through a screen into a graduated cylinder.

Procedure

A known quantity of powder was poured into measuring cylinder carefully level the powder without compacting , if necessary and read the unsettled apparent value. Calculate the bulk density, in gm per ml, by the formula.

$$\rho_b = m / V_b$$

Where,

ρ_b = Bulk density

m = mass of powder

V_b = initial/bulk volume

c) Tapped density

Tapped density is the ratio of mass of powder to the tapped volume**.**

Procedure

A quantity 5gm of the powder (W) from each formula was introduced in to a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Calculate the tapped density, in gm per ml, by the formula**.**

$$\rho_t = m / V_t$$

Where,

ρ_t = Tapped density

m = Mass of the powder

V_t = Final/tapped volume

d) Measurement of powder compressibility

The compressibility index is measures of the propensity of a powder to be compressed. As such, it measures relative importance of inter particulate

interactions. In a free flowing powder, such interactions generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index calculated by the formula.

$$\% \text{ compressibility} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Table No 6: Compressibility index limits.

% Compressibility	**Flow ability**
5-12	Excellent
12-16	Good
18-21	Fair
23-25	Poor
33-38	Very poor
More than 40	Very, very poor

e) Hausner ratio

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

Hausner ratio = V_b/V_t or ρ_t/ρ_b

Table No 7: Hausner Ratio index limits

Hausner Ratio	**Flowability**
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.3-1.4	Poor

6.1.6 Drug –excipient compatibility studies

In any dosage form, the drug is in intimate contact with one or more excipients, the latter could affect stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information is already be in existence for known drugs. For new drugs or new excipients, the pre formulations scientist must generate the needed information.

Procedure by FT-IR Studies

The IR spectrums of levofloxacin with excipients were taken by preparing dispersion in dry potassium bromide under dry condition. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the standards.

6.1.7 Calibration curve of Levofloxacin in 0.1N Hydrochloric acid solution [60]

Stock solution: Pure levofloxacin 50mg was dissolved in 100ml of 0.1N Hydrochloric acid. 5ml of this solution was further diluted to 100ml with same solvent to obtain 25µg/ml.

Working solution: From the stock solution (25µg/ml) suitable working solution of different concentrations of 2, 4, 6, 8 & 10µg/ml were made. The absorbance of these dilutions was measured at 293nm. Each point is an average of three determinations. Slope, y-axis intercept, and regression coefficients were calculated.

6.2 Formulations of levofloxacin floating microspheres

Floating microspheres were prepared by the solvent evaporation method using 1gm of levofloxacin and with different polymer were dissolved in methanol (5 ml), dichloromethane (5 ml) with vigorous agitation to form uniform drug polymerdispersion. This was slowly poured intothe dispersion medium consisting of light liquidparaffin (100ml) containing tween 80. The system is stirred using propeller at room temperature for 1hr 30min – 2 hr. The liquid paraffin wasdecanted and the microparticles were separated byfiltration through a whatmann filter paper, washedthrice with 180 ml of n-Hexane and air dried for 6-8hrs**.**

Table No 8 : Formulations of levofloxacin

INGREDIENTS	FORMULATION BATCHES									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
LVX (g)	1	1	1	1	1	1	1	1	1	1
HPMC K4M (g)	1	-	-	-	0.5	0.5	0.5	-	-	-
Sodium alginate (g)	-	1	-	-	0.5	-	-	0.5	0.5	-
Sodium CMC (g)	-	-	1	-	-	0.5	-	0.5	-	0.5
HPMC K100M (g)	-	-	-	1	-	-	0.5	-	0.5	0.5
Methanol (mg)	10	10	10	10	10	10	10	10	10	10
Dichloromethane (mg)	10	10	10	10	10	10	10	10	10	10

6.3 Evaluation of levofloxacin floating microspheres

6.3.1. Micromeritic properties

a) Determination of bulk density and tapped density

A quantity 5gm of the powder (W) from each formula was introduced into a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and tapped density were calculated using the following the formula**.**

Bulk density (ρ_b)= m/ V_b

Tapped density(ρ_t)=) = m/ V_t

Where,

m = mass of the powder

$\mathbf{V_b}$ = initial or bulk volume

$\mathbf{V_t}$ = final or tapped volume

b) Angle of repose

5 gms of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and angle of repose was determined using the formula.

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

Where,

H = height

r = radius

θ = angle of repose

c) Measurement of compressibility index and Hausner ratio

Compressibility index and Hausner ratio were measured by using the following formula

$$\%\text{compressibility (carr'sindex)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio $= V_b / V_t$

Where,

V_b = initial or bulk volume

V_t = final or tapped volume

6.3.2 Percentage yield of microspheres

The prepared microspheres of all batches were accurately weighed. The weighed quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation.

$$\text{Percentage yield} = \frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \text{X } 100$$

6.3.3 Drug entrapment efficiency

According to dose, actual drug present in total microspheres (drug 1gm+ excipients) is calculated. The amount was mixed with 100ml phosphate buffer by sonication. Pipette out 1ml into 10ml volumetric flask and made up to 10ml using buffer. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula.

$$\text{Percentage drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

6.3.4 Buoyancy studies [61-62]

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of f 0.1 N HCL containing tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

$$\% \text{ Buoyancy} = \frac{W_f}{(W_f + W_s)} \times 100$$

Where,

W_f = weight of the floating

W_s = settled microspheres respectively.

6.3.5*Invitro* dissolution studies [63]

Invitro release from floating microsphere was analyzed using USP dissolution test apparatus 2 (paddle) with stirrer at 100rpm. Predetermined quantities of microspheres were placed in bowl. 900ml of 0.1N HCL was used as the dissolution media. Dissolution Studies were conducted at *37*°±2°C.Samples were taken at suitable time intervals and replaced with the same quantity of fresh dissolution medium. Collected samples filtered through 0.45µm syringe absorbance was measured.

$$\% \text{ Purity} = \frac{\text{Absorbance} \times 900 \times \text{dilution factor}}{\text{Slope} \times 1000 \times \text{label claim}} \times 100$$

6.3.6 Kinetics of drug release [63]

The *in-vitro* dissolution profile of all batches were fitted to zero order, first order, higuchi model and korsemeyer-peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

Zero order- kinetic model

Zero order release would be predicted by the following equation.

$$A_t = A_o - K_o t$$

Where,

A_t - Drug release at time‘t’

A_o- Initial drug concentration

K_o - Zero order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vstime and the plot is linear , then the data obeys Zero-order equal to K_o.

First order kinetics

First order release would be predicted by the following equation

$$\mathbf{LogC = logC_o - K_t/2.303}$$

Where,

Log C - Amount of drug remained at time 't'

$logC_o$ - Initial drug concentration

K - First order rate constant (hr^{-1})

When the data plotted as log cumulative % remainingVstime yields a straight line, then the release obeys first order kinetics. The constant 'K'obtained by multiplying 2.303 with the slope values.

Korsemeyer-peppas model.

To study the mechanism of drug release from microspheres, the *in-vitro* data were fitted to the well known exponential equation (korsemeyerpeppasmodel) which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{Mt/M\alpha = Kt^n}$$

Where,

Mt/Mα - The fraction of drug released at 't'

K - Constant incorporating structural and geometrical characteristics of the drug / polymer system

n - Diffusion exponent related to mechanism the drug release

When the data plotted as log % drug released Vslog time yields a straight line with a slope equal to 'n' and the K can be obtained by y- intercept.

Mechanism of drug release as per korsemeyer-peppas equation / peppas model

Table No 9: Mechanism of drug release

S. No.	n values	Drug release
1	0-0.5	Fickian release
2	0.5-1.0	Non-Fickian release
3	>1.0	Class II transport

6.3.7 Scanning Electron Microscopy [64]

The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron Microscope. The sample was loaded on copper sample holder and sputter coated with carbon followed by gold.

6.3.8 Stability study [65-66]

Stability studies The optimized formulation was subjected to stability studies as per ICH guidelines for a period of six months at 25°C/60 %RH, 30°C/65% /RH and 40°C/75% /RH respectively and monitored for changes in drug content and release pattern.

7. RESULTS AND DISCUSSIONS

7.1 Pre formulation studies

7.1.1 Organoleptic properties

These test were performed as procedure given in 6.1.1. The results are illustrated in following table.

Table No 10 : Organoleptic properties

Test	**Observations**
Color	light yellowish-white to yellow-white powder
Taste	Bitter
Odour	Odorless

The results complies as per specifications

7.1.2 Melting point

It was determined as per procedure given in 6.1.2. The results are illustrated in following table**.**

Table No 11: Melting point

Material	**Material point range**	**Result**
Levofloxacin hemihydrate	222°C	Complies

7.1.3 pH of the solution

It was determined as per procedure given in 6.1.3. The results are illustrated in following table**.**

Table No 12: pH

Material	Specification	Observation
Levofloxacin hemihydrate	6 to 5.8	5.8

The result complies as per specification

7.1.4 Solubility

It was determined as per procedure given in 6.1.4. The results are illustrated in following table**.**

Table No 13: Solubility of drug

Test	Specification	Result
Solubility	Slightly soluble in water, soluble in glacial acetic acid, slightly soluble or soluble in dichloromethane, slightly soluble in methanol.	Complies

The results complies as per specification.

7.1.5 Physical characteristics

a) Angle of repose

It was determined as per procedure given in 6.1.5. The results are illustrated in following table**.**

Table No 14: Flow properties

Material	Angle of repose
Levofloxacin hemihydrate	30°.11”

The result shows that drug having poor flow

b) Bulk density and tapped density.

It was determined as per procedure given in 6.1.5. The results are illustrated in following table

Table No 15: Bulk Density and Tapped density

Materials	**Bulk Density(gm/ml)**	**Tapped density(gm/ml)**
Levofloxacin hemihydrate	0.22	0.28

c) Measurement of powder compressibility and Hausner ratio

It was determined as per procedure given in 6.1.5. The results are illustrated in following table**.**

Table No 16: Powder compressibility

Material	**Compressibility index**	**Hausner ratio**
Levofloxacin hemihydrate	26.57%	1.37

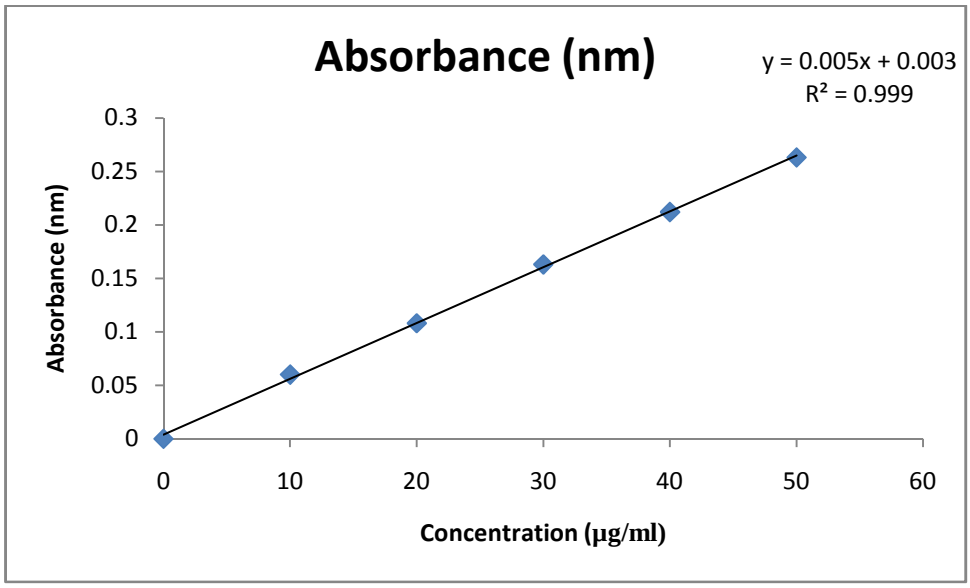
6.1.7 Calibration curve of Levofloxacin in 0.1N Hydrochloric acid solution

Calibration curve data of levofloxacin in 0.1 N HCL at 293nm.Standard calibration curve with a regression value of 0.993. The curve was found to be linear in the concentration range of 10-50 μg/ml.

Table No 17: Calibration curve data for levofloxacin

S.No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	10	0.07
3	20	0.098
4	30	0.163
5	40	0.212
6	50	0.293

Fig No: 5 Calibration curve of levofloxacin



7.1.6 Drug –excipient compatibility studies

Drug excipient interactions play a vital role with respect to release of drug from formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipient used. In the present study, it has been observed that there is no chemical interaction between levofloxacin and the polymers used. From the above figures, it was observed that

there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which shows there were no physical interactions because of some bond formation between drug and polymer.

Table No 18: Drug – Excipients Compatibility Study Results

Principle peaks	Levofloxacin (cm^{-1})	Levofloxacin Floating microsphere (cm^{-1})	Compatible
-COOH monomeric strechting and bending	2500-3300	All the peaks are present in drug loaded formulation F7 Confirms the presence of the drug in the polymer without any interaction	Yes
Alkanes -CH_3 and Aromatic rins	1710-1720		
C=O stretching Vibration of COOH group	1030-1230		

Fig No: 6 FTIR of levofloxacin

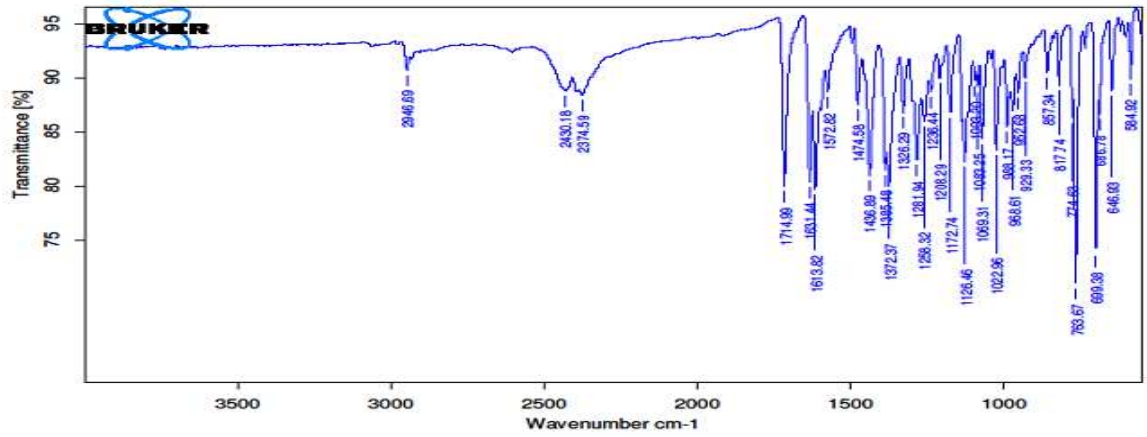


Fig No: 7 FTIR of Levofloxacin + HPMC K4M

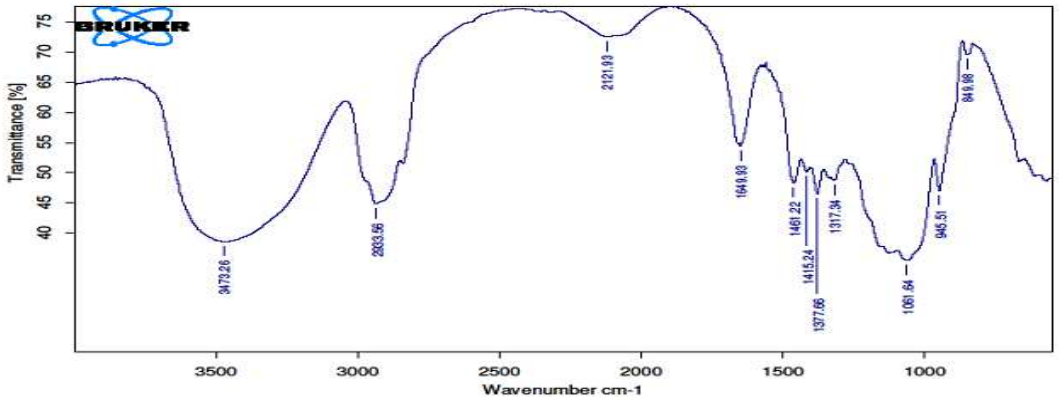


Fig No: 8 FTIR of Levofloxacin + HPMC K100M

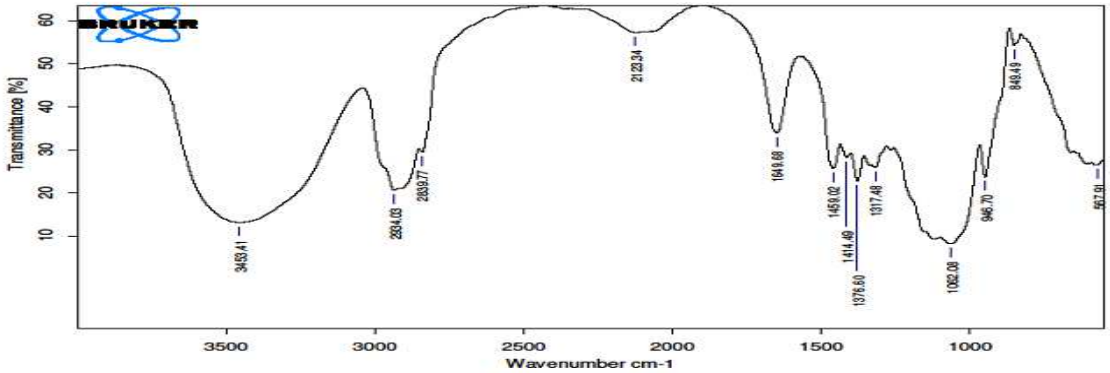
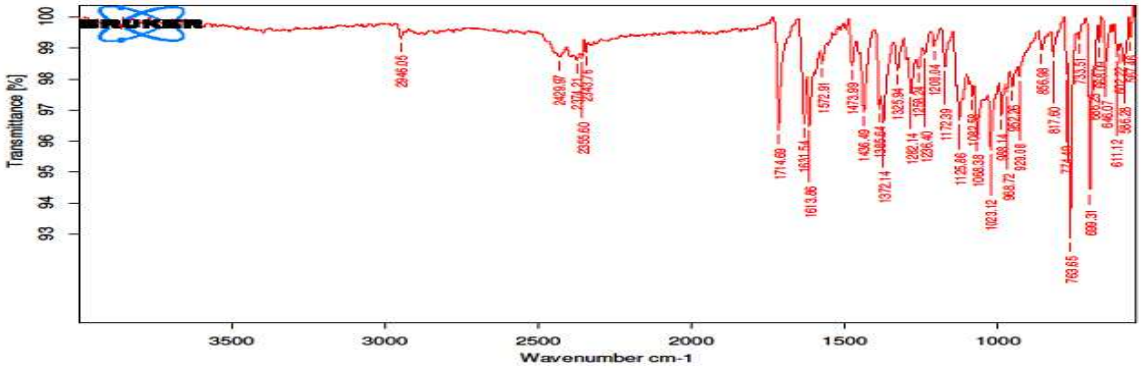


Fig No: 9 FTIR of F7



7.2 Evaluation of levofloxacin floatingmicrospheres

7.2.1. Micromeritic properties

a) Determination ofbulk density, tapped density, angle of repose, carr's index, and hausner ratio.

The bulk density, tapped density, angle of repose, carr's index, and hausner ratio of all the selected formulations were calculated. In the result it was found that the values were well within the limit and showed that the prepared levofloxacin floating microsphere had good flow property. F7 showed better result when compared other formulations

Table No 19: Bulk density, tapped density, angle of repose, carr's index, and hausner ratio

Formation code	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of repose (θ)	Carr's Index (%)	Hausner Ratio
F1	1.05±0.045	0.52 ± 0.09	28.60±0.2	16.60±0.2	1.26 ±0.31
F2	1.03±0.033	0.54±0.07	27.58±0.15	16.19±0.1	1.21±0.04
F3	1.09±0.056	0.53±0.08	28.52±0.19	16.48±0.6	1.28±0.08
F4	0.83±0.032	0.89±0.06	25.64±0.37	16.23±0.6	1.25±0.08
F5	0.85±0.044	0.92±0.07	25.92±0.20	14.79±0.8	1.17±0.09
F6	0.84±0.034	0.91±0.03	25.54±0.13	15.44±0.7	1.27±0.08
F7	0.77±0.055	0.85±0.09	24.26±0.019	13.3±0.6	1.22±0.08
F8	0.79±0.045	0.87±0.04	25.08±0.15	14.6±0.6	1.15±0.09
F9	0.78±0.059	0.84±0.06	24.38±0.25	14.5±0.2	1.20±0.07
F10	0.57±0.064	0.66±0.02	27.88±0.72	17.8±0.27	1.23±0.02

7.2.2 Percentage yield

The floating microspheres were prepared with different and combination of two polymer of HPMC K4M, HPMC K100M, Sodium Alginate and Sodium CMC to investigate the influence of encapsulation efficiency and were used to determine its influence on floating behavior.

The maximum percentage yield was found in F7 formulation and was noted to be 90.12 % among all formulations.

7.2.3 Entrapment efficiency

The percentage entrapment efficiency of various formulation parameters of the preparedmicrospheres were given in table no 19. The entrapment efficiency varied from 78.61 to 88.69. The formulation F7 is having high encapsulation efficiency of 88.96% and F4 is having low encapsulation efficiency of 78.61%.

The low encapsulation was because of using single polymer of HPMC K100M than the drug concentration where the quantity of HPMC K100M is insufficient to entrap the drug. The high encapsulation efficiency is because of using combination of polymers of HPMC K100M, HPMC K4 where the increase in the HPMC concentration forms microspheres encapsulating more amount of drug.

7.2.4*In-vitro* Buoyancy

The different polymers with same ratios of formulation were selected for optimization of their buoyancy property. The formulations in which combination of HPMC K4M, HPMC K100Mare giving the better results.

From the results of all the ten formulations, it is confirmed that the change in polymers of sodium alginate, sodium CMC, HPMC K4M, K100M influences the

properties of the formulations. The formulation F7 with drug and combination of two polymer, was giving the best result of buoyancy property.

The microspheres, having lower densities (having a hollow core) exhibited buoyancy and are expected to be retained in gastric environment for more than 12 hrs. This may be attributed to a decrease in density of microspheres with an increase in polymer concentration.

Table No 20: Percentage yield, *In-vitro* buoyancy and Entrapment efficiency

Batch No.	Percentage yield	*In-vitro* buoyancy	Entrapment efficiency
F1	84.42	85.56	82.62
F2	82.89	83.57	81.37
F3	83.45	84.28	82.71
F4	79.98	80.32	78.16
F5	85.51	86.42	83.40
F6	88.19	89.45	87.93
F7	90.12	91.67	88.96
F8	86.87	87.62	83.29
F9	85.95	86.29	83.74
F10	87.63	88.24	85.12

7.2.5 In-Vitro drug release studies

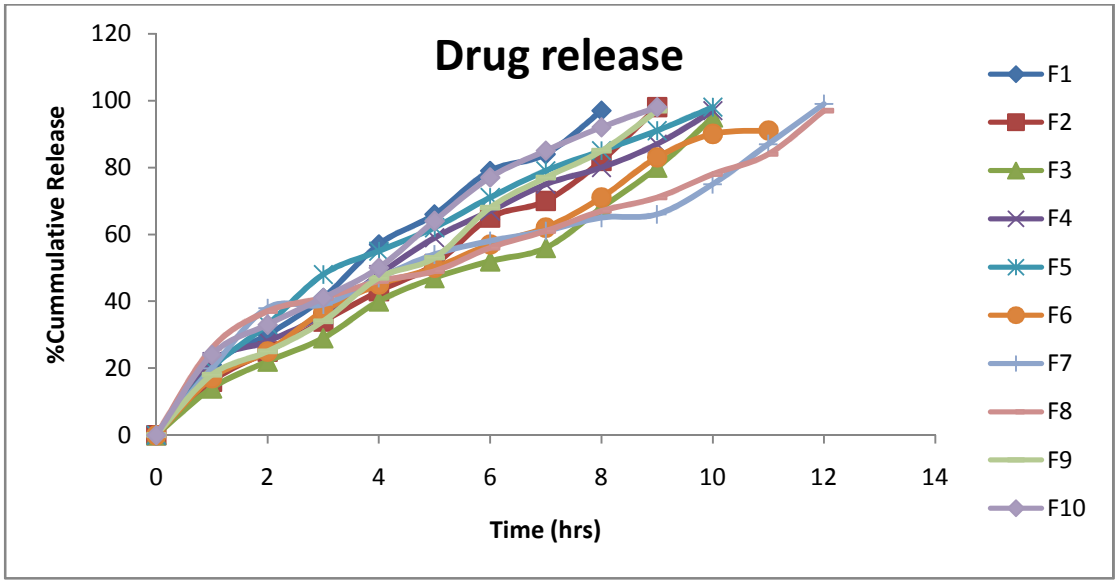
The result showed in the below table. Formulation F7 showed high release of about 99% within 12 hours when compared to the other formulations. That shows that more extended release was observed with the increase in the percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed

to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism.

Table No 21: *In-Vitro* drug release studies

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	21.98	16.97	14.12	22.99	20.98	17.92	20.16	26.97	18.31	24.32
2	30.92	25.85	22.03	28.87	33.74	25.35	38.24	37.86	25.13	33.51
3	41.85	34.77	29.14	36.75	48.31	37.84	39.33	41.68	34.29	41.28
4	57.76	43.68	40.54	48.92	55.85	45.79	47.42	46.56	47.58	50.14
5	66.51	51.63	47.97	59.26	62.24	50.23	54.14	49.52	53.67	64.69
6	79.63	65.74	52.83	67.21	71.18	57.39	58.75	56.37	68.15	77.28
7	84.42	70.34	56.41	75.3	79.26	62.21	61.99	61.66	77.36	85.57
8	97.36	82.26	68.55	80.41	85.2	71.3	65.42	67.23	85.24	92.37
9		98.72	83.17	87.92	91.17	83.41	66.37	71.56	97.63	98.72
10			98.67	97.52	98.97	90.57	75.29	87.43		
11						91.66	87.51	98.72		
12							99.32			

Fig No 10: *In-Vitro* drug release studies



7.2.6 Drug release kinetics

The release kinetic study was performed for the optimized formulation F7. The 'R^2' values for Zero order, First order, Higuchi, and Korsmeyar-peppas models were shown in the below figs. In the present study the release profiles were suggesting that the drug release from the formulation does not follows zero order & first order that was confirmed by low 'R^2' values. The release profile of the optimized formulation F7 mimic the Higuchi with the 'R^2' value, so it may be weight based release (delayed release). In addition, the korsmeyer–peppas model, the value of 'n' showed a Fickian diffusion mechanism. Results are given the table 21.

Table No 22:Drug release kinetics

Formulation	Zero order 'R^2'	First order 'R^2'	Higuchi 'R^2'	Korsmeyar-peppas	
				'R^2'	'n'
F8	0.9834	0.9376	0.903	0.9917	1.4179

Fig No 11:First order release order

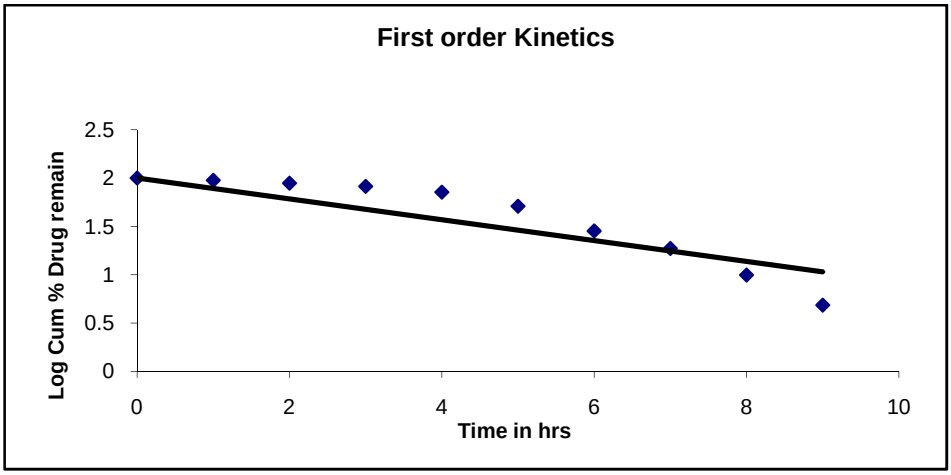


Fig No 12:Higuchi release.

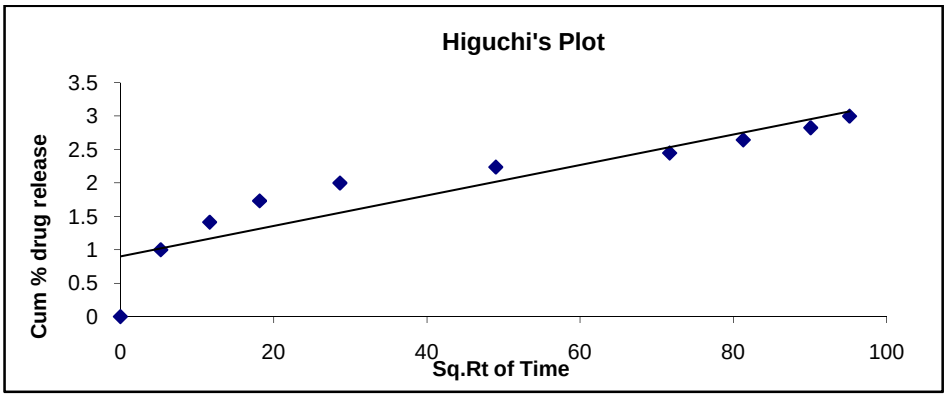
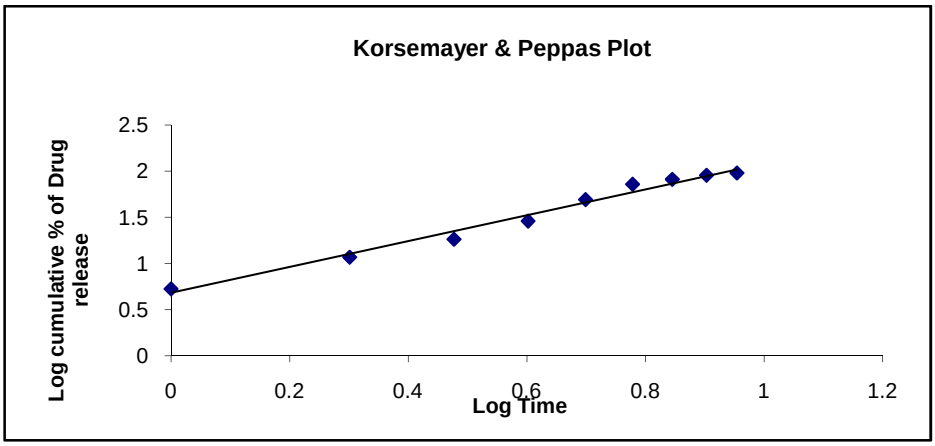


Fig No 13:Korsemayer&mpeppas release.



7.2.7 Scanning Electron Microscopy (SEM)

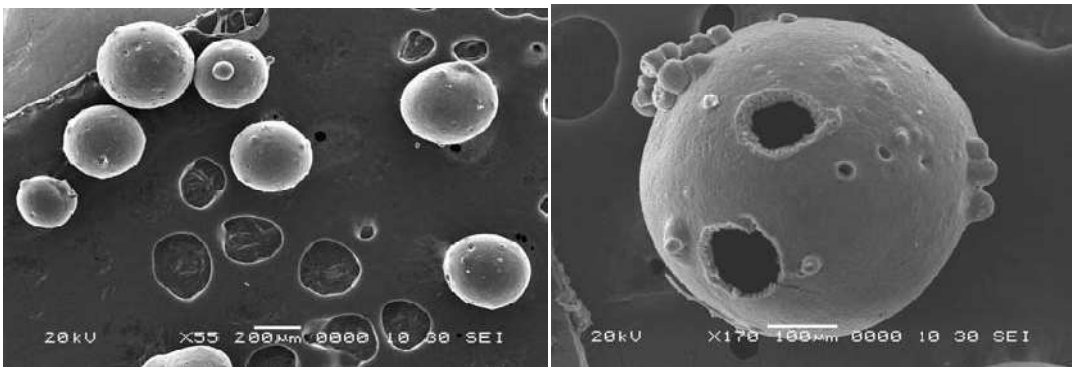
Average particle size of levofloxacin floating microspheres were calculated using optical microscopy results showed in table. Increase particle size because of the increase in the viscosity of polymer solution.

Table No 23 : Average particle size of floating microspheres.

Formulations code	Average particle size(µm)
F7	60 ± 3.8

From the SEM analysis, it was indicated that the microspheres were spherical discrete units , compact, continuous and uniform and is porous in nature, completely covered with polymer coat and the microspheres were, free flowing and of monolithic type. The surface showing hollow nature of floating microspheres in the interior which makes them to float on the GIT fluid.

Fig No 14: Scanning electron microphotographs of floating microsphere of final F7



Smoothness of the surface of spherical shaped microsphere and internal view of the shell having porous structure.Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the

internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

7.2.8 Stability study

The optimized formulation was found to be stable for three months as per ICH guidelines with no significant changes in dissolution behavior and physical stability.

Table No 24: Effect of storage on levofloxacin floating microspheres

Duration	**% Cumulative release**			
	0 days	**1 month**	**2 month**	**3 month**
25 □ C/60 %RH	99.11	98.98	98.51	98.39
30 □ C/65 %RH	99.11	98.96	98.81	98.42
40 □ C/75%RH	99.11	98.94	98.55	98.26

8. SUMMARY AND CONCLUSION

This thesis deals with the investigation carried out on the formulation and evaluation of Levofloxacin loaded loaded floating microsphere so as to improve its gastric residence time, to decrease dosing frequency, maintain prolonged therapeutic levels of the drug following dosing and to reduce the dose to achieve same pharmacological effect.

Based on the literature studies various excipients HPMC K4M, sodium alginate, sodium CMC, HPMC K100M, Methanol, Dichloromethane were selected for the preparation of floating microspheres.

In preformulation studies, compatibility of the selected polymers and levofloxacin were carried by FT-IR peak matching method and results indicated no interaction between drug and excipients.

Floating microspheres were prepared by solvent evaporation method and the effect of certain polymers and formulation was studied. The study on various polymers revealed that all the polymers are important in formulation of floating microspheres. F7 prepared showed maximum release and was selected as ideal batch.

Levofloxacin floating microsphere were evaluated formicromeritics properties, entrapment efficiency, Buoyancy studies, *in-vitro* release studies and kinetics of drug release. In order to elucidate mode and mechanism of drug release the *in-vitro* data was transformed and interpreted at graphical interface constructed using kinetic models. The mechanism of drug release from microspheres follows Non-Fickian release.

It was concluded that solvent evaporation method was suitable for producing floating microsphere Levofloxacin hemihydrate was successfully incorporated into the microspheres using selective polymers. Floating microsphere provided sustained release of the drug. It was concluded that levofloxacin hemihydrate floating microspheres was prepared successfully with increased gastric residence time for better delivery of antibioticsfor improved therapy.

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