ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Formulation and Evaluation of Gastroretentive Floating Microballoons Containing Selected Anti-Ulcer Drug

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Abstract

Microballoons are drug delivery system that promises to be a potential approach for gastric retention. Microballoon drug delivery systems have shown to be of better significance in controlling the release rate for drugs having site-specific absorption. The floating microballoon showed gastro retentive controlled release delivery with efficient means of enhancing the bioavailability and promises to be a potential approach for gastric retention. In the present study, an attempt was made to design and evaluate gastroretentive floating microballoons of omeprazole to increase the gastric residence time and thereby improves bioavailability, reduces dosing frequency and provide better patient compliance. Gastroretentive floating microballoons were prepared by emulsion solvent diffusion method using ethyl cellulose and hydroxyl propyl methyl cellulose. The prepared microballoons were evaluated for preformulation parameters, micromeritic properties, particle size, entrapment efficiency, SEM, percentage yield and i*n vitro* buoyancy. The microballoons were encapsulated into a capsule shell. The omeprazole floating microballoons were then evaluated for *in vitro* dissolution by using USP type II apparatus at 100 rpm in 900 ml of pH 0.1 N HCL for 8 h at 37± 0.5 °C. FTIR analysis results showed that there was no interaction between drug and the excipients. The formulation F6 was found optimized with desirable characteristics for microballoons and showed drug release up to 6 h. The data obtained from *in vitro* release study were fitted to various mathematical models. The *in vitro* drug release showed highest regression coefficient values for the first order model, indicating diffusion to be the predominant mechanism of drug release. The study showed that floating microballoons of omeprazole effectively improve the bioavailability by increasing the gastric residence time. The floating microballoons could be prepared in a cost effective manner and promises better therapeutic effect from conventional dosage forms.

Keywords

Dichloromethane; Emulsion solvent diffusion; Ethyl cellulose; Hydroxy propyl methyl cellulose; Omeprazole.

INTRODUCTION

Oral route is the most preferred route of administration of drugs because of its low cost of therapy, ease of administration, patient compliance etc. Conventional oral dosage forms like tablets; capsules etc provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma concentration of drug levels. Numerous oral delivery systems have been developed nowadays to act as drug reservoirs from which the active substance can be released over a certain period of time at a predetermined and controlled rate. A major constraint is that not all drug candidates are absorbed uniformly throughout the GIT. Drugs which are absorbed in a particular segment of GIT only or are absorbed to a different extent in various segments of GIT are said to have an 'absorption window'. But in case of 'narrow absorption window' drugs, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. Again after crossing the absorption window, the released drug goes in vein with negligible or no absorption. This phenomenon will lead to shortage of time available for drug absorption after it, which is then accompanied by lesser bioavailability. Thus, oral controlled drug delivery has faced some difficulties related to physiological adversities, like short gastric residence time (GRT) and unpredictable gastric emptying time (GET). Prolonged GRT improves the bioavailability of drugs, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. This has triggered the attention towards the development of various gastroretentive drug delivery technologies to deliver drugs having 'narrow absorption window' with improved bioavailability [1].

Gastroretentive dosage forms are designed to retain in the gastric region for prolonged time and release entrapped drug and thereby enable sustained and prolonged input of the drug to the upper part of the GIT and thus ensuring its optimal bioavailability. Thus, they not only prolong the dosing intervals, but also increase the patient compliance beyond the level of existing controlled release dosage forms. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two systems [2]:

1) Effervescent systems
   - ✓ Volatile liquid containing systems
   - ✓ Gas-generating Systems
2) Non-Effervescent Systems
   - ✓ Colloidal gel barrier systems
   - ✓ Microporous Compartment System
   - ✓ Alginate beads
   - ✓ Hollow microspheres

Floating drug delivery systems (FDDS) have a bulk density lower than gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a long duration. While the system is floating on gastric contents, the drug released slowly at desired rate from system. After the release of drug, the residual system is eliminated from the stomach. It results in increased GRT and better control over fluctuation in plasma concentration. A minimal gastric content and a minimal level of floating force is needed to allow proper achievements of the buoyancy retention effect [2].

Physiology of stomach

Stomach is anatomically divided into fundus, body and antrum. Proximal part of fundus and body acts as reservoir for undigested material. Antrum is an important site for mixing and acts as a pump for gastric emptying by propelling action. Gastric emptying will occur in both fasting and fed states. During the fasting state an interdigestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 h. It is called interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) divided into 4 phases.

- Phase I (basal phase) - lasts from 30 to 60 min with rare contractions.
- Phase II (preburst phase) - lasts for 20 to 40 min with intermittent action potential and contraction. Intensity and frequency also increases as the phase progresses.
- Phase III (burst phase) - lasts for 10 to 20 min. It includes intense and regular contraction for short period. It is called housekeeper wave.
- Phase IV - lasts for 0 -5 min and occur between phases III and 1 of 2 consecutive[2,3].

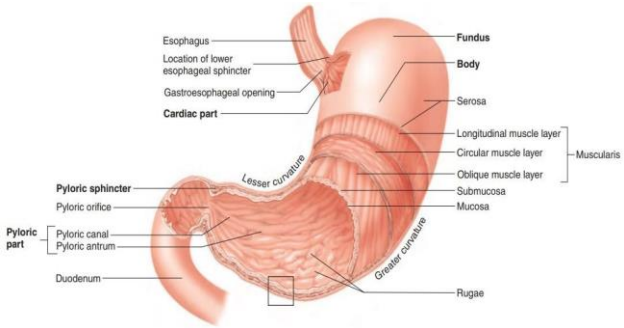

Figure 1: Anatomy of stomach

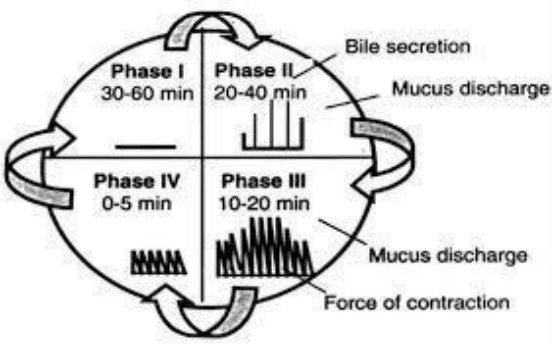

Figure 2: Interdigestive myloelectric cycle

Factors affecting gastric retention

- Size of dosage form

Dosage form unit with diameter of more than 7.5 mm have increased GRT compared with a diameter of 9.9 mm.

- Shape of dosage form

Shape and size are important in designing dosage forms. Ring shaped and tetrahedron shaped devices are better GRT (90-100% at 24 h) as compared with others.

- Density of dosage form

Dosage forms having density lower than gastric contents can float in the gastric fluids and provide gastric retention while high density systems sink to bottom. Both dosage form isolate the dosage system from the pylorus.

- Food intake and its nature

Food intake, viscosity and volume of food, caloric value, frequency of feeding have effect on gastric retention of dosage forms. Presence of food increases GRT. A heavy meal containing high proteins and fats can increase GRT by 4 -10 h.

- Effect of gender, posture and age

Females have slower gastric emptying rates than male. Upright, ambulatory, and supine state doesnot have any significant difference in GRT. Gastric emptying will slow down in elderly patients [3].

Microballoons

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Microballoons are considered as one of the most favourable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The novel techniques involved in their preparation include simple solvent evaporation method, emulsion-solvent diffusion method, single emulsion technique, double emulsion technique, phase separation coacervation technique, polymerization technique, spray drying, spray congealing and hot melt encapsulation method. The slow release of drug at desired rate and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit S and hydroxy propyl methyl cellulose, cellulose acetate are used in the formulation of hollow microspheres, the release of drug can be modulated by optimizing polymer concentration and the polymer - plasticizer ratio [4].

Advantages

- ✓ Reduces dosing frequency and thereby improve the patient compliance.
- ✓ Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects and despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

- ✓ Hollow microspheres are used to decrease material density and gastric retention time is increased because of buoyancy.
- ✓ Enhanced absorption of drugs which solubilise only in stomach.
- ✓ Drug releases in controlled manner for prolonged period.
- ✓ Site-specific drug delivery to stomach can be achieved.
- ✓ Superiorto 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 [4].

Limitation

Some of the disadvantages were found to be as follows:

- ✓ The modified release from the formulations.
- ✓ The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- ✓ Differences in the release rate from one dose to another.
- ✓ Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- ✓ Dosage forms of this kind should not be crushed or chewed[4].

Drug candidates suitable for gastroretentive drug delivery

- Drugs having narrow absorption window in GIT

Eg: L Dopa, p-aminobenzoic acid, furosemide, riboflavin

- Drugs those are locally active in stomach

Eg: misoprostol, antacid

- Drugs those are unstable in intestinal/ colonic environment

Eg: captopril, ranitidine HCl, metronidazole

- Drugs that disturb normal colonic microbes

Eg: antibiotics used for the eradication of Helicobactor pylori, such as tetracycline, clarithromycin, amoxicillin.

- Drugs that exhibit poor solubility at high pH values

Eg : diazepam, chlordiazepoxide, verapamil [5]

Applications

- ✓ Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are.
- ✓ Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating helicobacter pylori from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
- ✓ These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system.
- ✓ The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem hydrochloride, verapamil hydrochloride and riboflavin, aspirin, griseofulvin, ibuprofen, terfenadine etc.
- ✓ Floating microspheres can greatly improve the pharmacotherapy of stomach through local drug release. Thus, eradicating Helicobacter pylori from sub-mucosal tissue of the stomach are useful in the treatment of peptic ulcers, chronic gastritis, gastro oesophageal reflux diseases etc. Floating bio adhesive microspheres of aceto hydroxamic acid are formulated for treatment of Helicobacter pylori infection. Hollow microspheres of ranitidine hydrochloride are also developed for the treatment of gastric ulcer.
- ✓ Floating microspheres are 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 a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
- ✓ Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastroretentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 h in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 h e.g., metoclopramide and glipizide loaded chitosan microspheres.
- ✓ The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, amino glycosides and tetracyclines) are taken up only from very specific

sites of the GI mucosa.

- ✓ Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of indomethacin are quiet beneficial for rheumatic patients[5].

Composition

- ✓ Drugs: Drugs with narrow absorption window in GI tract, primarily absorbed from stomach and upper part of GIT, locally act in the stomach, degrade in the colon, disturb normal colonic bacteria. E.g. aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin, para aminobenzoic acid, furosemide, calcium supplements, chlordiazepoxide & scinnarazine riboflavin, levodopa, antacids and misoprostol, Ranitidine and metronidazole, amoxicillin trihydrate.
- ✓ Polymers: Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide.
- ✓ Solvents: It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. e.g. ethanol, dichloromethane, acetonitrile, acetone, isopropyl alcohol, dimethylformamide.
- ✓ Processing medium: It is used to harden the drug polymer emulsified droplets when the drug-polymer solution is poured into it, should not interact with the former; mainly used are liquid paraffin, polyvinyl alcohol and water.
- ✓ Surfactant: They are stabilizers or emulsifiers; play the role of hardening the microspheres as well e.g. tween 80, span 80 and sodium lauryl sulphate.
- ✓ Cross linking agent: Chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using diacid chlorides such as terephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent.
- ✓ Hardening agent: This helps to harden the microspheres formed in the processing medium. e.g. n-hexane, petroleum ether (in case the processing medium is liquid paraffin)[5].

Mechanism of floating microballoons

When microballoons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to 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 microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments[6].

Methods of preparation

❖ Solvent Evaporation Method

Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants /polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinylacetate, carbopol, agar, polyethylene oxide and polycarbonate.

❖ Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes [7].

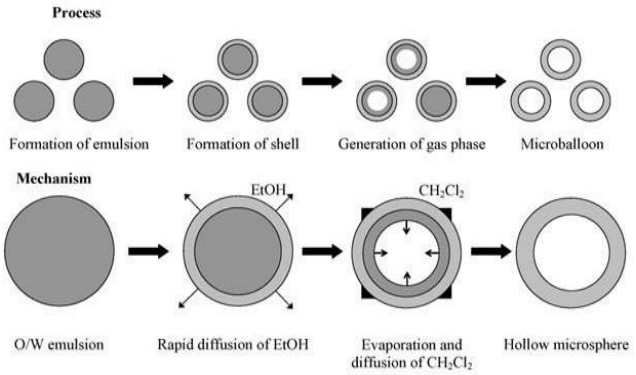

Figure 3: Formulation of microballoons.

Criteria for selection of drug

The criteria of drugs that can be used for formulation of microballoons are,

- Drugs having narrow absorption window in GIT.
- Drugs those are locally active in stomach.
- Drugs those are unstable in intestinal/colonic environment.
- Drugs that disturb normal colonic microbes.
- Drugs that exhibit poor solubility at high pH values.

Omeprazole is a benzimidazole with selective and irreversible proton pump inhibition activity. Omeprazole forms a stable disulfide bond with the sulfhydryl group of the hydrogen- potassium (H+ - K+) ATP ase found on the secretory surface of parietal cells, thereby inhibiting the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen and suppressing gastric acid secretion. This agent exhibits no anticholinergic activities and does not antagonize histamine H2 receptors. Omeprazole belongs to biopharmaceutical classification system class II which is having low solubility and high permeability. Omeprazole is a suitable candidate for the preparation of microballoons because it has short half life and low bioavailability. By formulating omeprazole into microballoons oral bioavailability of the drug can be improved.

MATERIALS AND METHODS

Materials

Omeprazole obtained from Balaji Drugs, Gujarat and HPMC, Ethyl cellulose, Dichloromethane, Ethanol obtained from Yarrow chem. Products, Mumbai, India.

METHODS

FORMULATION OF FLOATING MICROBALLOONS:

Floating microballoons were prepared by the emulsion solvent diffusion method. Six formulations of floating microballoons were prepared. Different ratios of HPMC K4M and ethyl cellulose were mixed in a mixture of ethanol and dichloromethane (DCM) in the ratio of 1:1. The resulting suspension was added slowly into stirring to 250 ml water containing 0.01 ml tween 80 at room temperature. The emulsion formed was stirred continuously for 2 h using a mechanical stirrer at 300 rpm. The temperature was maintained at 40°C. The finely dispersed droplets of the polymer solution of the drug were solidified in an aqueous phase via the diffusion of the solvent, leaving the cavity of microspheres filled with water. Microballoons formed were filtered and washed repeatedly with distilled water. The collected floating microballoons were dried at room temperature and stored in desiccators.

EVALUATION OF FLOATING MICROBALLOONS

DEVELOPMENT OF ANALYTICAL METHODS

Determination of λ_{max} for pure drug Omeprazole

- **Preparation of stock solution**

The standard solution of omeprazole at 1000 µg / ml was prepared by weighing 100 mg of pure omeprazole using an analytical scale, put into a 100 ml measuring flask, then partially added 0.1 N HCl, shaken, then supplied with 0.1 N HCl until boundary mark.

- **Determination of λ_{max}**

Omeprazole stock solution was diluted by measuring 10 ml of the solution into a 100 ml volumetric flask and diluted it with solvent until the boundary marks, then homogenize. From this solution of omeprazole of 100 µg / ml, pipetted 10 ml into a 100 ml volumetric flask and then added solvent to the limit, mixed homogeneously to obtain a concentration of 10 µg / ml. Measure the absorbance in the wavelength range 200-400 nm with the UV-Vis spectrophotometer to obtain the maximum wavelength of omeprazole. 0.1 N HCl was used as blank.

CONSTRUCTION OF STANDARD CALIBRATION CURVE OF OMEPRAZOLE

- **Preparation of standard solution**

The standard solution of omeprazole at 1000 µg / ml was prepared by weighing 100 mg of pure omeprazole using an analytical scale, put into a 100 ml volumetric flask, then added 0.1 N HCl, shaken, then volume is made with 0.1 N HCl.

- **Preparation of the calibration curve of omeprazole**

Five series of omeprazole solutions prepared with concentrations of 10 µg/ ml, 12 µg / ml, 14 µg / ml, 16 µg / ml, 18 µg / ml are used for the determination of calibration curves. 10 ml of the standard stock solution of omeprazole solution was pipetted into 100 ml standard flask and volume was made upto 100 ml which gave a concentration of 100 µg / ml. Again pipetted out 10 ml of the secondary stock solution into 100 ml volumetric flask and the volume were made upto 100 ml with 0.1N HCl. After which 1 ml, 1.2 ml, 1.4 ml, 1.6 ml, and 1.8 ml of the standard omeprazole solution of 10 µg / ml was pipetted into a 10 ml measuring flask, diluted with 0.1 N HCl and suffice up to the boundary mark. Measure the absorbance with UV-Vis spectrophotometry at a wavelength of 304.80 nm.

PREFORMULATION STUDIES

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Objective of preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physico-chemical parameter of new drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability plays important role in preformulation study. Polymorphism having crystal and amorphous forms shows different chemical, physical and therapeutic description of the drug molecule. Preformulation investigations are designed to identify those physicochemical properties of the resulting product. Studies performed for preformulation evaluation are given below.

ORGANOLEPTIC EVALUATION

Organoleptic characters of drug was evaluated and recorded by using descriptive technology. Following characters of omeprazole were determined.

- Colour
- Odour
- Taste

DETERMINATION OF MELTING POINT

The temperature at which a solid melts and becomes a liquid is the melting point. Pure crystalline substances have a clear, sharply defined melting point. It is a physical property of a solid and can be used to identify a substance. A solid usually melts over a range of temperature rather than at one specific temperature. If the compound melts over a narrow range, it can usually be assumed that the compound is relatively pure. Compounds that melt over a wide range are assumed to be impure. Melting point of omeprazole was determined by capillary method. Filled the melting point capillary tube with finely ground drug powder, which has one end closed. The melting point capillary tube filled with the sample was inserted into the melting point apparatus. The temperature at which the sample gets melted gives the melting point of the sample.

DETERMINATION OF SOLUBILITY

Solubility may be defined as the amount of a substance that dissolves in a given volume of solvent at a specified temperature. Solubility is expressed in terms of maximum volume or mass of the solute that dissolve in a given volume or mass of a solvent. Pharmacopoeias give solubility's in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid.

Procedure: Solubility test of omeprazole was determined using various solvents like water, ethanol, acetone, chloroform, dichloromethane and diethyl ether.

DRUG EXCIPIENT COMPATABILITY STUDIES

Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutical properties and stability of the dosage form. A complete characterization and understanding of physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In a dosage form, an API comes in direct contact with other components (excipients) of the formulation that facilitate the administration and release of an active component as well as protect it from the environment. Although excipients are pharmacologically inert, they can interact with drugs in the dosage form to affect drug product stability in physical aspects such as organoleptic properties, dissolution slow down or chemically by causing drug degradation. Careful selection of the excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the fore front of drug product science and technology research.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

Fourier Transform-Infrared Spectroscopy (FTIR) is an analytical technique used to identify organic (and in some cases inorganic) materials. This technique measures the absorption of infrared radiation by the sample material versus wavelength. The infrared absorption bands identify molecular components and structures. When a material is irradiated with infrared radiation, absorbed IR radiation usually excites molecules into a higher vibrational state. The wavelength of light absorbed by a particular molecule is a function of the energy difference between the at-rest and excited vibrational states. The wavelengths that are absorbed by the sample are characteristic of its molecular structure. The FTIR spectrometer uses an interferometer to modulate the wavelength from a broadband infrared source. A detector measures the intensity of transmitted or reflected light as a function of its wavelength. The signal obtained from the detector is an interferogram, which must be analyzed with a computer using Fourier transforms to obtain a single-beam infrared spectrum. The FTIR spectra are usually presented as plots of intensity versus wavenumber (in cm^{-1}). Wavenumber is the reciprocal of the wavelength. The intensity can be plotted as the percentage of light transmittance or absorbance at each wavenumber.

Procedure for FTIR

Integrity of the drug in the formulations was checked by IR spectrum of selected formulation along with the drug and other excipients. The spectra were taken by using Shmiadzu IR Prestige-21 Spectrometer and compared with standard spectra. In this study pelletzing material was potassium bromide (KBr). Before forming the pellet of potassium bromide, it was completely dried at 100^0C for one hour and after drying it was thoroughly mixed with the sample and 100 parts of KBr. The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which is further subjected to interpretation.

- **Physical examination**

The prepared omeprazole floating microballoons were visually inspected for their colour and appearance.

- **Micromeritic properties**

✓ **Bulk density**

An accurately weighed 2 g sample of powder was placed into 10 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm^3)

$$\textbf{Bulk density} = \frac{\textbf{Weight of sample}}{\textbf{Bulk volume of the sample}}$$

✓ **Tapped density**

An accurately weighed 2 g of powder sample was placed in 10 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm^3)

$$\textbf{Tapped density} = \frac{\textbf{Weight of sample}}{\textbf{Tapped volume}}$$

✓ **Carr's Index**

Flow property of blend depends upon compressibility index. The Carr's Index is an indication of the compressibility of a powder.

$$\textbf{Carr's Index} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}} \times 100$$

✓ **Angle of repose**

The angle of repose is the angle a pile forms with the ground. Angle of repose was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. The accurately weighed blend is allowed to pass through the funnel freely onto the surface. The height and diameter of the powder cone were measured and angle of repose was calculated using the following equation.

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

Where, h = height of pile, r = radius of pile, and θ = angle of repose

✓ **Hausner's ratio**

The Hausner ratio indicates the compressibility and flow property of a powder. Hausner ratio greater than 1.25 is an indication of poor flowability. This is calculated from the values of bulk density and tapped density by using the formula:

$$\textbf{Hausner ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

✓ **Particle size analysis**

The particle size analysis of microballoons was determined with an optical microscopic method. The particle size of the prepared microballoons were determined by dispersing in glycerin, and a drop of the above dispersion was transferred on a glass slide and observed under an optical microscope under regular polarized light. The mean particle size was calculated by measuring 100 microballoons (n=3) with the help of a calibrated eyepiece micrometer and stage micrometer. The average diameter was calculated using the following formula:

$$\textbf{Average diameter} = \frac{\textbf{Total diameter of microballoons}}{\textbf{Number of microballoons}} \times \textbf{Calibration factor}$$

- **Entrapment efficiency**

The floating microballoons (10 mg) were taken and dissolved in 10 ml of ethanol and volume was made up with 0.1 N HCl. The solution was filtered and analyzed spectrophotometrically at 301.85 nm using calibration curve. Each batch should be examined for drug content in triplicate manner. The entrapment efficiency of floating microballoons can be calculated by the following formula:

$$\textbf{Entrapment efficiency} = \frac{\textbf{Actual drug content}}{\textbf{Theoretical drug content}} \times 100$$

- **Scanning electron microscopy (SEM)**

The external and internal morphology of the microspheres were studied by using scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the microballoons powder on a double adhesive tape which stuck to a stub. The stubs were then coated with platinum under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The samples were then randomly scanned, and the photomicrographs were taken on higher magnification for surface morphology.

- **Percentage yield**

Percentage yield of floating microballoon formulation was determined by weighing after drying. The actual weight of microballoons was divided by the total weight of all the non volatile components used for the preparation of microballoons and is represented by the following formula:

$$\textbf{Percentage yield} = \frac{\textbf{Actual weight of floating microballoons}}{\textbf{Total weight of drug and excipients}} \times 100$$

- ***In vitro* buoyancy**

Floating microballoons were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 h the layer of buoyant microballoons was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types was dried in a desiccator until constant weight was achieved. Both the fractions of microballoons were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\%\ \textbf{Buoyancy of Microballoons} = \frac{\textbf{Weight of floating microballoons}}{\textbf{Intial weight of floating microballoons}} \times 100$$

- ***In vitro* dissolution study**

In vitro dissolution studies were carried out in a USP type II paddle dissolution assembly. 100 mg of microballoons were weighed accurately and added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 ºC. Samples were withdrawn at each hour and analyzed by UV spectroscopy at 301.85 nm.

- **Kinetic study**
- **Dissolution profile modeling**

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles are as follows:

- **Zero order kinetics**

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

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

Dividing this equation by W_0 and simplifying:

$$F_t = k_0 t$$

Where F_t=1-(W_t/W_0) and F_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant.

First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\mathbf{Log\ Q_t = Log\ Q_0 + \frac{k_1 t}{2.303}}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

- **Korsmeyer Peppas model**

Korsmeyer developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$\frac{Q_t}{Q_\alpha} = Kt^n$$

Where K is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism as shown in the table 5.6.

Table a: Drug release mechanism

Release Exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
Higher than 1.0	Super case transport	t^{n-1}

The release exponent can be obtained from the slope and the constant (K) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

- **Higuchi model**

$$\mathbf{Q_t = K_H t^{1/2}}$$

Where Q_t= the amount of drug released at time t and K_H = Higuchi release rate.

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square roots of time versus concentrations indicates that the drug release follows strict fickian diffusion.

- **Stability testing**

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40 RH for 3 months. At the end of - 2ºC and 75% ± 5 % studies, samples were analyzed for the physical appearance and drug content.

RESULTS AND DISCUSSION

- **Drug excipient compatability studies**

The characteristic peaks were obtained of wave numbers at 1645.28 cm^{-1} , 3444.87 cm^{-1}, 1338.60 cm^{-1} of pure drug which corresponds to alkene (C=C), amino (NH), cyano (CN) groups. These characteristic peaks remained unaltered in both the spectrum of physical mixture including drug & polymer and mixture of drug and excipients. Thus it was concluded that the drug and excipients were compatible.

Table b: Composition of floating microballoons

INGREDIENTS	F1	F2	F3	F4	F5	F6
Omeprazole (in mg)	20	20	20	20	20	20
Ethyl Cellulose(in mg)	100	100	100	200	300	400
HPMC K4M(in mg)	200	300	400	100	100	100
Ethanol(in ml)	10	10	10	10	10	10
Dichloromethane(in ml)	10	10	10	10	10	10
Tween 80(in ml)	0.01	0.01	0.01	0.01	0.01	0.01

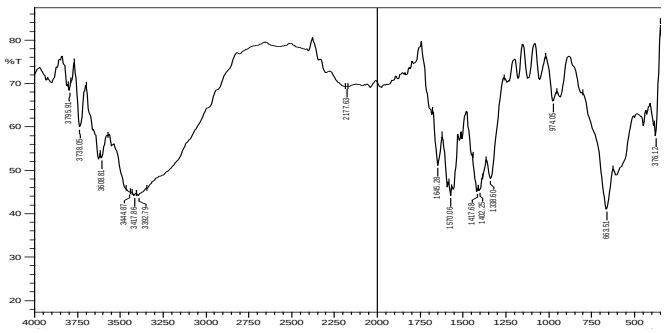

Fig 4: FTIR spectrum of omeprazole

Table c: Spectral analysis of omeprazole

Sl. No	Functional group	Characteristic peak range cm^{-1}	Characteristic peak cm^{-1}
1	C=C	1610-1680 cm^{-1}	1645.28 cm^{-1}
2	NH	3300-3500 cm^{-1}	3444.87 cm^{-1}
3	CN	1180-1360 cm^{-1}	1338.60 cm^{-1}

The interpretation of FTIR spectrum of omeprazole is given in table c. The spectrum of omeprazole gave intense peaks for alkene, amino, cyano groups.

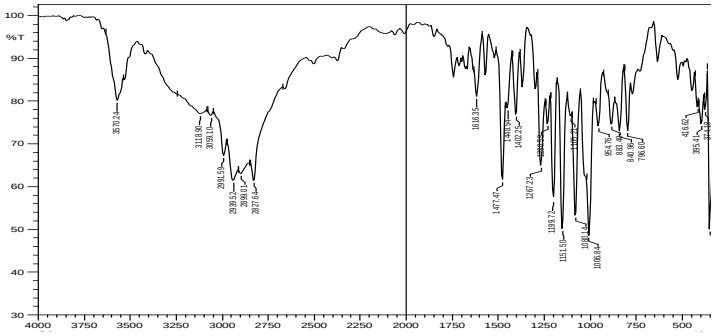

Fig 5: FTIR spectrum of omeprazole and HPMC K4M

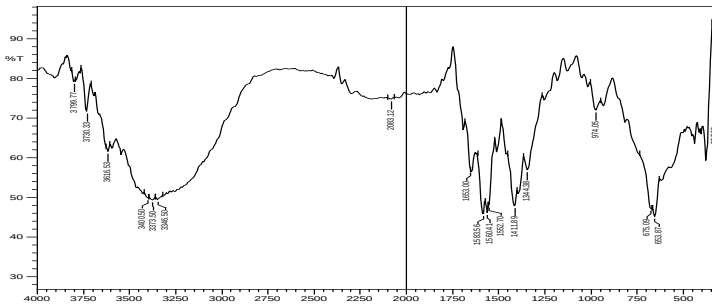

Fig 6: FTIR spectrum of omeprazole and ethyl cellulose

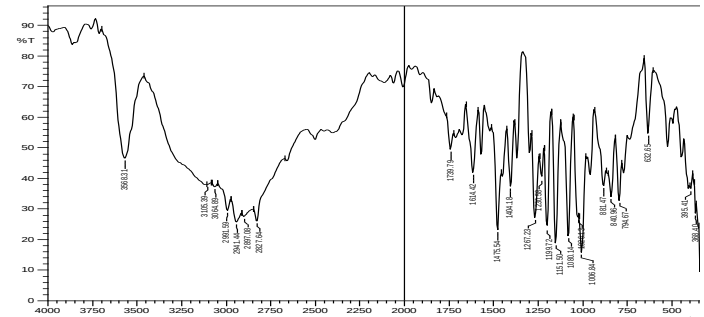

Fig 7: FTIR spectrum of omeprazole and ethanol

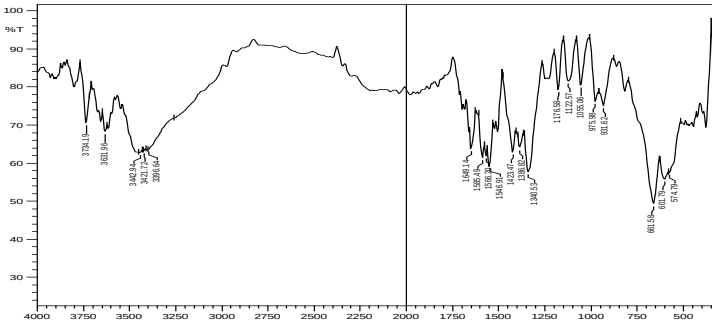

Fig 8: FTIR spectrum of omeprazole and dichloromethane

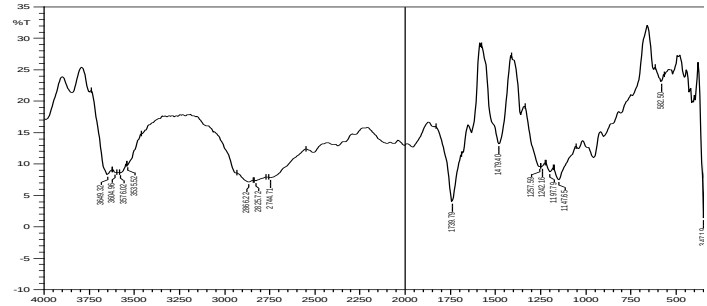

Fig 9: FTIR spectrum of omeprazole and tween 80.

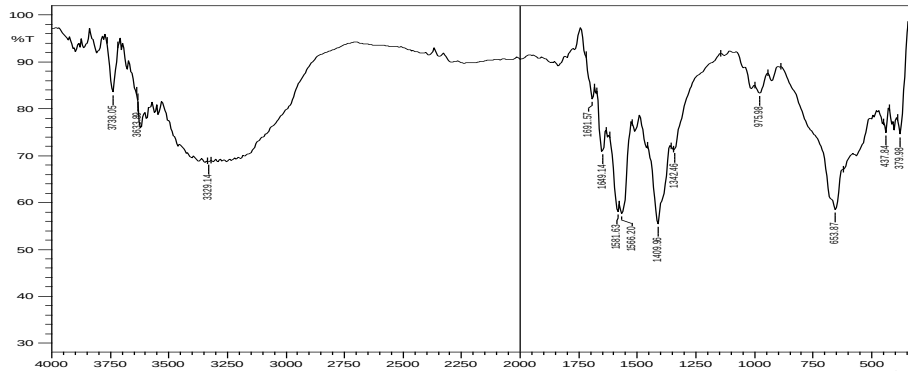

Fig 10: FTIR spectrum of omeprazole and excipients.

FTIR analysis was done for pure drug and drug polymer mixture. FTIR spectrum of drug showed the prominent peaks with respect to functional groups. From the FTIR spectrum of physical mixture of drug with polymer it can be concluded that there is no significant interaction between the drug, polymer and excipients. In the spectrum of drug polymer mixture, the characteristic peak of drug was not altered significantly.

- **FORMULATION DEVELOPMENT**

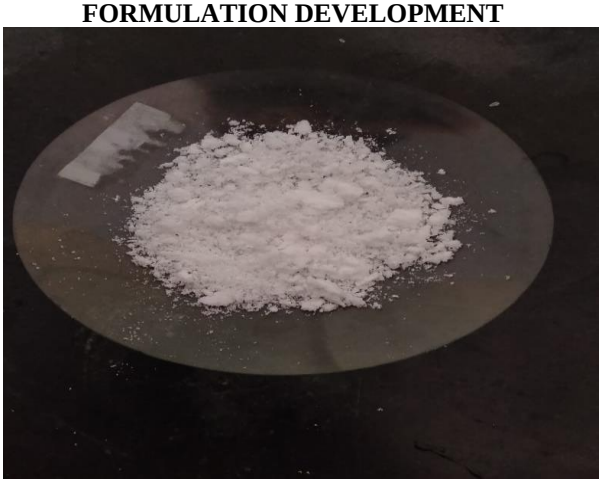

Fig 11: Omeprazole floating microballoon powder

Fig 12: Omeprazole floating microballoon capsule

The obtained microballoons were stored in air tight containers and subjected to evaluation.

EVALUATION OF OMEPRAZOLE LOADED FLOATING MICROBALLOONS

- **Physical examination**

The results of physical evaluations of floating microballoons are shown in the Table d. On the physical evaluation of all the batches formulated, it was observed that the floating microballoons of all the batches had desirable physical properties. Colour varied from white to off white.

Table d: Physical evaluation of floating microballoons

Sl No.	Formulation code	Colour	Appearence
1	**F1**	White	Powder
2	**F2**	White	Powder
3	**F3**	Off white	Powder
4	**F4**	Off white	Powder
5	**F5**	Off White	Powder
6	**F6**	White	Powder

- **Micromeritic properties**

The powder blends of floating microballoons were evaluated for their flow properties, the results were shown in the Table e. Angle of repose was in the range of 28.12±0.05 to 28.96±0.09 which indicated good flow of the powder for all formulations. The values of bulk density were found to be in the range of 0.16±0.01 to 0.20±0.01 gm/cm^3.The tapped density was in the range of 0.18±0.01 to 0.22±0.01 gm/cm^3. The values of compressibility index were found to be in the range from 10.69±0.73 to 9.86±0.83 gm/cm/sec. The values of hausner's ratio were found to in the range from 1.10±0.03 to 1.14±0.06. These values indicated that the micromeritic properties of the floating microballoons are within the acceptable limits, and they exhibited good flow properties.

Table e: Micromeritic studies of floating microballoons

Formulation code	Bulk density gm/cm^3 *± S.D	Tapped density gm/cm^3 *± S.D	Angle of repose$^{(°)}$	Compressibility index (gm/cm/sec) *± S.D	Hausner's ratio *± S.D
F1	0.16±0.01	0.18±0.01	28.12±0.05	10.69±0.73	1.10±0.03
F2	0.18±0.01	0.19±0.01	29.88±0.10	5.32±0.16	1.05±0.01
F3	0.20±0.01	0.22±0.01	30.76±0.20	11.95±0.41	1.10±0.05
F4	0.18±0.01	0.21±0.01	29.32±0.16	17.38±0.39	1.20±0.03
F5	0.20±0.01	0.23±0.01	29.88±0.10	13.24±0.34	1.15±0.01
F6	0.20±0.01	0.22±0.01	28.96±0.09	9.86±0.33	1.14±0.06

*Average of 6 determinants, SD= Standard deviation

- **Particle size analysis of floating microballoons**

The particle size of the formulated microballoons was determined by optical microscopy and recorded in Table f. The average particle size of all the formulations ranged from 124.02±1.2 µm to 147.70±1.23 µm. The increase in the particle size is related to the increased viscosity due to the presence of ethyl cellulose, which results in the formation of larger droplets leading to larger floating microballoons.

Table f: Particle size analysis of floating microballoons.

Sl. No	Formulation code	Particle size (µm)*±S.D
1.	**F1**	124.02±0.29
2.	**F2**	129.58±0.42
3.	**F3**	134.23±0.35
4.	**F4**	139.41±0.48
5.	**F5**	142.62±0.56
6.	**F6**	147.70±0.62

*Average of 6 determinants, SD= standard deviation

- **Entrapment efficiency**

The entrapment efficiency of omeprazole floating microballoon formulations are given in Table g. The entrapment efficiency in formulations from F1-F6 ranged between 85.60± 0.69% to 92.80± 0.97%.

Table g: Entrapment efficiency of floating microballoons

Sl. No	Formulation code	Entrapment efficiency (%)*±S.D
1	**F1**	85.60±0.69
2	**F2**	72.82±0.37
3	**F3**	67.39±0.67
4	**F4**	87.61±0.76
5	**F5**	85.40±0.84
6	**F6**	92.80±0.97

*Average of 6 determinants, SD= standard deviation

The formulation F6 was found to have the larger value for entrapment efficiency. From the evaluation of entrapment efficiency of prepared microballoons, it is concluded that with increase in the concentration of ethyl cellulose the values of entrapment efficiency increases.

- **Scanning electron microscopy (SEM)**

The external and internal morphology of floating microballoons were studied by SEM. SEM photograph of floating microballoons, shown in the Figure 13 and 14, in which the prepared microballoons were spherical with smooth surface and having a hollow cavity.

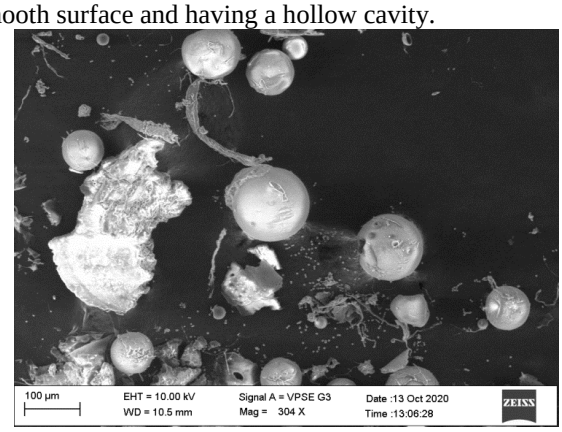

Fig 13: SEM image of floating microballoons

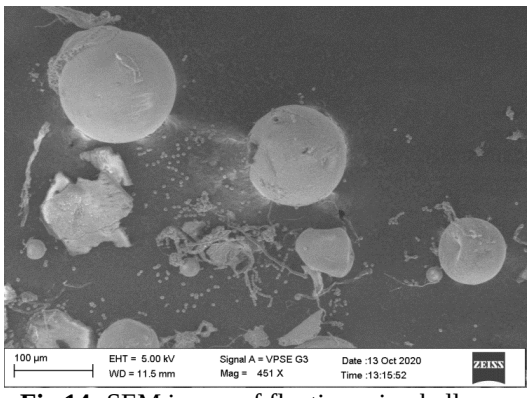

Fig 14: SEM image of floating microballoons

- **Percentage yield**

Percentage yield of microballoons were shown in Table h. The percentage yield of the prepared floating microballoons of omeprazole was in the range of of 66.75±0.92% to 97.75±0.84%. This evaluation parameter revealed that F6 have the good production yield of 97.75±0.84. F1 has the lowest percentage yield i.e, 66.75±0.92%. The percentage yield of microballoons containing ethyl cellulose was observed high when compared with more HPMC containing microballoons.

Table h: Percentage yield of floating microballoons

Sl. No:	Formulation code	Percentage yield (%) *±S.D
1	**F1**	66.75±0.92
2	**F2**	71.11±0.97
3	**F3**	70.30±0.85
4	**F4**	82.88±0.48
5	**F5**	90.70±0.50
6	**F6**	97.75±0.84

* Average of 6 determinants, SD= Standard deviation

- ***In vitro* buoyancy**

The buoyancy was found to be satisfactory in the range of 84.49±0.76 to 89.94±0.79%. The F6 showed the highest buoyancy value of 89.94±0.79% which was prepared with ethyl cellulose and HPMC K4M. The formulation F1 showed lower value for *in vitro* buoyancy and F6 showed the larger value for *in vitro* buoyancy i.e, 89.94±0.79%. The microballoon with high concentration of ethyl cellulose showed good *in vitro* buoyancy due to insolubility of ethyl cellulose in simulated gastric fluid pH 1.2.

Table i: Percentage buoyancy of floating microballoons

Sl. No	Formulation code	Percentage buoyancy (%)*± S.D
1	**F1**	84.49±0.76
2	**F2**	68.39±0.68
3	**F3**	66.12±0.67
4	**F4**	82.15±0.70
5	**F5**	85.59±0.51
6	**F6**	89.94±0.79

*Average of 6 determinants, SD= standard deviation

- ***In vitro* dissolution study**

The *in vitro* drug release study of all formulations of omeprazole floating microballoons were carried out in 0.1 N HCl using USP type II paddle apparatus. The *in vitro* release profile from F6 showed maximum release of 90.19±0.48% at the end of 6 h. The results were tabulated in Table j. Comparative dissolution profile of the prepared formulation were shown in Fig 15 and 16. As the concentration of polymer is increased, the density of polymer matrix also increased which resulted in increased diffusional path length which in turn decreased the overall values of drug release profile. The combination of water soluble polymer and controlled release polymer in the formulation F6 resulted in a sustained release of drug. It was found that quantity of ethyl cellulose alone or in combination with HPMC K4M, has a predominant effect in sustaining the drug release from microballoons.

Based on the results obtained from *in vitro* buoyancy, entrapment efficiency and *in vitro* drug release studies, **F6** was selected as optimized formulation.

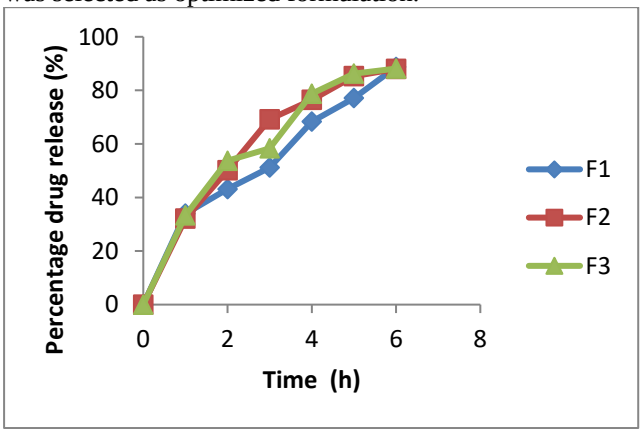

Figure 15: Comparative *in vitro* release study of F1-F3.

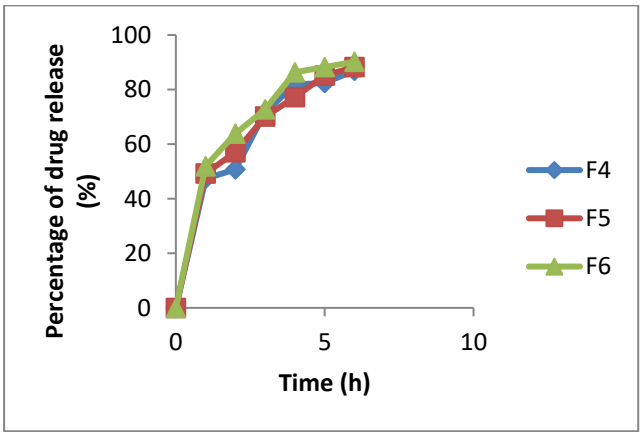

Figure 16: Comparative in vitro release study of F4-F6.

Table j: *In vitro* drug release study of F1-F6

Cumulative percentage of drug released (%)*± S.D							
Sl. No	**Time (h)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	0	0	0	0	0	0	0
2	1	33.97±0.68	32.12±0.56	33.31±0.47	47.36±0.54	49.25±0.44	51.90±0.43
3	2	43.15±0.47	50.16±0.40	53.73±0.61	50.77±0.42	57.08±0.72	63.84±0.26
4	3	51.17±0.81	69.19±0.64	58.35±0.60	71.69±0.40	70.12±0.42	72.76±0.32
5	4	68.34±0.42	76.45±0.52	78.77±0.56	81.76±0.44	77.22±0.58	86.35±0.59
6	5	77.12±0.34	85.29±0.60	86.25±0.64	82.46±0.85	85.15±0.43	88.23±0.78
7	6	88.71±0.46	88.02±0.46	88.13±0.44	86.90±0.30	88.23±0.33	90.19±0.48

*Average of 6 determinants, SD= Standard deviation

- **Kinetic study**

Table k: Pharmacokinetic values of the study.

Time (h)	Cum % drug released	% drug remaining	Square root time	Log cum % drug remaining	Log time	Log cum % drug released	% Drug released	Cube root of % drug remaining (W_t)	$W_0 - W_t$
0	0	100	0.000	2.000	0.00	0.000	100	4.642	0.00
1	51.9	48.1	1.000	1.682	0.00	1.715	51.9	3.637	1.00
2	63.84	36.16	1.414	1.558	0.30	1.805	11.94	3.307	1.33
3	72.76	27.24	1.732	1.435	0.47	1.862	8.92	3.009	1.63
4	86.35	13.65	2.000	1.135	0.60	1.936	13.59	2.390	2.25
5	88.23	11.77	2.236	1.071	0.69	1.946	1.88	2.275	2.36
6	90.19	9.81	2.449	0.992	0.77	1.955	1.96	2.141	2.50

The dissolution profile of optimized formulation F6 was fitted to various kinetic models like zero order, first order, higuchi model and korsmeyer peppas. The values were recorded to Table l and kinetic plots were presented in Fig 17- 20.

Table l: Regression value of kinetic models

Formulation	Kinetic models			
F6	Zero order	First order	Korsemeyer peppas plot	Higuchi
R^2	0.711	0.961	0.601	0.952
n	9.73	0.166	2.20	40.91

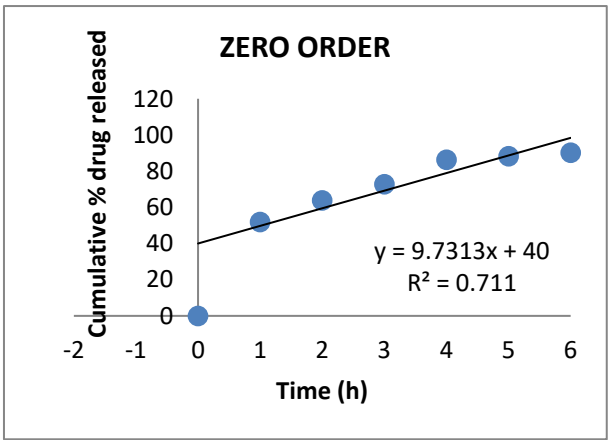

Figure 17: Zero order plot for F6

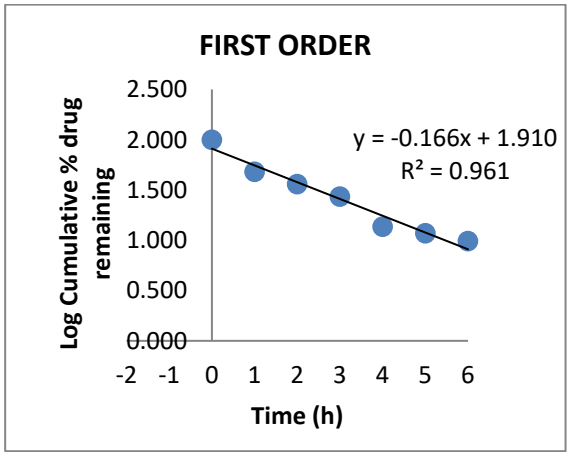

Figure 18: First order plot for F6

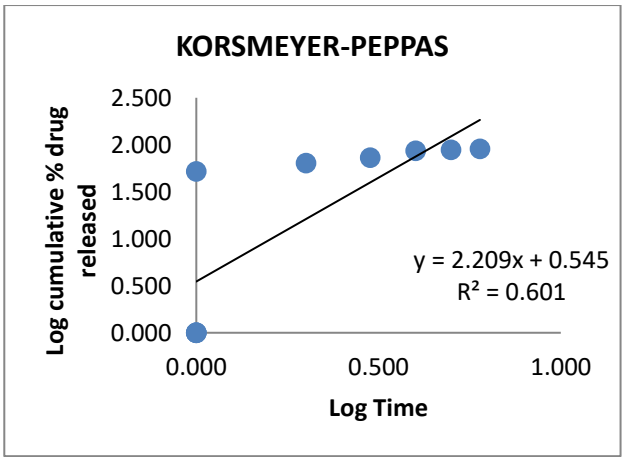

Figure 19: Korsmeyer-Peppas model for F6

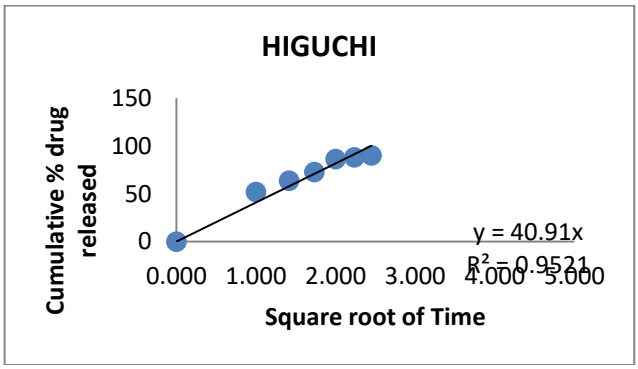

Figure 20: Higuchi plot for F6

The dissolution profile of optimized formulation F6 was fitted to various kinetic models like zero order, first order, higuchi model and korsmeyer-peppas. The values of co-efficient of correlation were shown in Table l. It was found that the *in vitro* drug release of drug from omeprazole floating microballoons was best explained by first order model as it showed the highest value for R^2 (0.961), followed by higuchi model (0.952). The 'n' value determined is less than 0.5 indicating that it follows fickian diffusion.

- **Stability studies**

The stability studies were carried out for 0 to 90 days. The results are shown in the Table m. On physical observation of the stored samples, there were no change in colour, odour and taste of floating microballoons. The drug

content, percentage buoyancy, *in vitro* drug release did not change significantly on storage. These studies showed that prepared floating microballoons were physically and chemically stable even after three months under test conditions.

Table m: Data of stability study

Time (Days)	Physical changes	Percentage buoyancy (%) *± S.D	Cumulative percentage drug release (%)*± S.D
0	-	89.94±0.74	90.19±0.48
30	No change	87.65±0.87	89.65±0.63
60	No change	87±0.45	89.56±0.54
90	No change	86.7±0.65	88.37±0.78

CONCLUSION

From the present study, an attempt was made to prepare floating microballoons of omeprazole. The floating microballoons were prepared by emulsion solvent diffusion mechanism with different concentration of HPMC K4M and ethyl cellulose, and proved that they can meet ideal requirements for sustained drug delivery. Thus it was concluded that, as per the pre established objectives, the physico-chemical characterization, in vitro evaluation and stability studies of omeprazole floating microballoons were performed and obtained satisfactory results. The formulation F6 exhibited good release profiles hence, selected as the best formulation. The present research proved that floating microballoons are potential gastroretentive drug delivery systems that will have significant impact in the community, as this will increases gastric residence time and improve bioavailability of drugs. Hence the objectives of the envisaged research work were fulfilled.

Acknowledgement

I would like to express my sincere thanks and gratitude to Prof (Dr) Shaiju S Dharan (Principal, Ezhuthachan College of Pharmaceutical Sciences), Dr. Mathan S (Professor and Head, Department of Pharmaceutics), Dr. Merlin NJ (Professor and Head, Department of Pharmacology) for guidance and support. I wish to acknowledge Ezhuthachan College of Pharmaceutical Sciences, KUHS, Thiruvananthapuram, India, for necessary motivation and support.

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