DEVELOPMENT OF FORMULATION, OPTIMIZATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM IN OLMESARTEN MEDOXOMIL

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Submitted by

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I hereby declare that this dissertation Entitiled **"DEVELOPMENT OF FORMULATION, OPTIMIZATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM IN OLMESARTEN MEDOXOMIL"**, is a bonafide work carried out by us under my guidance of in the Department of Pharmaceutical Analysis, Padmavathi College of Pharmacy & Research Institute, Periyanahalli, Dharmapuri.

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Declaration

The research work embodied in the dissertation entitled **"DEVELOPMENT OF FORMULATION, OPTIMIZATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM IN OLMESARTEN MEDOXOMIL"** was carried out by me in the Department of Pharmaceutics Padmavathi college of Pharmacy, Dharmapuri, under the guidance of **Prof. Mr. S.RAJESH KUMAR,** M.Pharm, (Ph.D,). The extent and source of information derived from the existing literature have been indicated throughout the thesis at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree of this or any other University/Institute.

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1. **External Examiner**

2. **Internal Examiner**

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I humbly owe the completion of this dissertation work to the **almighty** whose love and blessing will be with me every moment of my life.

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Mohammad lawand sorake

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INTRODUCTION

Introduction to drug delivery system

Historically, the oral route of administration has been used the most for both conventional and novel drug delivery system. These systems have the obvious advantages of ease of administration and patient acceptance, least sterility constraints and flexibility in the design of dosage form. One would always like to have an ideal drug delivery system that will possess two main properties:

- It will be a single dose for the whole duration of treatment.
- It will deliver the active drug directly at the site of action.

Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible. More than 50% of drugs, available in the market are meant for oral administration. The conventional drug therapy results in fluctuation of drug concentration in systemic circulation, causing either toxic effect or no therapeutic effect.

Now recent scientific and technological advancement have been made in the research and develop of rate controlled oral drug delivery systems by overcoming physiological adversities and short gastric residence time. Invariably, conventional drug dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repetitively using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve frequent dosing for drugs with short biologic half-life, and above all the patient non compliance. Now recent scientific and technological advancement have been made in the research and develop of rate controlled oral drug delivery systems by overcoming physiological adversities and short gastric residence time [1].Invariably, conventional drug dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time.

Anatomy of the stomach

The gastro intestinal tract can be divided into three main regions

- Stomach
- Small intestine- duodenum, jejunum, and ileum
- Large intestine.

PARTS OF STOMACH

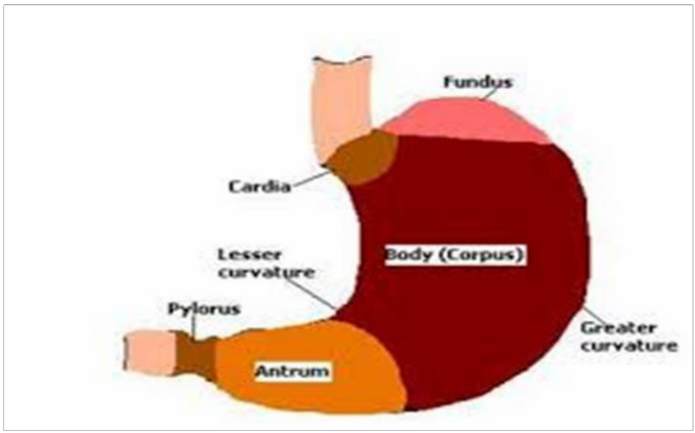

Figure 1: Shows parts of Stomach

The git is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layer called oblique muscle and it is situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided into fundus, body and pylorus[2]. The stomach is a J shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily , grind it and releases slowly in to the duodenum.

Physiology of the stomach

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rugae. There are 4 major types of secretary epithelial cells that covers the stomach and extends into gastric pits and glands.

1. mucous cells- secrete alkaline mucus
2. parietal cells – secrete HCL
3. chief cells- secrete pepsin
4. G cells- secrete hormone gastrin[3].

Physiology of gastrointestinal tract

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made up of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states**.** The pattern of motility is however distinct in the two states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.

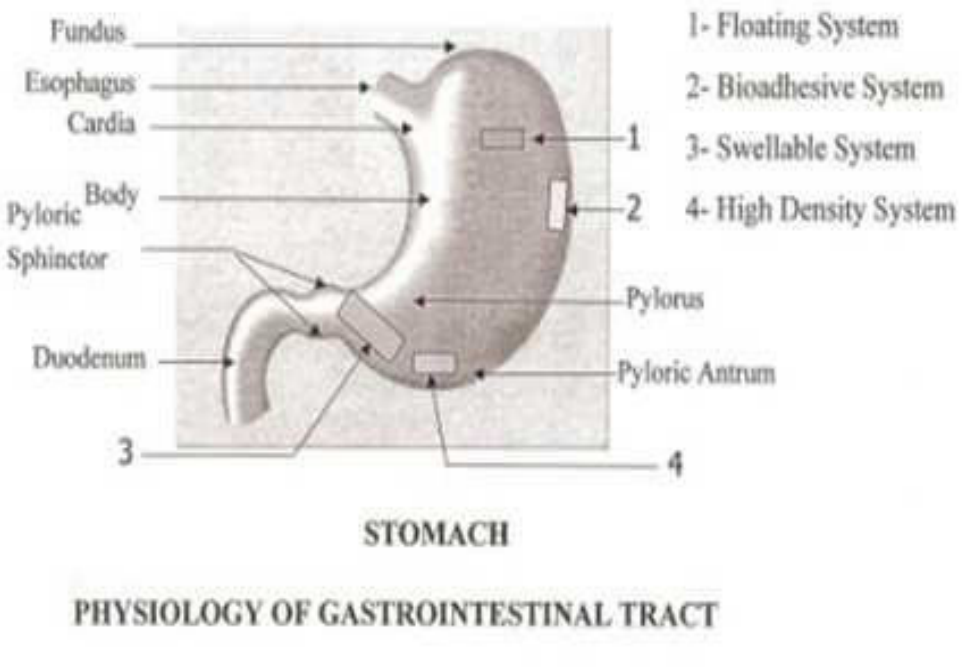

Fig2: Physiology of Gastrointestinal Tract

This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by **Wilson and Washington.**

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles [16].

Gastric emptying and problems

The process of the gastric emptying occurs both during fasting and fed stages.

Scintinography study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities,

The short GRT (Gastric Residence Time)

Variable (unpredictable) GET (Gastric Emptying Time)

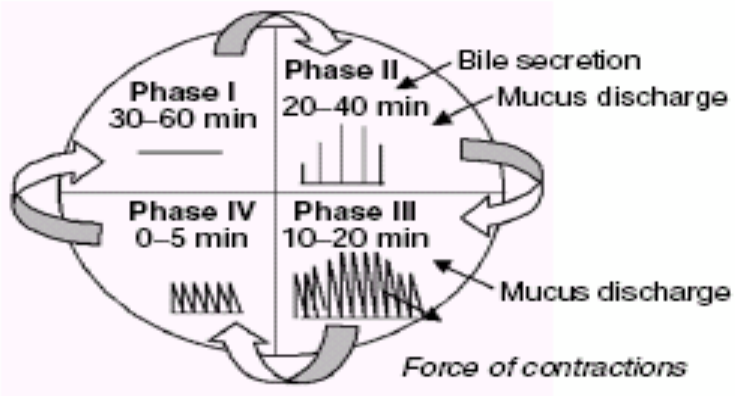

Fig 3: Motility patterns of the GIT in fasted state

Table 1.1: salient features of upper gastrointestinal tract

Section	Length (m)	Transit (h)	time	pH	Microbial count	Absorbing surface	are a	Absorption pathway
						(m2)		
Stomach	0.2	Variable		1-4	<103	0.1		P, C, A
Small Intestine	6-10	3 ± 1		5-7.5	103 – 1010	120-200		P, C, A, F, I, E, CM

P – Passive diffusion ,C – Aqueous channel transport ,A – Active transport, F- Facilitated transport,
I – Ion-pair transport ,E – Entero-or pinocytosis ,CM – Carrier mediated transport

The basic rationale of the controlled drug delivery system (CDDS) is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route [4]. Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit. Controlled release denotes the system in which release rate of the drug from the system is temporal (related to time) or spatial (related to site) nature or both. In other words system attempts to control the drug concentration in the target tissue or cells.

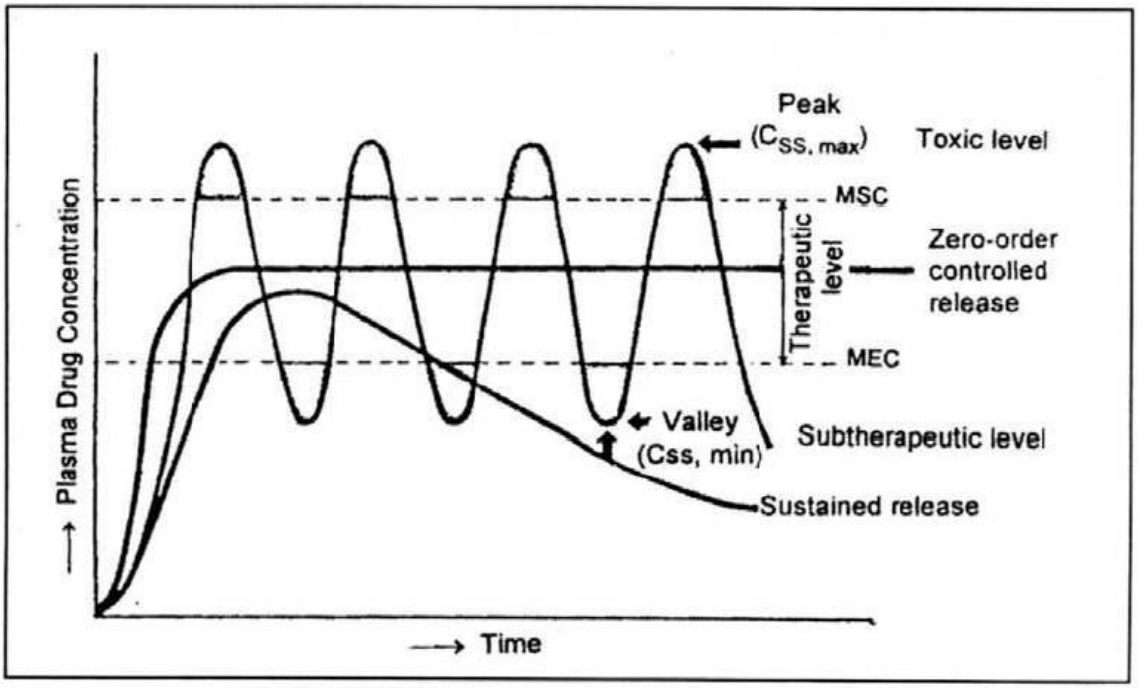

Fig 4:Plasma level profiles following conventional and controlled release dosing.

The broad objectives of controlled release drug delivery system are as follows

- Prolongs the duration of action of the drug at a predetermined rate by maintaining a relatively constant, effective drug level in the body with the minimization of the adverse effect associated with a peak valley kinetic pattern.
- Localization of drug action by spatial placement of controlled releas
- system near to or in the diseased tissue or organ , site or even receptor.

Target drug action by using carrier or chemical derivatization to deliver drug to a particular target , cell type. Ideally it is desirable to release the drug at the target sites whether it is a tissue , population of cells or receptors , leaving rest of the body drug free [3].

Merits of Controlled Drug Delivery

- Reduction in fluctuation in steady state levels and therefore better control of disease and Reduce intensity of local or systemic side effect.
- Improved patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.
- Decreased incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- Controlled rate and site of release.
- Reduce wastage of the drugs.
- More uniform blood concentrations.

- Less therapeutic index.
- A greater selectivity of pharmacological activity.[4]

Demerits of Controlled Drug Delivery

- Toxicity due to dose dumping.
- Increased cost.
- Increased variability among dosage units.
- Stability problems.
- Retrieval of drugs in difficult in case of toxicity, poisoning or hypersensitivity reactions [5].

Classification of oral controlled drug delivery system

Oral controlled drug delivery systems can be broadly classified on the basis of their mechanism of drug release. Primarily, controlled release is achieved by diffusion, degradation and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release systems. Diffusion occurs when bioactive agent passes through the polymer, which forms the building block of controlled release system.

1. Dissolution-controlled release

a) Encapsulation Encapsulation dissolution control

b) Matrix dissolution control

2. Diffusion-controlled release

a) Reservoir devices

b) Matrix devices

3. Osmotic controlled release

4. Ion exchange resins

5. Gastroretentive systems

Gastro retentive Systems

Variability in GI transit time is a concern for oral controlled drug delivery systems. A major constraint in oral controlled release drug delivery is that not all the drug candidates are absorbed uniformly throughout the GIT (gastrointestinal tract). Some drugs are absorbed in a particular portion of GI tract only or absorbed to a different extent in various segments of GI tract. Such drugs are said to have an absorption window. Thus only the drugs which are released in the preceding region and in close vicinity to the absorption window are available for absorption. After crossing the absorption window, the release drug goes to waste with negligible or no absorption. Thus the time available for drug absorption drastically decreases**.**

Gastro retentive dosage form

Gastro retentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment [6].Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (7).

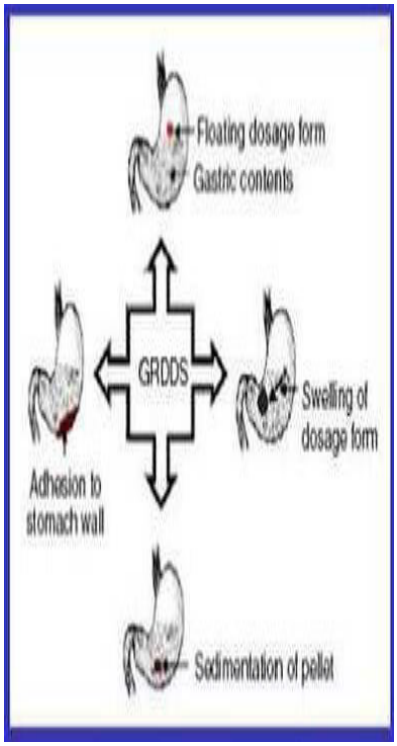

Fig 5: Gastro retentive approaches

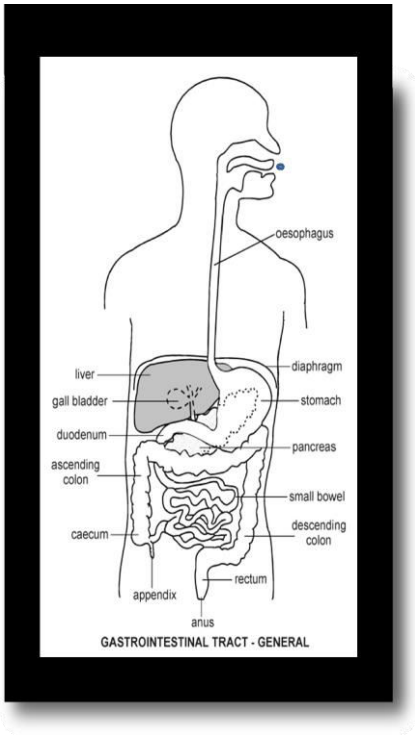

Fig 6: Gastrointestinal Tract-General

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. One of the most feasible approaches for achieving and predictable drug delivery profile in GIT is to control the GRT so that gastric emptying process can be extended from few minutes to 12 hr using GRDF's that offers new and better option for drug therapy(8-11).

Gastric retention can be achieved by mechanism of mucoadhesion or bio adhesion, expansion system, super porous hydro gels, raft forming system, low density system, floatation and simultaneous administration of pharmacological agents that delay the gastric emptying [12].

Potential candidates for gastro retentive drug delivery system

- Drugs that are primarily absorbed in the stomach eg Amoxicillin.
- Drugs that are poorly soluble in alkaline pH eg Furosemide , Diazepam.
- Drugs that have narrow absorption window eg Levodopa, Methotrexate.
- Drugs that degrade in the colon eg Ranitidine , Metformin HCL
- Drugs that disturb normal colonic microbes eg Antibiotics against Helicobacter pylori.
- Drugs rapidly absorbed from the gi tract eg Tetracycline.
- Drugs acting locally in the stomach eg Misoprostol [13].

Gastroretentive technologies

A number of systems have been pursued to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention.(14)

Expandable systems

These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach.(15)

Bio/Muco-adhesive systems

This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary[18].

High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region. Commonly used excipients are Barium sulphate, Zinc oxide, Titanium dioxide and Iron powder, These materials increase density by up to1.5–2.4g/cm^3(19).

Limitations of gastroretentive drug delivery system

1. Aspirin and NSAID'S can cause gastric lesions and slow release of such drug in the stomach is unwanted.
2. Drugs such as isosorbide dinitrate which are equally absorbed throughout the GIT will not be benefit from incorporation into a gastric retention system.
3. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of the technique
4. Physical integrity of the system is very important and primary requirement for the success of the system.
5. High variability in gastric emptying time due to variations in emptying process , unpredictable bioavailbility.

Advantages of gastro retentive drug delivery system

1. It increases patient compliance by reducing dosing frequency
2. Buoyancy increases gastric residence time
3. Better therapeutic effect of short half life drugs
4. Site specific drug delivery to stomach can be achieved
5. In this drug is released in a controlled manner
6. Gastric irritation can be avoided by designing sustained release
7. No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly. (1,17)

Factors affecting gastric retention

Density of dosage form

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids (≅1.004 gm/ml) floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Size and shape of dosage form

To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT (≅ 90 to 100 %) retention at 24 hours compared with other shapes [18].

Fasting or fed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state [19].

Nature of the meal (food)

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same.

Effect of liquid, digestible solid and indigestible solid type food

It has been demonstrated using radio labeled technique that there is a difference between gastric emptying times of a liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (>1 mm) indigestible objects from stomach was dependent upon inter digestive migrating myoelectric complex.

Biological factors

Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. GRT can vary between supine and upright ambulatory states of the patients. Stress increases gastric emptying rates while depression slows it down [20].

Frequency of feed

The gastro retentive time can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Mean ambulatory GRT in meals (3.4 ± 0.4 hours) is less compared with their age and race-matched female counterparts (4.6± 1.2 hours), regardless of the weight, height and body surface [21].

Posture

Gastro retentive time can vary between supine and upright ambulatory states of the patients. [22].

FLOATING DRUG DELIVERY SYSTEM

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle.

Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxyl propyl methyl celluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy [23].

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intra gastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time [24].

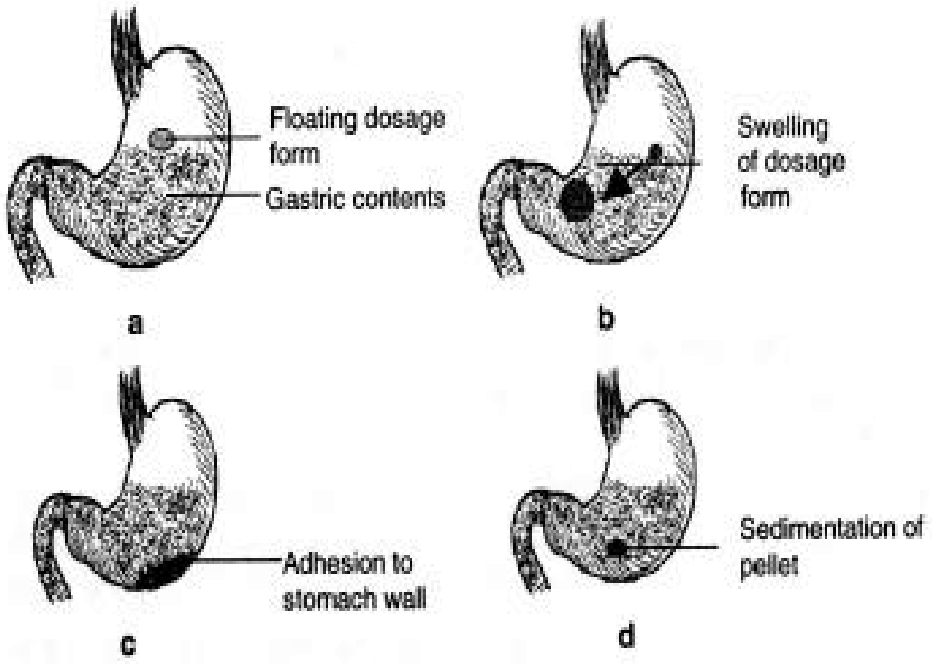

Fig 7: Various forms of gastro retentive systems; (a) Floating gastro retentive drug delivery systems; (b) Swelling gastro-retentive drug delivery systems; (c) Bio adhesive gastro-retentive drug delivery systems; (d) High- density gastroretentive drug delivery systems.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for

a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.[25]

Classification of floating drug delivery system (FDDS)

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

A. Effervescent System, and

B. Non- Effervescent System.

Effervescent System

These are the matrix types of with the help of swellable systems prepared polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate tartaric acid, and citric acid. They are formulated in a such a way that when in contact with the acidic gastric contents, CO_2 is liberated and entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms [26]

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems

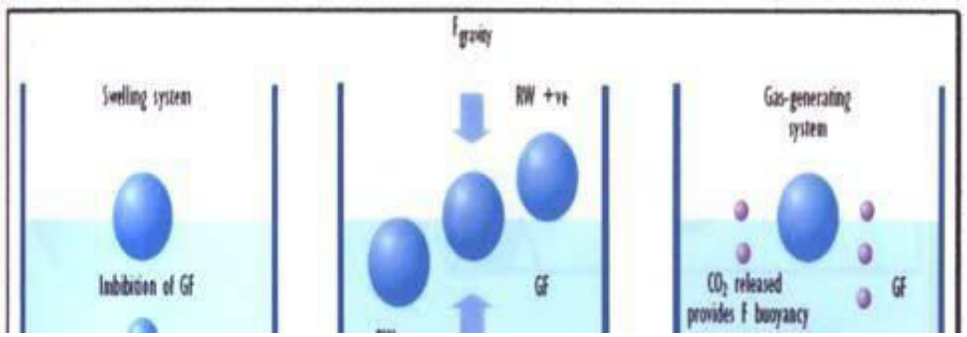

Figure 8: Shows working of effervescent FDDS

Gas – Generating Systems

Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach for a prolonged period.

Intra Gastric Bi-layer Floating Tablet

These are also compressed tablet containing two layers i.e., Immediate release layer, Sustained release layer. These are as formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet.

Multiple Unit type floating pills

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid [27].

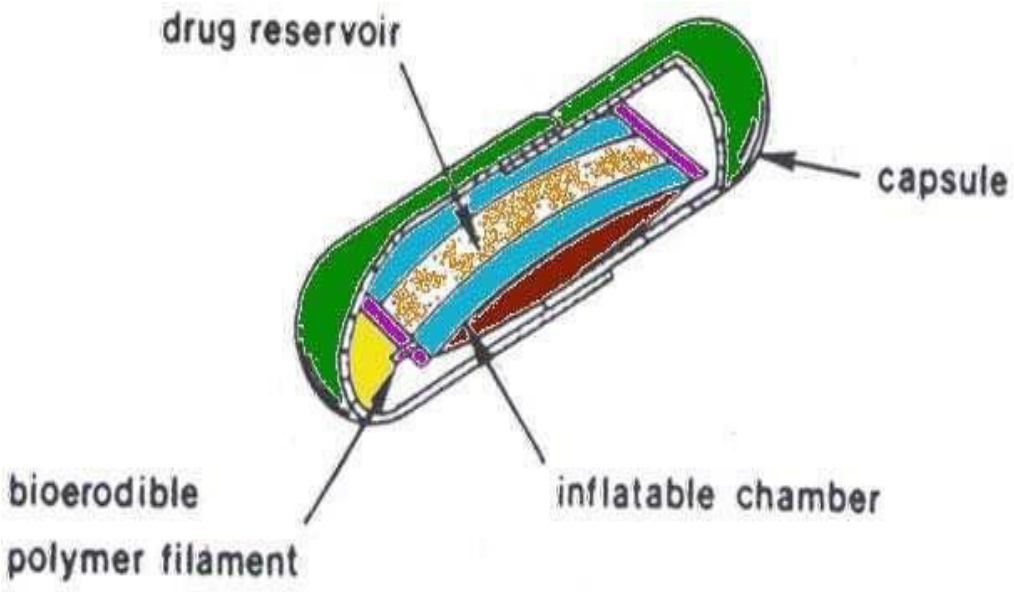

Fig 9: Inflatable Gastrointestinal Delivery System

Intra-gastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra- gastric osmotically controlled drug delivery device[23]. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt[28].

The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach [29].

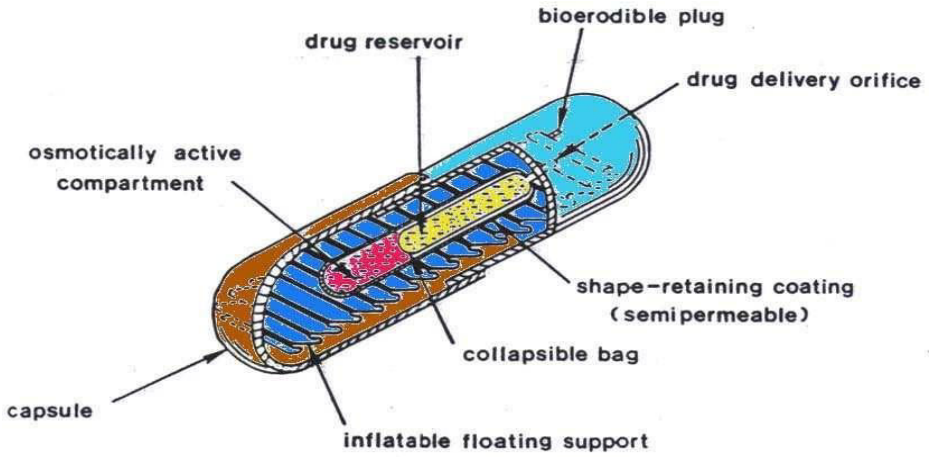

Fig 10: Intragastric Osmotically Controlled Drug Delivery System

Non Effervescent System

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol [30].

Working principle of this type of FDDS

Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time[31].

Various types of non effervescent floating Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity[32].

Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from the system while another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[33].

Alginate Beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours [34].

Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 400C.

Formulation of floating dosage form

Following types of the ingredients can be incorporated in to HBS dosage form in addition to drugs.

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous [35].

Advantages of floating dosage forms Enhanced bioavailability

The bioavailability of Riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be

considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input [37].

Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [38].

Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.[39]

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency [40].

Disadvantages of floating dosage forms

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).

- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed through out the gastrointestinal tract [41].

Evaluation of floating drug delivery system

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

Floating time

The test for buoyancy is usually performed in simulated gastric and intestinal fluid maintained at 37ºC. The floating time is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the testing medium maintained at 37ºC . The time for which the dosage form floats is termed as the floating or floatation time [42].

Swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling Index} = \frac{Wt - Wo}{Wt} \quad \text{.....eq (vi)}$$

Where, W0 is the initial weight of tablet, and Wt is the weight of the tablet at time t.

In-vitro release studies

The release rate of floating drug delivery system was determined in dissolution apparatus. Different types of dissolution apparatus are used according to formulation.

The dissolution fluid was maintained at 37 ± 1°C at a rotation speed. Perfect sink conditions prevailed during the drug release study [43].

In-vivo study

In vivo gastric residence time of a floating dosage form is determined by X-ray diffraction studies, gamma scintigraphy, or roentgenography. In X-ray method the formulation is modified to incorporate Barium Sulphate as X-ray opaque substance. The study is carried out by administering the gastro retentive tablets to human volunteer [44]. The tablet was administered in the fasting state. The X-Ray opaque formulation is administered along with 250 ml of water. The subjects are allowed to remain in sitting or upright position. A light meal is given to volunteer 2 hour after administration of the tablet to evaluate effect of food of gastro retentive property. The position of tablet is monitored by X-Ray screening technique X-Ray photographs taken at desired intervals to monitor tablet position in human gastrointestinal tract [45].

X-ray / gamma scintigraphy

It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form in the git. The inclusion of a radio opaque material into solid dosage form enables it to be visualized by the X-ray[45]. The inclusion of a gamma emitting radionuclide in the formulation allows indirect external observation using gamma camera, the gamma rays emitted by radionuclide is focused on the camera which helps to monitor the location of the dosage form[46].

Gastroscopy

It comprises of peroral endoscopy used with a fibereoptic and video system. It is used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS [45][47].

Future potentials

- The floating drug delivery concept can be used in development of anti reflux formulations
- Buoyant delivery system is beneficial in the treatment of gastric and duodenal ulcers.
- Developing a controlled release of drugs which is used to treat Parkinson disease.
- To explore the eradication of helicobacter pylori by using narrow spectrum antibiotic.

Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a pre- determined period throughout the course of GI transit. Gastro retentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. One of the most

feasible approaches for achieving and predictable drug delivery profile in GIT is to control the GRT so that gastric emptying process can be extended from few minutes to 12 hr using GRDF's that offers new and better option for drug therapy.

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist**.** Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. Olmesartan medoxomilis indicated for the treatment of mild to moderate essential hypertension.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan. Olmesartan medoxomil inhibits the pressor effect of an angiotensin II infusion in a dose- dependent manner at doses of 2.5 to 40 mg. The inhibition was 90% at doses of olmesartan medoxomil >40 mg 24 hours post dose.

AIM AND OBJECTIVE

Aim of present research is development of formulation, optimization and evaluation of gastro retentive floating drug delivery system of olmesarten medxomil.

The objective of the present study was to develop an optimized gastroretentive floating drug delivery system of Olmesartan Medoxomil and investigate the effect of hydrophilic retardant on invitro release by using 3^2 full factorial design.

Floating tablets of olmesartan medoxomil were prepared by direct compression method using effervescent technique by employing two different grades of HPMC. (HPMC K4M and HPMC K100M). Sodium bicarbonate was incorporated as gas generating agent.

The concentration of HPMC K4M (X_1) and concentration of HPMC K100M (X_2) were selected as independent variables. The floating lag time, total floating time and t ime taken to 80 % drug release were selected as dependent variables. Targets were defined for each response so as to select the optimam formula using numerical optimization.

All the floating matrix tablets formulations were subjected to pre-compression and post-compression parameter evaluation.

LITERATURE REVIEW

A.Hemdan et al., validated chromatographic method for determination of some anti-hypertensive drugs. Accurate, precise and reproducible isocratic RP-HPLC method was developed and subsequent validated for the analysis of Torasemide (I), Irbesartan (II) and Olmesartan Medoxomil (III) at ambient temperature, using Atlantis 4.6 mm x 250 mm RP-C18 Column, with a flow rate of 1.5 $ml.min^{-1}$, and UV. Detector at 288 nm and 260 nm for (I) and (II and III), respectively. By adopting the entioned chromatographic technique, (I) and (III) were determined in the presence of their acidic and alkaline-degradates separately as stability-indicating methods utilizing phosphate buffer pH= 3:acetonitrile (60:40, v/v), phosphate buffer pH = 3.2:acetonitrile (60:40, v/v) as a mobile phase, respectively, while (II) was determined in presence of Hydrochlorothiazide (HCTZ), using phosphate buffer pH = 4:acetonitrile (70 :30, v/v. The obtained results were statistically compared to the reference methods of analysis [for I and "II and III", respectively] and no significant differences were found.

A.T. Hemke et al., UV spectrophotometric determination of hydrochlorothiazide and olmesartan medoxomil in pharmaceutical formulation. UV spectrophotometric method includes simultaneous equation method (Method I) 271.5 nm and 257.0 nm λmax of both the drugs were selected, absorbance Ratio method (Method II)261.5 nm an isoabsorptive wavelength and 257.0 nm were selected for estimation of hydrochlorothiazide and olmesartan medoxomil respectively. The two drugs follow Beer's law over the concentration range of 5-25 µg/mL. The % recoveries of the both the drugs were found to be nearly 100 % representing the accuracy of the proposed methods. Validation of the proposed methods was carried out for its accuracy, precision, specificity and ruggedness according to ICH guidelines. The proposed methods can be successfully applied in routine work for the determination of hydrochlorothiazide and olmesartan medoximil in combined dosage form.

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C. Narendra et al., developed an optimized gastric floating drug delivery system (GFDDS) containing metoprolol tartrate (MT) as a model drug by the optimization technique. A 2^3 factorial design was employedin formulating the GFDDS with total polymer content-to drug ratio (X1), polymer-to-polymer ratio (X2), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) (X3) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, T50%, diffusion coefficient, and floating time. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that X1 and X2 significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was no significant. Regression analysis and numerical optimization were performed to identify the best formulation. Fickian release transport was confirmed as the release mechanism from the optimized formulation.

Chen YC, Ho H, Lee TY, Sheu MT. Physical characterizations and sustained release profiling of gastroretentive drug delivery system with improved floating and swelling capabilities. *International Journal Of Pharmaceutics*, 2013.

Deckanth Sharma Oral delivery of drugs is by far the most preferable route of drug delivery. This route has high patient acceptability, primarily due to ease of

administration. Effective oral drug delivery depend upon the factors such as gastric emptying process, gastrointestinal transit time of the dosage form ,drug release from the dosage form, and site of absorption of drug. In the recent years, scientific and technological advancement have been made in the research and development of gastroretentive drug delivery system. Henceforth a wide spectrum of dosage form have been developed for the drugs which have narrow absorption window, unstable at intestinal pH , soluble in acidic pH and have site of action specific to stomach.The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. These includes floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits , demerits and applications of gastroretentive drug delivery systems.

Dr. S. D. Barhate et al., formulated and optimized the bilayer floating tablets of famotidine, by using HPMC K100LV, HPMC K4MCR, sodium bicarbonate, sodium alginate, sodium starch glycolate, croscarmellose, crospovidone and lactose. Box-Behnken factorial design was used to statistically optimize the controlled release layer composition and evaluation of the effect of amount of HPMC K100LV (X1), amount of HPMC K4MCR (X2) and amount of sodium bicarbonate (X3) on release rate of famotidine. The polymers HPMC K100LV, HPMC K4MCR showed better control over drug release. The formulated formulations of Box-Behnken factorial design showed zero- order drug release. The prognostic ability of Response Surface Methodology involving multiple response optimizations was proved in designing and optimization of controlled release pharmaceutical formulations. Response surface prediction plots are useful to show the effect of interactions on the responses and desirability approach is a promising tool for optimization.

Garg AK, Kapoor G, Sachdeva RK. Formulation and evaluation of nizatidine floating tablets. *American Journal of pharmatech Research*, 2012.

Girish S. Sonar et al., prepared and performed in vitro evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate Tablets were characterized using the official method. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The in vitro drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The release of rosiglitazone maleate from the tablets followed the matrix first- order release model.

Hünseler, C; *Paneitz, A; Friedrich, D; Lindner, U; Oberthuer, A; Körber, F; Schmitt, K; Welzing, L; Müller, A; Herkenrath, P; Hoppe, B; Gortner, L; Roth, B; Kattner, E; Schaible, T (Jan 2011). "Angiotensin II receptor blocker induced fetopathy: 7 cases". Klin Padiatr. "BENICAR Prescribing Information" (PDF). Retrieved 2011-01-20. De Petris G, Caldero SG, Chen L, et al. (May 2014). "Histopathological changes in the gastrointestinal tract due to medications: an update for the surgical pathologist (part II of II)". Int. J. Surg. Pathol.* Chandel A, Chauhan K. Gastroretentive approaches. *Aulakh GK, Sodhi RK, Singh M (August 2007), "An update on non-peptide angiotensin receptor antagonists and related RAAS modulators",*

Jamil F, Sunil K, Sharma S, Vishvakarma P, Singh L. Review on stomach specific drug delivery :development and evaluation. *IJRPBS*, 2011.

JH Guo., used a two roll milling method to prepare a new bioadhesive polymer patch formulation for controlled drug delivery consisting of CP, PIB and PIP. The strongest peel strength was found on buccal patches with a CP: PIB: PIP ratio of 50:43.75:6.25. He developed a formulation for buprenorphine - controlled delivery consisting of polyisobutylene, polyisoprene, and carboapol 934P. It was observed that the milling process did not change the thermal, rheological, or viscous properties of the individual polymers used.

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Mayavanshi AV and Gajjar SS. Floating drug delivery system to increase gastric retention of drugs. *RJPT*, 2008. Patel GM, Patel HR, Patel M. Floating drug delivery system an innovative approaches to prolong gastric retention. Pharmainfo.net 2007.

***"Olmesartan** is More Effective Than Other Angiotensin Receptor Antagonists in Reducing Proteinuria in Patients With Chronic Kidney Disease Other Than Diabetic Nephropathy".*

Pawar HA, Gharat PR, Dhavale RV, Joshi PR, Rakshit PP, Development and evaluation of gastroretentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. *ISRN*, 2013. Pawar V.K, Shaswat K, Garg G, Awasthi R. Gastroretentive dosage form: A review with special emphasis on floating drug delivery systems, *Informa Healthcare* 2011.

Pawar HA, Gharat PR, Dhavale RV, Joshi PR, Rakshit PP, Development and evaluation of gastroretentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. ISRN, 2013.

Prabhakar K. Verma et al., spectrophotometric estimation of olmesartan medoxomil in tablet dosage form with stability studies. A simple accurate and precise spectroscopic method was developed for determination of Olmesartan medoxomil in tablets. The dA/dλ was measured at 257nm for Olmesartan and calibration curves were plotted as dA/dλ versus concentration respectively. The method was found to be linear from 2-20µg/mL for Olmesartan (r2 ≥ 0.9979) at 257nm. The within day and between day variation showed coefficient of variation (CV%) valued less than 1.6% for drug. The limit of detection was 0.13µg/mL for Olmesartan. Results of analysis for method were

validated statistically and by recovery studies. The proposed method is economical and sensitive for the estimation of Olmesartan in bulk drug and its tablet dosage form.

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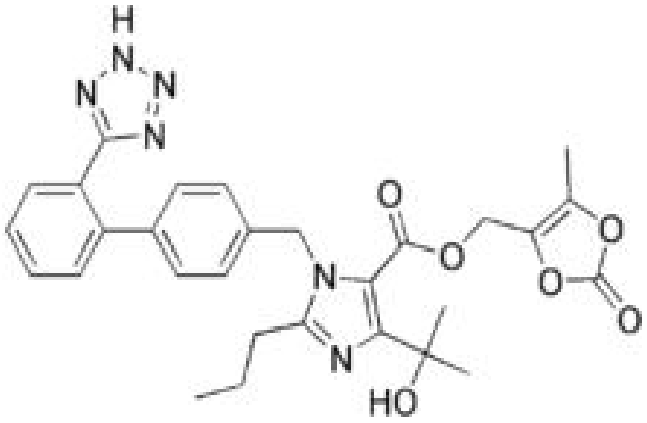
DRUG PROFILE

Olmesartan medoxomil

Olmesartan medoxomil is described chemically as 2,3-dihydroxy-2-butenyl 4-(1 hydroxy-1- methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5 carboxylate, cyclic 2,3- carbonate.



Generic Name: olmesartan (OL-me-SAR-tan)
Brand Name: Benicar

Trade names	Olmecip.
Pregnancy category	C (D if used in second or third trimester)
Routes of administration	Oral

Legal status	
Legal status	• In general: ℞ (Prescription only)

Pharmacokinetic data	
Bioavailability	26%
Metabolism	Hepatic (cannot be removed by hemodialysis)
Biological half-life	13 hours
Excretion	Renal 40%, biliary 60%

Identifiers	

Chemical and physical data	
Formula	$C_{29}H_{30}N_6O_6$
Molar mass	558.585 g/mol

Olmesartan medoxomil is an angiotensin II receptor antagonist which has been used for the treatment of high blood pressure. It was developed by Sankyo in 1995, and is sold under the trade name Benicar Olmecip(Cipla)Olsar (Unichem Laboratories). An ester prodrug, it is completely and rapidly hydrolyzed to the active acid form, olmesartan (RNH-6270).(48)

Indications

Olmesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.(49) The U.S. Food and Drug Administration (FDA) has determined that the benefits of Benicar continue to outweigh its potential risks when used for the treatment of patients with high blood pressure

according to the drug label.(50)Treating high blood pressure alone or with other medicines. It may also be used for other conditions as determined by your doctor.

Olmesartan is an angiotensin II receptor blocker (ARB). It works by relaxing blood vessels. This helps to lower blood pressure.

Before using olmesartan:

Some medical conditions may interact with olmesartan. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you:

- if you are pregnant, planning to become pregnant, or are breast-feeding
- if you are able to become pregnant.
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement.
- if you have allergies to medicines, foods, or other substances.
- if you have a history of angioedema (eg, swelling of the hands, face, lips, eyes, throat, or tongue; difficulty swallowing or breathing; hoarseness), including angioedema caused by treatment with an angiotensin-converting enzyme (ACE) inhibitor (eg, lisinopril).
- if you have a history of heart problems (eg, heart failure), blood vessel problems, blood flow problems, liver or kidney problems, diabetes, or gallbladder problems.
- if you have a history of stroke or recent heart attack.
- if you are dehydrated or have low blood volume.
- if you have electrolyte problems (eg, high blood potassium levels, low blood sodium levels) or are on a low-salt (sodium) diet.
- if you are on dialysis.

SOME MEDICINES MAY INTERACT with olmesartan.

- Diuretics (eg, furosemide, hydrochlorothiazide) because the risk of low blood pressure may be increased.
- Potassium-sparing diuretics (eg, spironolactone, triamterene) or potassium supplements because the risk of high blood potassium levels may be increased
- ACE inhibitors (eg, lisinopril) or aliskiren because the risk of certain side effects (eg, kidney problems, high blood potassium levels, low blood pressure) may be increased.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, celecoxib, ibuprofen, naproxen) because they may decrease olmesartan's effectiveness and the risk of serious kidney problems may be increased.
- Lithium because the risk of its side effects may be increased by olmesartan.

This may not be a complete list of all interactions that may occur. Ask your health care provider if olmesartan may interact with other medicines that you take. Check with your health care provider before you start, stop, or change the dose of any medicine.

Olmesartan is used alone or in combination with other medications to treat high blood pressure in adults and children 6 years of age and older. Olmesartan is in a class of medications called angiotensin II receptor antagonists. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently.

High blood pressure is a common condition and when not treated, can cause damage to the brain, heart, blood vessels, kidneys and other parts of the body. Damage to these organs may cause heart disease, a heart attack, heart failure, stroke, kidney failure, loss of vision, and other problems. In addition to taking medication, making lifestyle changes will also help to control your blood pressure. These changes include

eating a diet that is low in fat and salt, maintaining a healthy weight, exercising at least 30 minutes most days, not smoking, and using alcohol in moderation.

Contraindications

Contraindications for treatment with olmesartan include biliary obstruction. Another major contraindication is pregnancy; reports in the scientific literature reveal fetal malformations for pregnant women taking sartan-derived drugs.(51)

Adverse effects

The incidence of adverse effects with Benicar (the US trade name for olmesartan medoxomil) is reported as similar to placebo; the only adverse effect that occurred in >1% of patients treated with it and more frequently than placebo was dizziness (3% vs 1%). The full prescribing information for Benicar notes as with all drugs that act directly on the renin-angiotensin system, olmesartan is contraindicated in pregnancy and can cause injury and even death to the developing fetus. In studies of angiotensin II receptor antagonists such as olmesartan, patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.(52) Rarely, olmesartan can cause severe gastrointestinal issues. The symptoms, which include nausea, vomiting, diarrhea, weight loss, and electrolyte abnormalities, are common among those who have celiac disease.(53) Recent studies suggested this form of sprue-like enteropathy could be caused by the inhibition of TGF-β, a polypeptide cytokine that maintains intestinal homeostasis. However, it is still unclear why this action was never observed with other ARBs.(54)

Dosage and administration

The usual recommended starting dose of olmesartan is 20 mg once daily. The dose may be increased to 40 mg after two weeks of therapy, if further reduction in blood pressure is desirable. Doses above 40 mg do not appear to have greater effect, and

twice-daily dosing offers no advantage over the same total dose given once daily.No adjustment of dosage is typically necessary for advanced age, renal impairment, or hepatic dysfunction. For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics), olmesartan should be initiated with caution; consideration should be given to use of a lower starting dose in such cases. If blood pressure is not controlled by Benicar alone, a diuretic may be added. Benicar may be administered with other antihypertensive agents. Benicar may be administered with or without food.

Preparations

Olmesartan and Sevikar HCT combined is marketed worldwide by Daiichi Sankyo, in India by Abbott Healthcare Pvt. Ltd. under the trade name WinBP, by Zydus Cadila under the trade name Olmy, by Ranbaxy Laboratories Ltd. under the trade name Olvance, Olsar by Unichem Laboratories and in Canada by Schering-Plough as Olmetec. Several preparations containing olmesartan and other antihypertensives are available. Teva Pharmaceuticals produces a formulation containing olmesartan, amlodipine, and hydrochlorothiazide for once daily use.(55) Benicar HCT is the brand name of a medication containing olmesartan medoxomil in combination with hydrochlorothiazide. Benitec H, another medication containing olmesartan medoxomil and hydrochlorothiazide, is marketed by GlaxoSmithKline in India.

Research

Two clinical studies (MORE and OLIVUS(56)(57)report that Benicar reduced arterial plaque during therapy for high blood pressure.

In a small study with 44 patients with chronic kidney disease without a history of diabetes, olmesartan was more effective in reducing daily urinary protein (proteinuria) than losartan, valsartan, and candesartan.(58)

Other uses for this medicine

Olmesartan is also sometimes used to treat heart failure (condition in which the heart is unable to pump enough blood to the rest of the body) and diabetic nephropathy (kidney disease in people with diabetes and high blood pressure). Talk to your doctor about the possible risks of using this medication for your condition.

This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

Storage

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom).

Unneeded medications should be disposed of in special ways to ensure that pets, children, and other people cannot consume them. However, you should not flush this medication down the toilet. Instead, the best way to dispose of your medication is through a medicine take-back program. Talk to your pharmacist or contact your local garbage/recycling department to learn about take-back programs in your community.

Symptoms of overdose may include:

- fainting
- dizziness
- fast or slow heartbeat

WARNING

FETAL TOXICITY

- When pregnancy is detected, discontinue Benicar as soon as possible [see WARNINGS AND PRECAUTIONS]

- Drugs that act directly on the renin-angiotens in system can cause injury and death to the developing fetus [see WARNINGS AND PRECAUTIONS].

Olmesartan is used alone or in combination with other medications to treat high blood pressure in adults and children 6 years of age and older. Olmesartan is in a class of medications called angiotensin II receptor antagonists. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently.

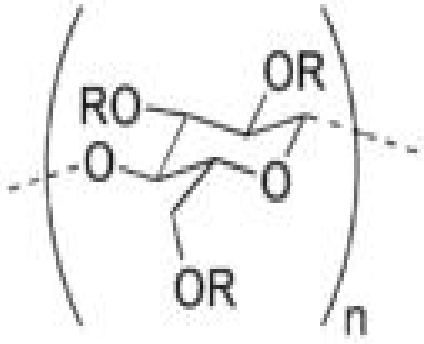
High blood pressure is a common condition and when not treated, can cause damage to the brain, heart, blood vessels, kidneys and other parts of the body. Damage to these organs may cause heart disease, a heart attack, heart failure, stroke, kidney failure, loss of vision, and other problems. In addition to taking medication, making lifestyle changes will also help to control your blood pressure. These changes include eating a diet that is low in fat and salt, maintaining a healthy weight, exercising at least 30 minutes most days, not smoking, and using alcohol in moderation.

Olmesartan may cause side effects.

- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- severe diarrhea
- weight loss
- difficulty breathing or swallowing
- hoarseness

Hypromellose

Hypromellose



$R = H$ or CH_3 or $CH_2CH(OH)CH_3$

Names

Other names

Hydroxypropyl methylcellulose; hydroxypropyl methyl cellulose; HPMC; E464

Identifiers

CAS Number	• 9004-65-3 ✓
ChemSpider	• 21241863 ✓
ECHA InfoCard	100.115.379
E number	E464 (thickeners, ...)
	• 36SFW2JZ0W ✓

Properties

Chemical formula	Variable
Molar mass	Variable

Pharmacology

ATC code	S01KA02 (WHO)

Hypromellose (INN), short for **hydroxypropyl methylcellulose** (**HPMC**), is a semisynthetic, inert, viscoelastic polymer used as eye drops, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.(59)

As a food additive, hypromellose is an emulsifier, thickening and suspending agent, and an alternative to animal gelatin. Its Codex Alimentarius code (E number) is E464.

Chemistry

Hypromellose is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. The compound forms colloids when dissolved in water. This non-toxic ingredient is combustible and can react vigorously with oxidising agents.[4]

Hypromellose in an aqueous solution, unlike methylcellulose, exhibits a thermal gelation property. That is, when the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule (which in turn depends on both the degree of substitution of the methoxy group and the molar substitution. That is, the higher the concentration of the methoxy group, the lower the critical temperature. The inflexibility/viscosity of the resulting mass, however, is directly

related to the concentration of the methoxy group (the higher the concentration, the more viscous or less flexible the resulting mass is).

Uses

There are many fields of application for hypromellose, including:

- Tile adhesives
- Cement renders
- Gypsum products
- Pharmaceutical
- Paints & coatings
- Food
- Cosmetics
- Detergents & cleaners
- Eye drops
- Contact lenses

Excipient/tableting ingredient

In addition to its use in ophthalmic liquids, hypromellose has been used as an excipient in oral tablet and capsule formulations, where, depending on the grade, it functions as controlled release agent to delay the release of a medicinal compound into the digestive tract. It is also used as a binder and as a component of tablet coatings.(60)

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist**.** Angiotensin II is formed from angiotensin I in a reaction catalyzed

by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. Olmesartan medoxomilis indicated for the treatment of mild to moderate essential hypertension. The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.Olmesartan medoxomil inhibits the pressor effect of an angiotensin II infusion in a dose- dependent manner at doses of 2.5 to 40 mg. The inhibition was 90% at doses of olmesartan medoxomil >40 mg 24 hours post dose.

Drug excipients compatibility study Fourier Transform Infrared (FTIR)

Drug excipients interactions play vital role in the release of drug from the formulation. Fourier Transform Infrared spectroscopy has been used to study the physical and chemical interaction between the excipients used. FTIR technique has been used to study the physical and chemical interaction between drug and excipients used.

Powder flow property

The flow properties of powder were determined included the following: bulk density, tapped density , carr's index, Hausner's ratio and angle of repose. All the above properties were measured according to USP XXXI.

SODIUM BICORBONATE

Names	
IUPAC name Sodium hydrogen carbonate	
Other names Baking soda, bicarb (laboratory slang), bicarbonate of soda, nahcolite	
Properties	
Chemical formula	NaHCO3
Molar mass	84.0066 g mol^{-1}
Appearance	White crystals
Odor	Odorless
Density	• 2.20 g/cm^3 as solid • 1.1 to 1.3 as powder
Melting point	(Decomposes to sodium carbonate starting at 50 °C

Solubility in water	• 69 g/L (0 °C) • 96 g/L (20 °C) • 165 g/L (60 °C) • 236 g/L (100 °C)
Solubility	0.02 wt% acetone, 2.13 wt% methanol @22 °C.[5]insoluble in ethanol
log P	−0.82
Acidity (pK_a)	• 10.329 • 6.351 (carbonic acid)
Refractive index (n_D)	nα = 1.377 nβ = 1.501 nγ = 1.583
Structure	
Crystal structure	Monoclinic
Thermochemistry	
Specific heat capacity (C)	87.61 J/mol K
Std molar entropy ($S^{\ominus}_{298}$)	102 J/mol K
Std enthalpy of formation ($\Delta_f H^{\ominus}_{298}$)	−947.7 kJ/mol

Gibbs free energy ($\Delta_f G^\circ$)	−851.9 kJ/mol
Pharmacology	
ATC code	B05CB04 (WHO) B05XA02 (WHO), QG04BQ01 (WHO)
Routes of administration	Intravenous, oral

Sodium bicarbonate (IUPAC name: **sodium hydrogen carbonate**) is a chemical compound with the formula $NaHCO_3$. It is a salt composed of sodium ions and bicarbonate ions. Sodium bicarbonate is a white solid that is crystalline but often appears as a fine powder. It has a slightly salty, alkaline taste resembling that of washing soda (sodium carbonate). The natural mineral form is nahcolite. It is a component of the mineral natron and is found dissolved in many mineral springs. It is among the food additives encoded by the European Union, identified as E 500.

Since it has long been known and is widely used, the salt has many related names such as **baking soda**, **bread soda**, **cooking soda**, and **bicarbonate of soda**. In colloquial usage, the names sodium bicarbonate and bicarbonate of soda are often truncated. Forms such as sodium bicarb, bicarb soda, bicarbonate, bicarb, or even bica are common. The word *saleratus*, from Latin *sal æratus* meaning "aerated salt", was widely used in the 19th century for both sodium bicarbonate and potassium bicarbonate.

Alkalinity/pH increase

It can be administered to pools, spas, and garden ponds to raise the total alkalinity, this will also raise the pH level and make maintaining proper pH easier. In the event that the pH is low and the alkalinity is adequate or high, Baking Soda (sodium bicarbonate) should not be used to adjust the pH.

Neutralisation of acids and bases

Sodium bicarbonate is amphoteric, reacting with acids and bases. It reacts violently with acids, releasing CO_2 gas as a reaction product. It is commonly used to neutralize unwanted acid solutions or acid spills in chemical laboratories.

A wide variety of applications follows from its neutralisation properties, including reducing the spread of white phosphorus from incendiary bullets inside an afflicted soldier's wounds.

Medical uses

Sodium bicarbonate mixed with water can be used as an antacid to treat acid indigestion and heartburn. Its reaction with stomach acid produces salt, water, and carbon dioxide:

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2(g)$$

Intravenous sodium bicarbonate is an aqueous solution that is sometimes used for cases of acidosis, or when insufficient sodium or bicarbonate ions are in the blood.[25] In cases of respiratory acidosis, the infused bicarbonate ion drives the carbonic acid/bicarbonate buffer of plasma to the left and, thus, raises the pH. It is for this reason that sodium bicarbonate is used in medically supervised cardiopulmonary resuscitation. Infusion of bicarbonate is indicated only when the blood pH is markedly (<7.1–7.0) low.

It is used for treatment of hyperkalemia, as it will drive K^+ back into cells during periods of acidosis.]Since sodium bicarbonate can cause alkalosis, it is sometimes used to treat aspirin overdoses. Aspirin requires an acidic environment for proper absorption, and the basic environment diminishes aspirin absorption in the case of an overdose. Sodium bicarbonate has also been used in the treatment of tricyclic antidepressant overdose. It can also be applied topically as a paste, with three parts baking soda to one part water, to relieve some kinds of insect bites and stings (as well as accompanying swelling).

Sodium bicarbonate has been found to have no effect on the blood pressure of several types of rat models susceptible to salt-sensitive hypertension, in contrast with sodium chloride. This was ascribed to the high concentration of chloride, rather than the sodium content in dietary salts.

Sodium bicarbonate can be used to treat an allergic reaction to plants such as poison ivy, poison oak, or poison sumac to relieve some of the associated itching.

Bicarbonate of soda can also be useful in removing splinters from the skin.

Some alternative practitioners, such as Tullio Simoncini, have promoted baking soda as a cancer cure, which the American Cancer Society has warned against due to both its unproven effectiveness and potential danger in use.

Sodium bicarbonate can be added to local anaesthetics, to speed up the onset of their effects and make their injection less painful. It is also a component of Moffett's solution, used in nasal surgery.

Magnesium stearate

Uses

Magnesium stearate is often used as an anti-adherent in the manufacture of medical tablets, capsules and powders.[4] In this regard, the substance is also useful, because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets. Magnesium stearate can also be used efficiently in dry coating processes.

Magnesium stearate is also used to bind sugar in hard candies like mints, and is a common ingredient in baby formulas.

Safety

Magnesium Stearate is generally considered safe for human consumption at levels below 2500 mg/kg per day. In 1979, the FDA's Subcommittee on GRAS (generally recognized as safe) Substances (SCOGS) reported, "There is no evidence in the available information on ... magnesium stearate ... that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future.

TALC

Talc is a clay mineral composed of hydrated magnesium silicate with the chemical formula $H_2Mg_3(SiO_3)_4$ or $Mg_3Si_4O_{10}(OH)_2$. In loose form, it, along with corn starch, was one of the most widely used substances known as baby powder (in the case of talc, often called simply **talcum powder**; It occurs as foliated to fibrous masses, and in an exceptionally rare crystal form. It has a perfect basal cleavage, and the folia are not elastic, although slightly flexible. use as a cosmetic (talcum powder), as a lubricant, and as a filler in paper manufacture

Industrial grade

In the United States, the Occupational Safety and Health Administration and National Institute for Occupational Safety and Health have set occupational exposure limits to respirable talc dusts at 2 mg/m^3 over an eight-hour workday. At levels of 1000 mg/m^3, inhalation of talc is considered immediately dangerous to life and health

MATERIALS AND METHODS

Olmesartan medoxomil was obtained as a gift sample from Micro labs Pharma Ltd. Hosur. HPMC K4M, HPMC K100M were obtained from Atoz pharma, pondicherry. All other reagents used were of analytical grade.

Preparation of standard curve of olmesartan medxomil in methanol

Accurately weighed olmesartan medoxomil (10 mg) was placed in 100 ml volumetric flask, 10 ml of methanol was added to it and sonicate for 1 minute and then made up the volume to 100 ml with methanol. From the above solution, 1 ml of solution was pipette out and diluted to 10 ml with methanol. The resultant solution obtained was 10 µg/ml and was scanned in UV range of 200 to 400 nm. Olmesartan medoxomil showed maximum absorbance at 257 nm. Thus, 257 nm was taken as λmax**.**

Preparation of floating tablets of olmesartan medoxomil

The composition of different formulations of Olmesartan Medoxomil floating tablets is shown in table 1. Direct compression method had been employed to prepare floating tablets of Olmesartan Medoxomil with HPMC K4M and HPMC K100M . All ingredients were weighed accurately and passed through mesh #60. In order to mix thoroughly polymer and drug blended geometrically in mortar pestle for 15 mins and then sodium bicarbonate, citric acid, magnesium sterate, talc and lactose were mixed one by one. After thorough mixing these ingredients the powder blend was passed through mess #44. The tablets were compressed on rotary tablet press.[61].

Experimental Design

A 3^2 full factorial design was used for the optimization.

Optimization of floating tablets of Olmesartan Medoxomil by 3^2 full factorial design

In the present study three levels two factors, full factorial design was employed for the optimization of floating tablets of olmesartan medoxomil. The concentration of HPMC K4M and HPMC K100M were selected as independent variable and floating lag time, total floating time and T_{80} were selected as dependent variables.

X_1 code for amount of HPMC K4M and X_2 code for amount of HPMCK100M.

Table no 1: Full factorial design layout

BATCH CODE	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table no 2: Coded values X1 code for amount of HPMC K4M and X2 Code for amount of HPMCK100M

Coded value	Amount of HPMC K4M in mg (X1)	Amount of HPMCK 100 M in mg (X2)
-1	0	0
0	40	40
1	80	80

Formulation of factorial batches and Statistical modeling for optimization

A three level, two factor experimental design as shown below described the proportion in which independent variables- concentration of HPMC K4M and HPMC K100M was used in the formulation. The concentration of polymer was varied at three level 0, 40 mg and 80 mg. floating lag time, total floating time and T_{80} of 9 formulations were analysed. The run or formulation which are designed based on factorial design are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis is floating lag time, total floating time and T_{80}. The multiple regression analysis was done using DESIGN EXPERT 9.0.3.1 D- optimal type. Which is specially meant for this optimization. Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F test , using the regression coefficient of factor , the polynomial equation for each response is generated.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Table no 3: statistical model for optimization

Factor		Level		
Independent variables	**High(1)**	**Medium(0)**	**Low (-1)**	**Dependent variable**
HPMC K4M	**80**	**40**	**0**	**Floating lag time**
HPMC K100M	**80**	**40**	**0**	**Total floating time &**
				T_{80}

Table no 4: Composition Of Floating Tablet Of Olmesartan Medoxomil Ingredients Formulations code (All the quantities are In mg.)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Olmesartan medoxomil	50	50	50	50	50	50	50	50	50
HPMC K4M	0	0	0	40	40	40	80	80	80
HPMC K100M	0	40	80	0	40	80	0	40	80
Sodium bicarbonate	70	70	70	70	70	70	70	70	70
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7
Lactose	230	190	150	190	150	110	150	110	70
Citric acid	35	35	35	35	35	35	35	35	35

Where Y is the dependent variable, b_0 is the arithmetic mean response and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms(X_1^2 and X^2) are included to investigate non linearity. On the basis of preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables ie concentration of HPMC K4M and HPMC K100M on dependent variable ie floating lag time, total floating time and T_{80}.Analysis of variance, contour and RSM plots represent the effect of the independent variables graphically.

Regression Analysis Equation for LT

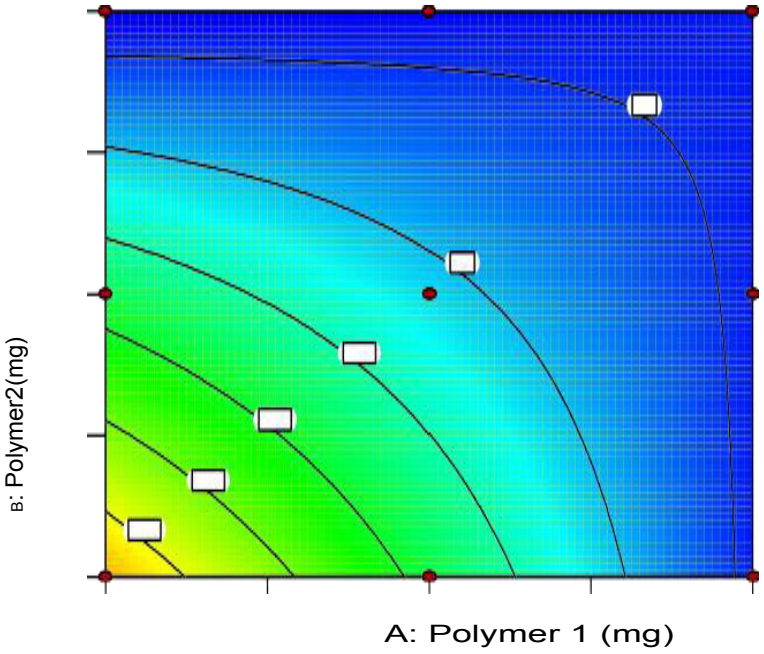


Fig 11: Contour plot to study the effect of two HPMC grade polymer concentrations on floating lag time

X1 = A: Polymer 1 X2 = B: Polymer 2

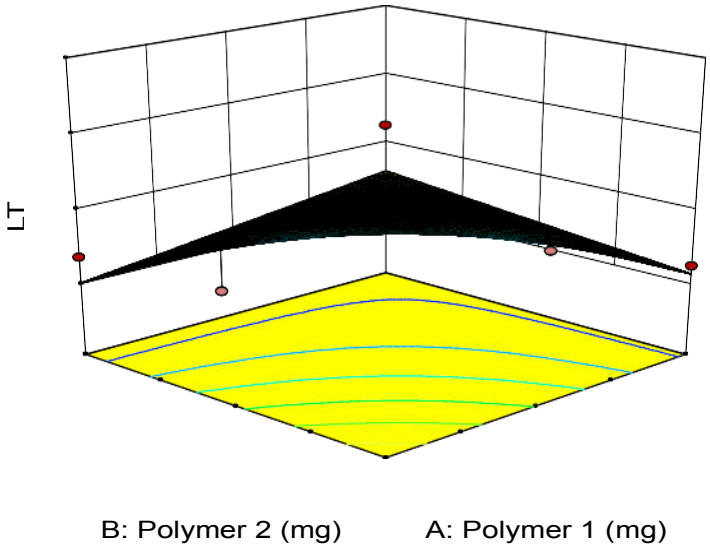


Fig 12: RSM plot to study the effect of two HPMC grade polymer concentrations on floating lag time LT= 174.4166-1.4729X1-1.55208X2+0.0195X1X2

Regression Analysis for total floating time

TFT (hrs)

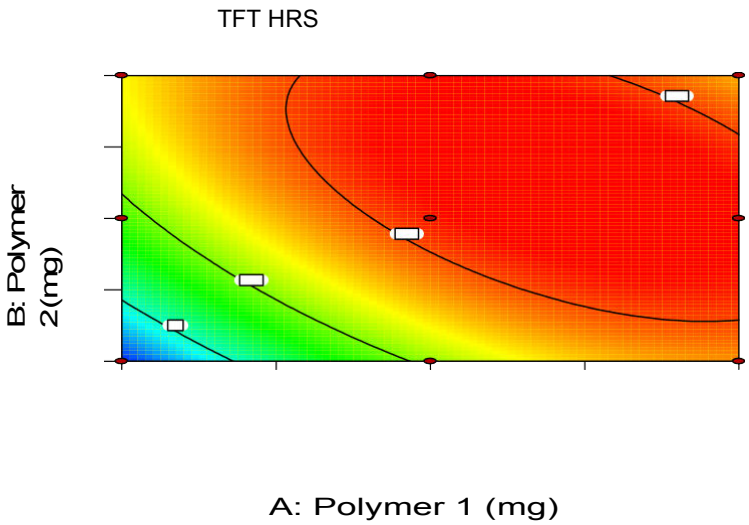


Fig 13: Contour plot to study the effect of two HPMC grade polymer concentrations on total floating time.

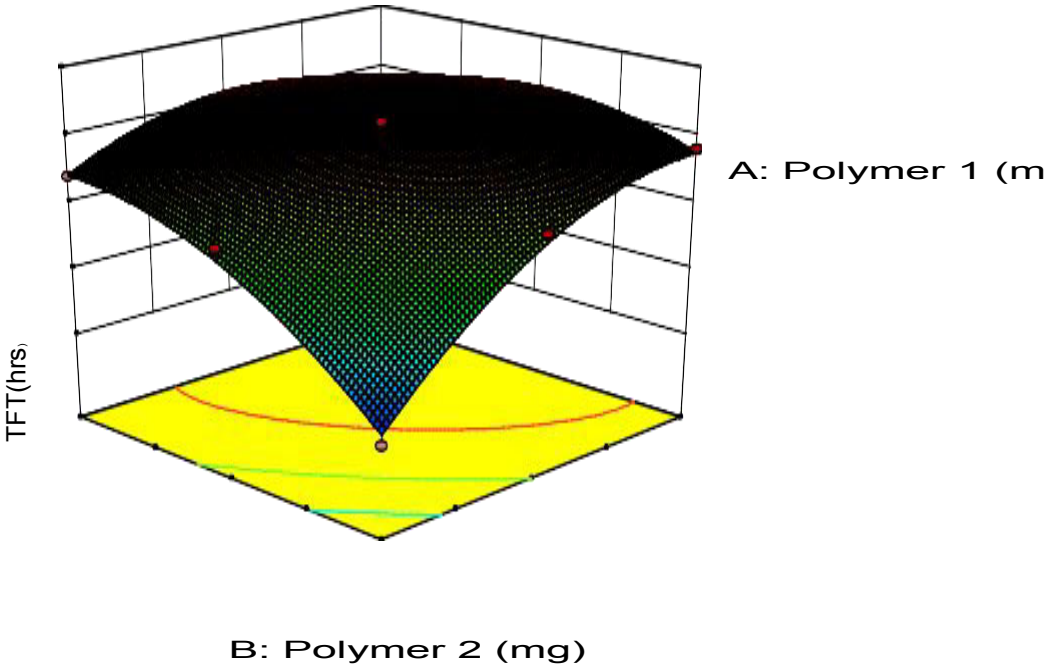


Fig 14: RSM plot to study the effect of two HPMC grade polymer concentrations on total floating time

$$TFT=0.7778+0.32083X1+0.27500X2-1.87500X1X2-1.97917X1^2\ 1.6667X2^2$$

Total floating time gives correlation co-efficient 0.7778. The P value for variable X1 and X2 were 0.0127 and 0.0059 respectively ($P<0.05$), it indicate that X1 and X2 variable shown significant effect on drug release Combination co-efficient was positive and the P value less than 0.05, which indicates that combination of independent variable showed significant effect on floating lag time. The co-efficient of X1 and X2 were positive indicate that when concentration of both the variable increase than total floating time was increased.

Regression Analysis for T80

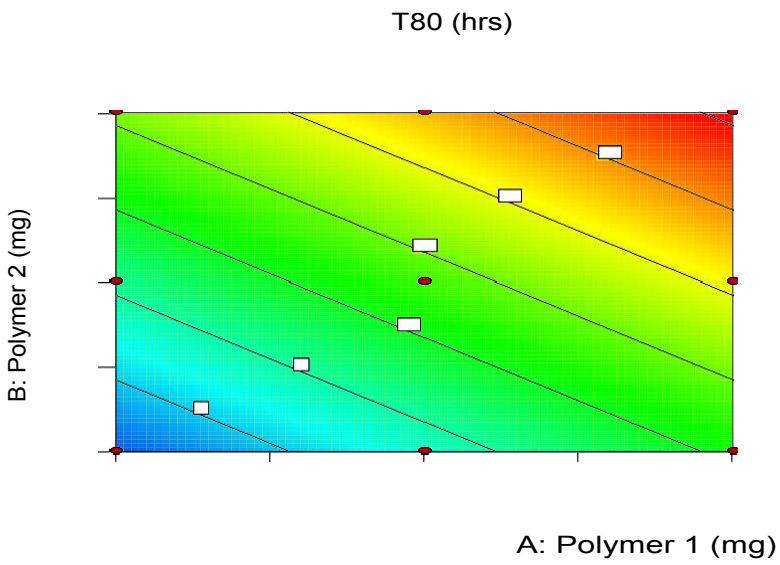


Fig 15: Contour plot to study the effect of two HPMC grade polymer concentrations on T80

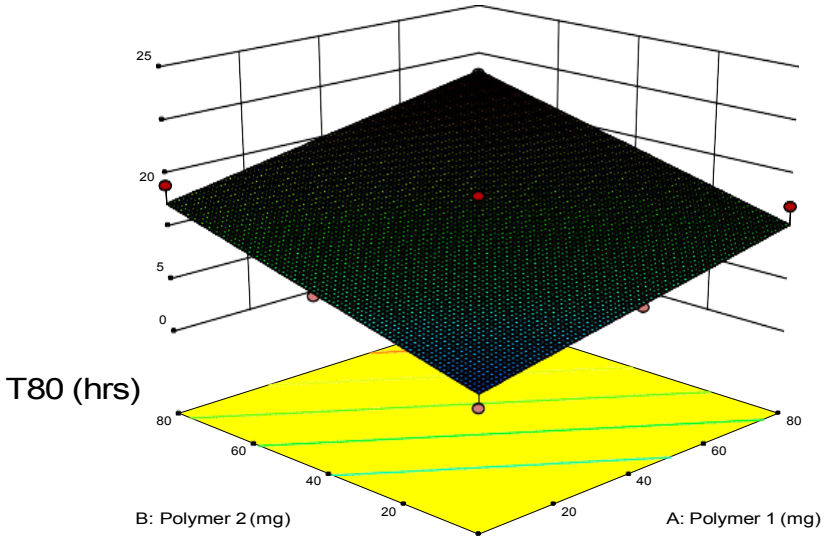


Fig 16: RSM plot to study the effect of two HPMC grade polymer concentrations on T80.

$$T80 = 4.3333 + 0.07500X1 + 0.10000X2$$

T80 gives correlation co-efficient 4.3333. The P value for variable X1 and X2 were 0.0030 and 0.0007 respectively (P<0.05), it indicate that X1 and X2 variable shown significant effect on drug release. Combination co-efficient was positive and the P value less than 0.05, which indicates that combination of independent variable showed significant effect on T80.

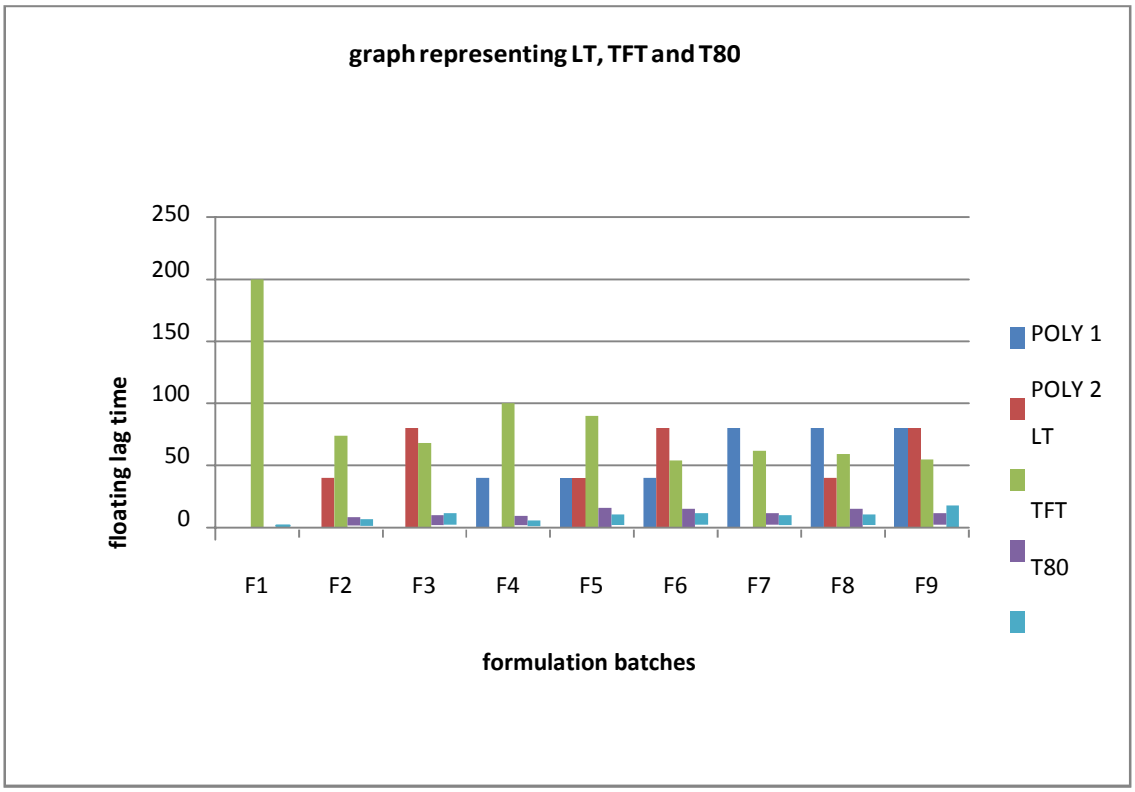


Fig 17: Comparision of TFT, LT and T80 of different formulation batches with respect to polymer concentration.

Evaluation of floating tablet:

The prepared tablets were evaluated for the following parameters:

Thickness of Tablets

The thickness of six tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined**.** (62)

Hardness

The hardness of the tablet was determined by Monsanto hardness tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded**.**(63)

Friability

The Friability of tablets was performed in a Roche Friabilator. It consists of a plastic chamber that revolves at 25 rpm.

Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed. The friability (F) is given by the formula**.**(64)

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} * 100$$

Weight Variation

Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit. In-vitro buoyancy studies.

The in vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to float was determined as floating lag time. Total floating time was also determined**.(65)**

In-vitro Dissolution Studies

In vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 100 rpm. Dissolution test was performed using 0.1N HCL as dissolution medium and the temperature was maintained at 37 ± 0.5ºC. Aliquot of dissolution medium was withdrawn at specific time intervals 2,4,6,8,10,12,14,16,18,20,22,24.

The samples were filtered through a 0.45 membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 257 nm UV spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.(66)

Swelling index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = (W_t - W_0/W_0)*100$$

Where, W_0 is the initial weight of tablet, and W_t is the weight of the tablet at time t.(67)

Kinetic modeling and mechanism of drug release

To know the mechanism of drug release from these formulations, The data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), Korsmeyer (log cumulative percentage of drug released vs log time), equations along with zero order (cumulative amount of drug released vs time) pattern**. (68-70)**

Accelerated stability study

The tablets of best batch were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1 month in a humidity jar.(69)

RESULT AND DISCUSSION

Standard curve of Olmesartan Medoxomil

Standard curve of olmesartan was prepared in methanol. Standard curve data are subjected to linear

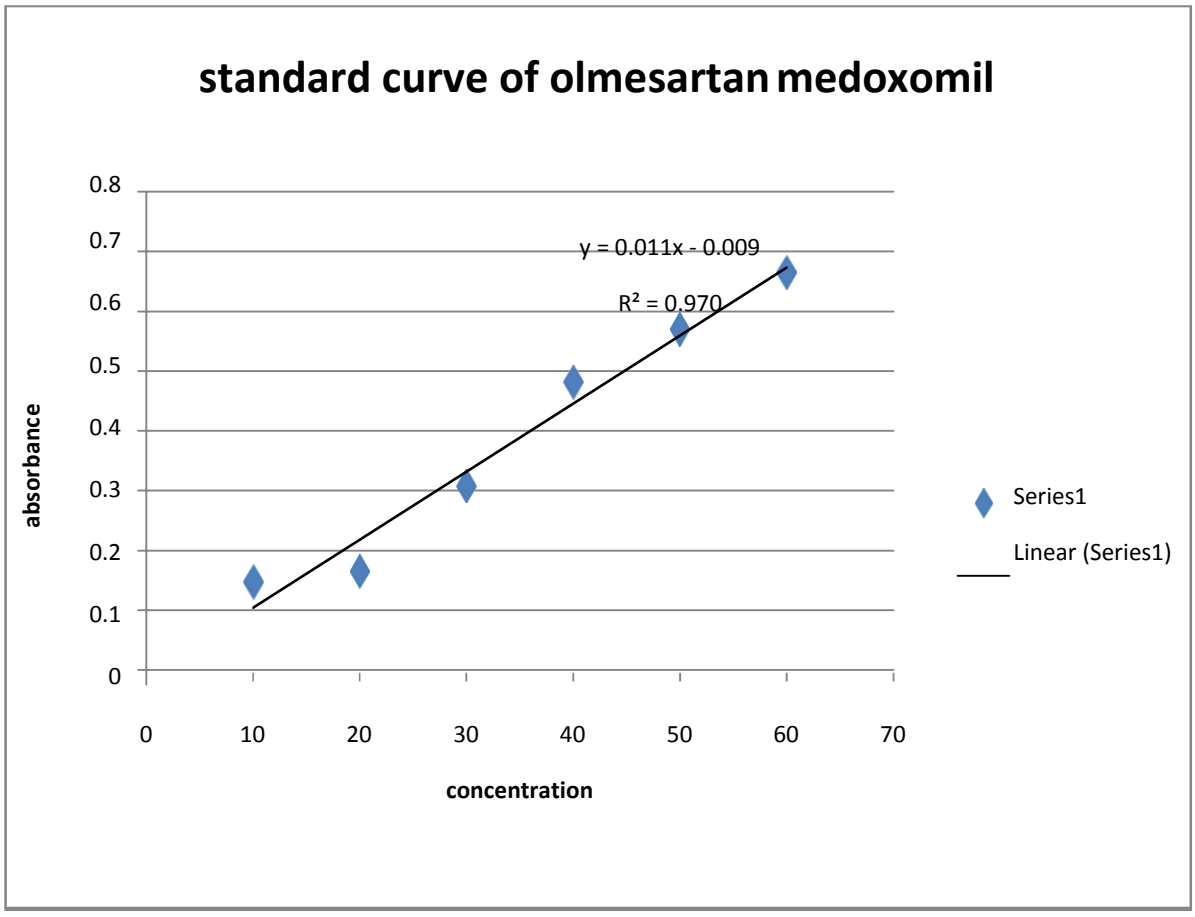


Fig 18: Standard curve of Olmesartan Medoxomil

Identification of pure drug

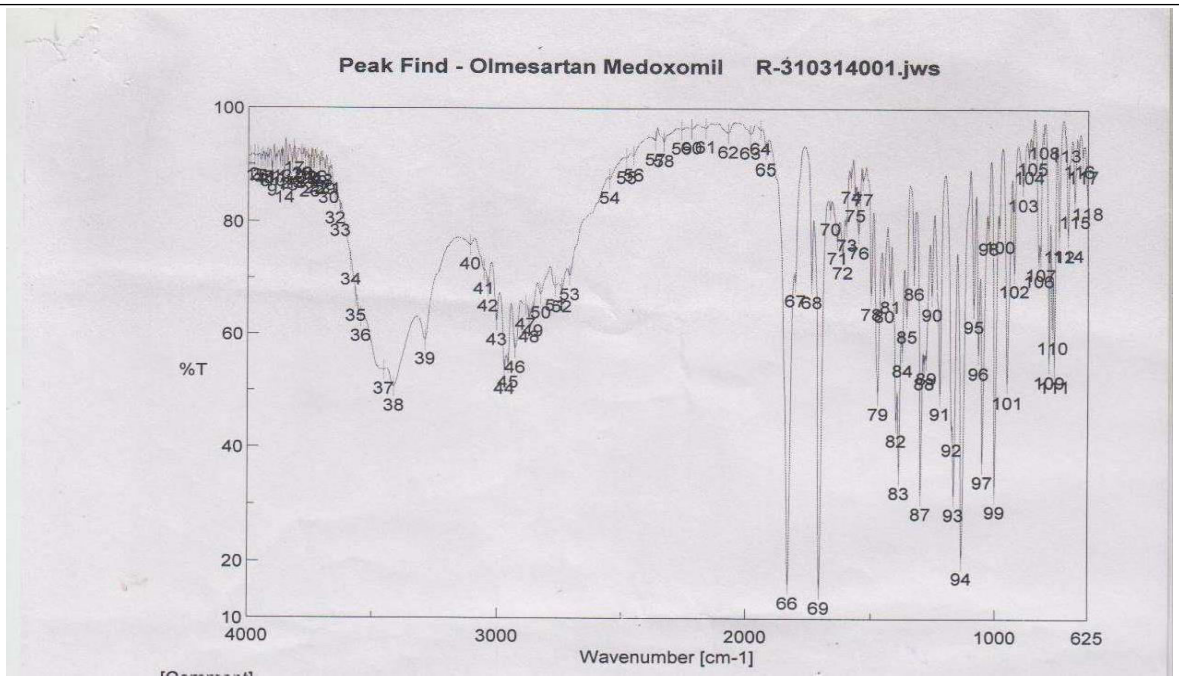


Fig19: FTIR of Olmesartan Medoxomil

Drug Polymer interaction Studies

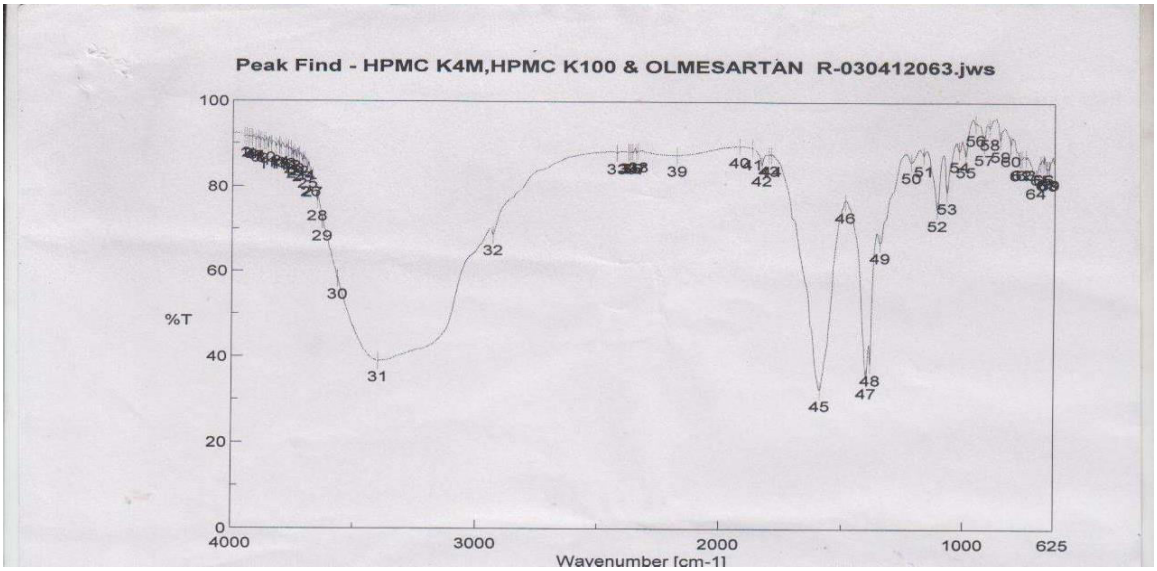


Fig 20: FTIR of the formulation

Olmesartan showed characterstic peak at 2974cm^{-1} (aliphatic C-H Streching),3039 cm^{-1} (aromatic C-H Streching), 3271cm^{-1} (broad peak intermolecular Hydrogen bond), 3720 cm^{-1} (C=O of carboxylic group), 1483 cm^{-1} (C-N Streching). The formulation containing polymer showed all the peaks of Olmesartan Medoxomil with no change in intensity.

Table no 5: Evaluation parameter of tablets of different batches

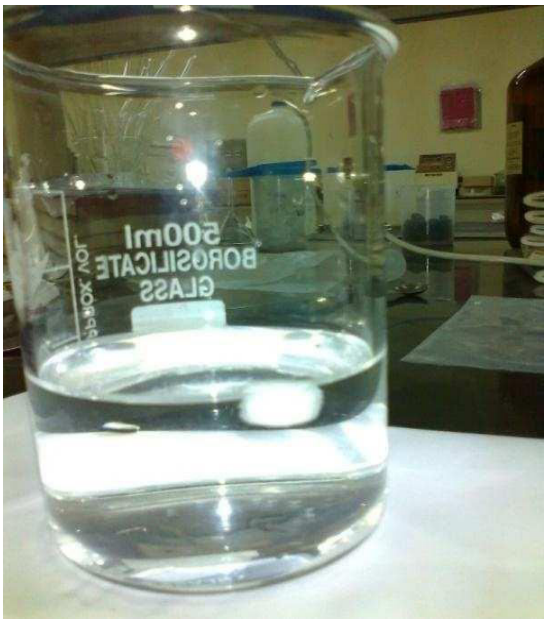
Tablet batch	weight variation test(mg)	thickness mm	hardness (kg/cm^2)	friability %
F1	398.47±2.31	4.25±0.31	5.0±0.40	0.45±0.020
F2	398.77±2.13	3.94±.02	4.5±0.20	0.36±0.015
F3	399.21±4.2	3.96±0.04	4.5±0.30	0.38±0.020
F4	398.37±1.01	4.03±0.05	5.0±0.40	0.28±0.030
F5	399.43±2.31	3.81±0.06	5.0±0.35	0.27±0.060
F6	400.20±0.41	4.34±0.23	5.5±0.50	0.32±0.035
F7	400.12±1.32	4.08±0.07	5.0±0.20	0.22±0.040
F8	401.53±0.86	3.93±0.06	4.0±0.30	0.28±0.015
F9	401.74±1.39	4.12±0.07	5.0±0.20	0.23±0.020

Table no 6: In vitro buoyancy studies

Batch	Floating lag time(sec)	Floating time
F1	200	0 hrs
F2	74	10hrs
F3	8	12hrs.
F4	100	11hrs.
F5	90	16hrs.
F6	54	15hrs.
F7	62	14hrs.
F8	59	15hrs
F9	55	14hrs

The in-vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to float was determined as floating lag time.

In vitro buoyancy study showed that all the batches from F1 to F9 have floating lag time less than 4 minutes because of evolution and entrapment of carbondioxide inside the hydrated polymer matrices, resulting from the interaction between gas generating agent and dissolution medium which led to lowering the density of matrices enabling the tablets to float.



At 0 sec after 40 secs

On the other hand, as a solvent front penetrated the polymer layer, swelling of HPMC K4M and HPMC K100M caused to increase in volume of tablet resulted in net reduction in density of the tablet, which prolonged the duration of floatation up to 18 hrs.

Fig 21: Buoyancy studies of tablet at different time

Table no 7: Dissolution studies of different batches

CUMMULATIVE PERCENT RELEASE

	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	38.39	18.34	17.32	22.43	19.21	17.32	19.43	20.11	11.92
3	79.54	42.12	30.21	41.56	38.42	34.42	40.24	36.75	16.93
5	98.22	65.86	39.42	66.76	46.34	47.59	48.25	41.44	21.84
7		74.41	48.64	80	59.52	53.54	56.11	53.33	32.06
8		80.64	56.42	88.53	63.54	58.67	64.66	60.51	39.46
10		92.45	61.36	94.36	68.98	64.77	73.22	68.67	48.47
12		98.55	67.48	97.87	72.32	70.52	78.98	75.34	55.12
13			72.49		79.87	75.33	85.33	81.43	59.49
14			78.87		87.41	80.32	89.89	89.54	62.11
15			85.64		91	85.66	94.31	93.77	68.42
16			92.48		96.73	91.29	97.75	98.24	71.45
17			98.56			98.43			78.74
18									81.72
19									88.89
20									93.21
21									97.54

Invitro buoyancy study showed that all the batches from F1 to F9 have floating lag time less than 4 minutes because of evolution and entrapment of carbondi oxide inside the hydrated polymer matrices, resulting from the interaction between gas generating agent and dissolution medium which led to lowering the density of matrices enabling the tablets to float. On the other hand, as a solvent front penetrated the polymer layer, swelling of HPMC K4M and HPMC.K100M caused to increase in volume of tablet resulted in net reduction in density of the tablet, which prolonged the duration of floatation up to 18 hrs. Among these formulations F9 give the desired release and retarded the 80% drug release for 18 hrs.

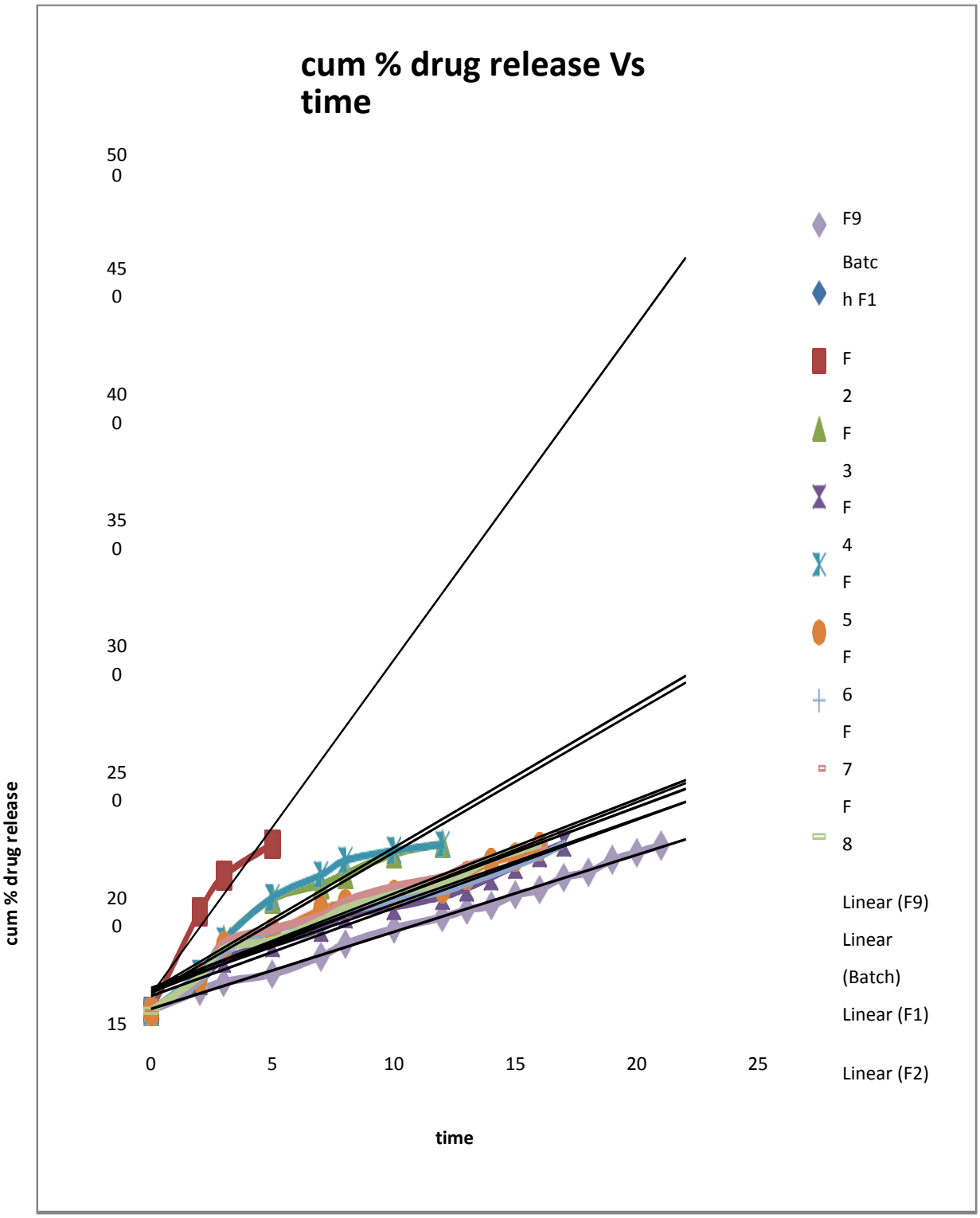


Fig 22: In vitro dissolution studies of different formulation batches

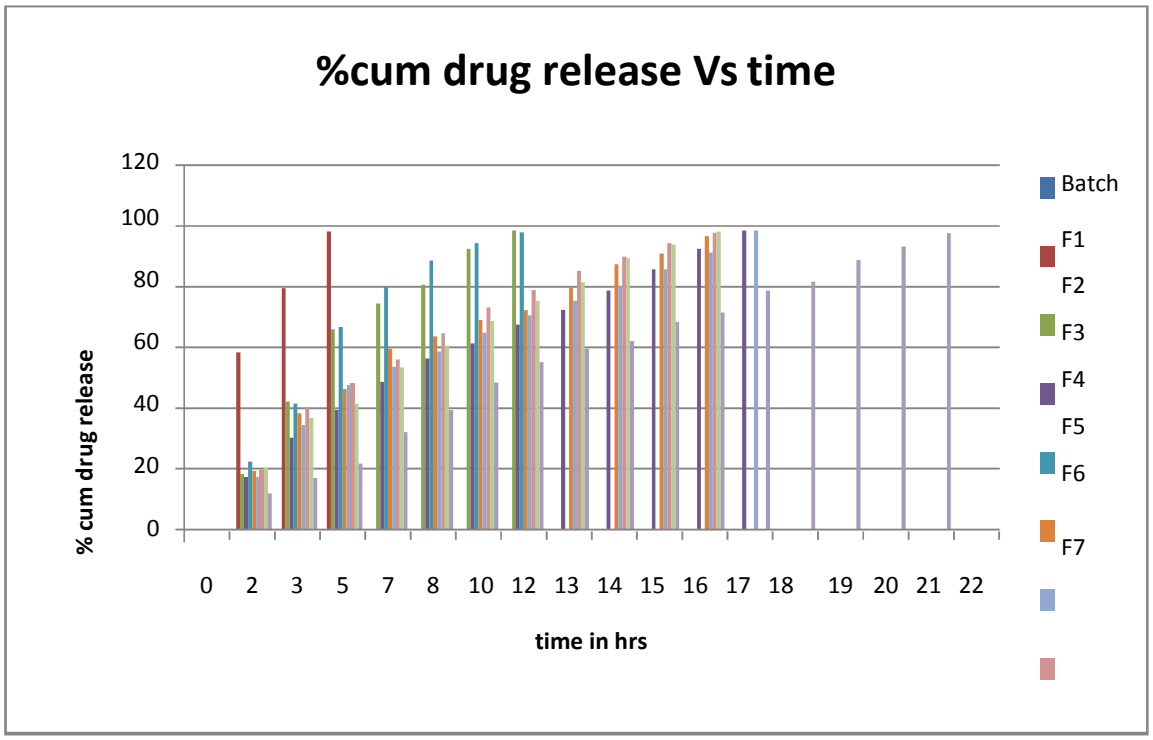


Fig 23: Dissolution profile of formulations F1 to F9

Table no 8: Invitro drug release kinetics study

Model	Zero order	First order	Higuchi plot	Korsmeyer peppas
R^2	0.997	0.728	0.922	0.992
Slope	4.527	11.51	23.47	0.908
Intercept	1.284	-6.627	-21.02	0.769

The data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square

root of time), Korsmeyer (log cumulative percentage of drug released vs log time), equations along with zero order (cumulative amount of drug released vs time) .The dissolution profile of the best batch was fitted to zero-order, first-order, Higuchi and korsmeyer models to ascertain the kinetic modeling of drug release. It may be concluded that the drug release from gastro retentive olmesartan medoxomil tablet is explained by zero model because R^2 value of zero order model has 0.997. The values n in korsmeyer peppas equation is 0.769 which is greater than 0.50, thus we can conclude that dissolution follows non fickain diffusion.

Swelling index

Swelling index of the tablet include the absorption of liquid medium then increases the weight of the tablet. This is very important characteristics of the polymer which control the drug release from the formulation via diffusion from the studies it was found that increase the concentration of HPMC K4M increases the swelling property.F9 showed maximum swelling among all HPMC containing formulations. HPMC K4M and HPMC K100M tablet when in contact with dissolution medium swell due to breakage of hydrogen bond between the polymer chain and form a thick gel layer and eroded simultaneously. This result indicated that the swelling index of all the formulations changed after different time interval.(74)

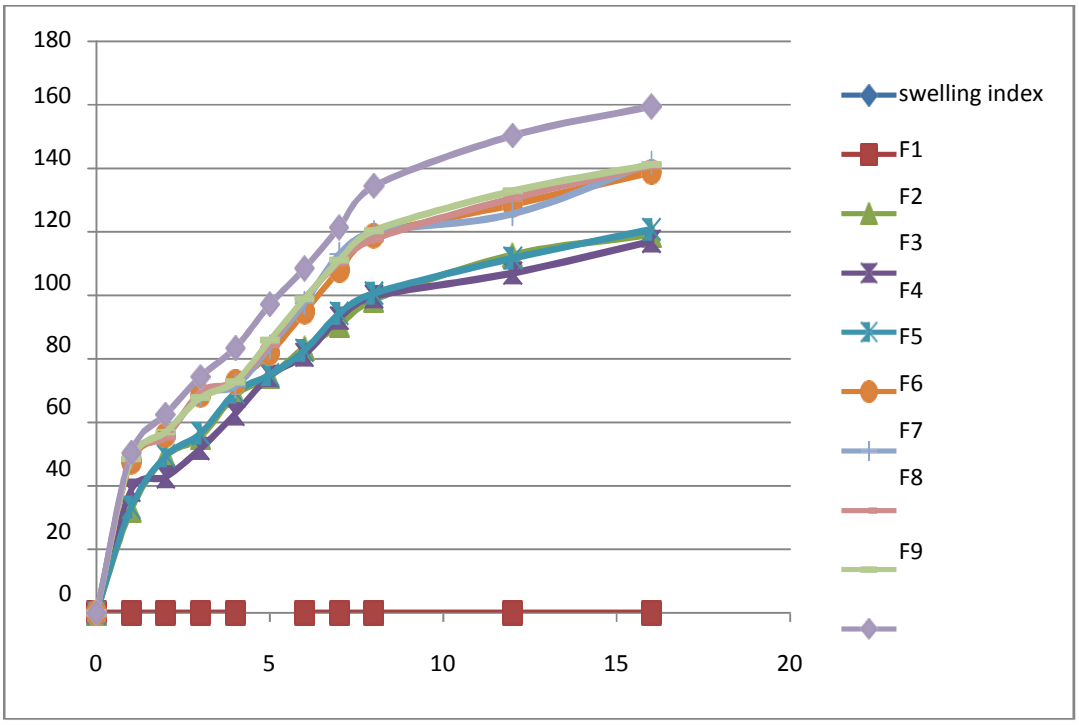


Fig 24: Swelling studies of formulation batches

Gastro retentive tablets of olmesartan medoxomil formulated in the present study were subjected to accelerated stability studies in Aluminum / Aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for site-specific drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch F9 were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1 months in a humidity jar (74).

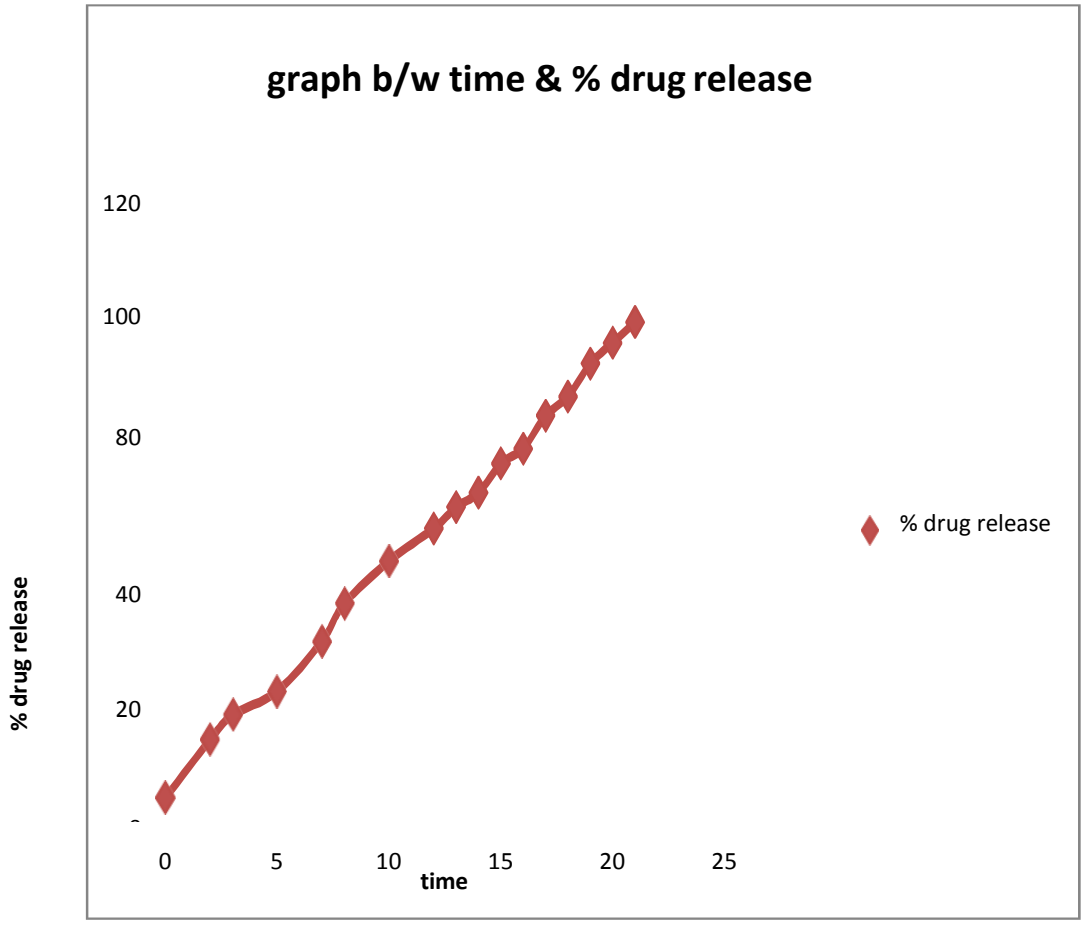


Fig 25: Accelerated stability studies of the optimized batch

CONCLUSION

In the present work floating tablets of Olmesartan Medoxomil were prepared by direct compression. All the tablets were subjected to weight variation, hardness, friability, dissolution, swelling index, drug excipient interaction studies. The tablets were found to be good in their integrity without any chipping, capping and sticking. Formulation F9 showed good result than rest of the formulations according to targets obtained. IR-spectroscopic studies indicated that there are no drug–excipients interactions. Formulation F9 showed best result with required floating lag time of 55 secs, total floating time of 14 hrs and T_{80} of18 hrs. drug release was decreased with increased concentration of polymers. IR spectroscopic studies indicated that there was no drug excipient interactions. Kinetic studies for optimized formulation F9 follows zero order and Higuchi model release systems. Zero order release describes the system where the drug release rate is independent of its concentration of dissolved substance.

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