DESIGN AND CHARACTERIZATION OF FLOATING TABLETS OF RANOLAZINE.

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LIST OF ABBREVATIONS

API	Active Pharmaceutical Ingredients.
HPMC	Hydroxy Propyl Methyl Cellulose.
MCC	Microcrystalline Cellulose.
FDDS	Floating Drug delivery System
SR	Sustained Release.
I.P	Indian Pharmacopoeia.
USP	United State Pharmacopoeia
B.D	Bulk Density.
T.D	Tapped Density.
FTIR	Fourier Transform Infrared Spectroscopy.
U.V	Ultra Violet Spectroscopy.
HPLC	High Performance Liquid Chromatography.
Std	Standard.
RH	Relative Humidty
FLT	Floating Lag Time
TFT	Total Floating Time
pKa	Partition co-efficient.
GIT	Gastro Intestinal Tract.
Fig	Figure.
q.s	Quantity sufficient.
SD	Standard Deviation.
RPM	Revolution per minute.
ppm	Parts per million.
mm	Millimeter.
ml	Milliliter.
Kg/cm2	Kilogram per centimeter.
w/w	Weight per Weight.

%	Percentage.

INTRODUCTION

Oral route remains the preferred route for the administration of therapeutic agents because low cost of therapy and ease of administration leads to higher level of patient compliance. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system in last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastro intestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastro retention helps to pro-vide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability. These systems are also advantages in improving GIT absorption of a drug with narrow absorption windows as well as for controlling release of those drugs which are having site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach for eg. Albuterol[5]. From the formulation and technological point of view, floating drug

delivery system (FDDS) is considerably easy and logical approach in development of GRDFs. Hence, this review article focuses on the current technological development in FDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug delivery [1].

Developments in Pharmaceutical Dosage Form Design [3]

A drug is rarely administered to human being as a pure chemical compound. What is given a drug product containing the drug. When a drug is prepared in a form suitable for administration it is called a dosage form or a drug product or, in a modern term delivery system.

1. The first generation drug delivery systems include conventional dosage forms such as tablets, capsules, elixirs, syrups etc.

2. The second generation drug delivery systems include repeat action, prolonged action, and timed release dosage forms.

3. The third generation drug delivery systems include controlled drug delivery that refers to the precise control of the rate at which a drug dosage is released from a delivery system.

4. The fourth generation drug delivery systems include targetable, modulated, pulsatile and self regulated, or feedback controlled drug delivery systems.

5. The Fifth Generation Drug Delivery Systems include gene therapy, intended to treat the cause of a disease rather than the symptoms.

1.2 Conventional Release Concept [1][2]

An ideal dosage regimen in the drug delivery of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at a particular frequency. The frequency of administration or the dosing interval of any drug depends upon its half–life or mean residence time (MRT) and its therapeutic index. In most cases, the dosing interval is much shorter than the half–life of the drug resulting in a number of limitations associated with such a conventional dosage form:

1. Poor patient compliance
2. A typical peak – valley plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentration.
4. The fluctuating drug levels may lead to precipitation of adverse effects.

To overcome such a situation concept and techniques of controlled and targeted delivery systems was developed.

Current Challenges in Drug Delivery [3]

The challenge of drug delivery is liberation of drug agents at the right time in a safe and reproducible manner, usually to a specific target site To achieve therapeutic levels that extend over time, the initial concentration of the drug in the body must be high, causing peaks that gradually diminish over time to an ineffective level in this mode of delivery, the duration of the therapeutic effect depends on the frequency of dose administration and the half-life of the drug.

In recent years, the pharmaceutical and biotech industries have developed more sophisticated and potent drugs. Many of these agents are proteins or DNA; the therapeutic window (i.e., the range of concentrations that bracket the effective and toxic regimes for the drug) for these drugs is often narrow; and toxicity is observed for concentration spikes, which renders traditional methods of drug delivery ineffective. A number of mechanisms can provide controlled release of drugs including transdermal patches, implants, inhalation systems, bioadhesive systems and microencapsulation and now there are pioneering, commercially available products in all of these categories.

Concept of Controlled Drug Delivery [1]

While the last three decades have seen considerable advances in drug delivery technology, major unmet needs remain. Among these are the broad categories of:

1. Continuous release of therapeutic agents over extended time periods and in accordance with a pre-determined temporal profile

2. Local delivery of agents at pre-determined rates to local sites, such as solid tumors, to overcome systemic drug toxicity and improve anti-tumor activity and

3. Improved ease of administration, which would increase patient compliance while minimizing the need for intervention by health care personnel and decreasing the length of hospital stays. Success in addressing some or all of these challenges potentially would lead to improvements in efficacy and patient compliance as well as minimization of side effects.

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages, which are:

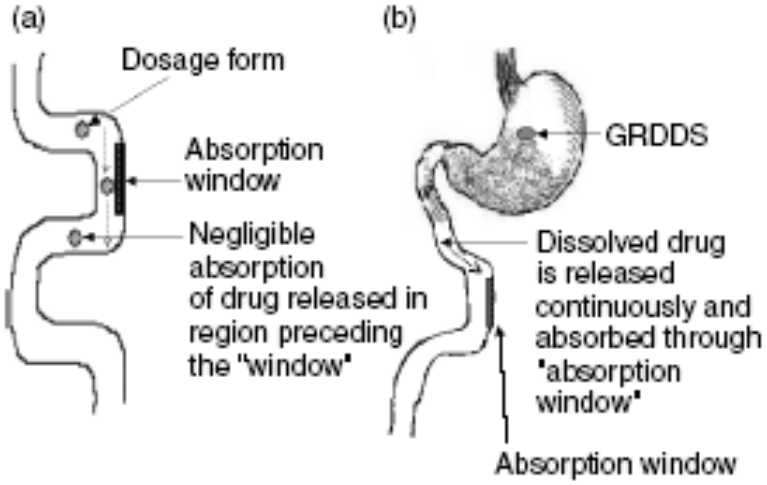
- Basic assumption is drug should absorb throughout GI tract.
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level.
- Intersubject variability.
- Relatively poor *in vitro* / *in vivo* correlation.
- Sometimes unpredictable and often reduced bioavailability.
- Possible dose dumping
- Narrow absorption window in GI tract e.g. Levodopa, Riboflavin
- Primarily absorbed from stomach and upper part of GI tract e.g. Atenolol, Cinnarazine, Chlordiazepoxide, Calcium Supplement
- Act locally in stomach e.g. Misoprostol, Antacids
- Drug that degrade in colon e.g. Ranitidine HCL, Metronidazole
- Drug that disturb normal colonic bacterial flora e.g. Amoxicillin trihydrate, Cefuroxime axetil, Clindamycin etc.

Thus the drug candidates having 'absorption window' in a particular region of GI tract are difficult to be designed as oral Controlled release drug delivery system (CRDDS). This is because only the drug released in the region preceding the 'window' and vicinity of 'absorption window' is available for absorption. Drug

released from the CRDDS after the 'absorption window' has been crossed goes waste with no or negligible absorption occurring. This phenomenon drastically decreases the time available for drug absorption, after release of drug from CRDDS, thus jeopardizing the success of delivery system.

The CRDDS possessing the ability of being retained in the stomach are called gastro retentive drug delivery systems (GRDDS) and they can help in optimizing the oral controlled delivery of drug having 'absorption window' by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

Need for GRDDS, (a) Conventional drug delivery system, (b) GRDDS



It is evident from the recent scientific and patent literature that an increased interest in NDDS that are retained in the stomach for prolonged and predictable period of time exists today in academic and industrial research groups. The most feasible approach for that is GRDDS.

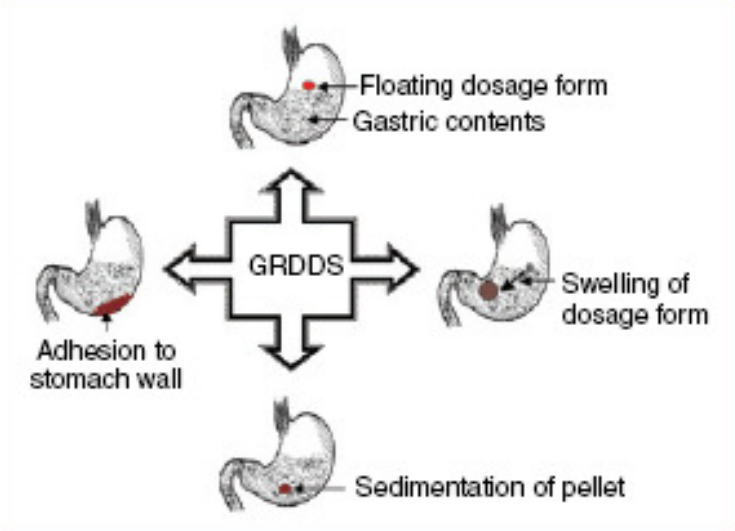
Gastro retentive technologies [4]

A number of techniques have been used to increase the gastric residence time (GRT) of dosage forms by employing a variety of concepts which are:

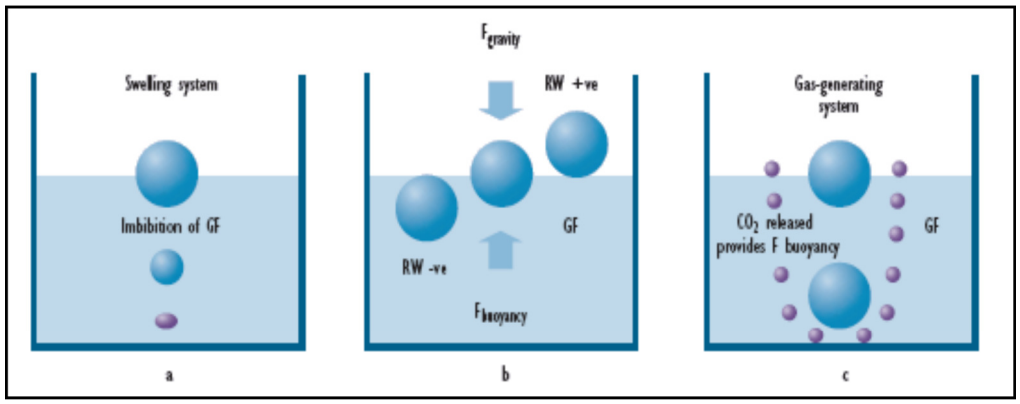
Floating systems [5]

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. Floating systems can be classified as effervescent and non-effervescent stems.

Classification of gastro retentive drug delivery systems.



Mechanism of GRDDS



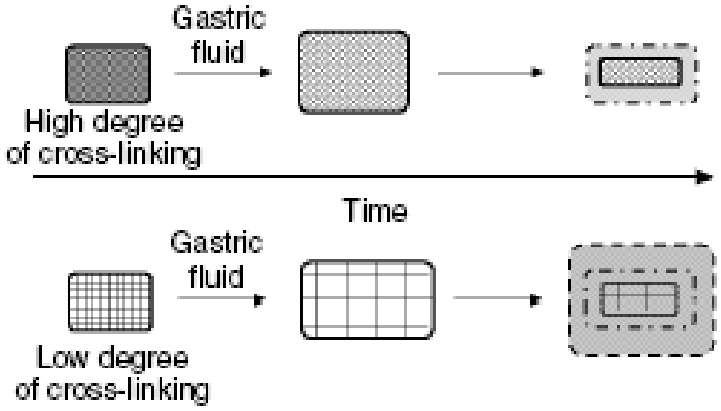
Bio/mucoadhesive systems [6]

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membraneThese can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion.

Swelling systems [6][7][8]

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus As a result, the dosage form is retained in the stomach for a long period of time.

Relationship between the degree of cross-linking of the polymeric chains and the swelling



An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution.

High-density systems [6][8]

These systems, which have a density of ~3 g/cm^3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm^3, such systems can be retained in the lower part of the stomach.

Gastro retentive dosage forms overcome the limitation of conventional oral controlled drug delivery system by:

- Prolonging the GRT by retaining dosage form in stomach and upper part of GI tract.
- Give sufficient time for drug to release from dosage form.
- Give sufficient time for drug to be absorbed through GI tract.
- Protecting the drug to degrade in colon.
- Protecting the degradation of normal GI flora by restricting the dosage form in stomach and upper part of GI tract.

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approach in development of gastroretentive dosage forms. Hence for the present study, formulation of GRDDS is prepared as floating drug delivery system.

FLOATING SYSTEMS

Floating drug delivery have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract (GIT), drugs which are poorly soluble and unstable in intestinal fluids. Recently various efforts are being made to design floating systems such as Floating Drug delivery systems (FDDS), Swelling and Expanding Systems, Bio adhesive systems, Modified shape systems, High density systems etc. These systems are advantageous in improving GIT absorption of drug with controlled release due to specific site absorption limitations. The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease side effects of drugs. These systems have more flexibility in dosage form design than conventional dosage form. Several approaches have recently been developed to

extend gastrointestinal transit time by prolonging residence time of drug delivery system in the GIT.

Basic of this drug delivery system is to optimize biopharmaceutic, pharmacokinetic and pharmacodynamic properties of drugs in such a way that to reduce dosing frequency to an extent that once daily dose sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug through reduction in local and systematic side effects and cure or controlled condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.

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.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

FACTORS AFFECTING GASTRIC RETENTION

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. 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.

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 meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time.

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. Stress increases gastric emptying rates while depression slows it down.

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken in body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form the fed state can also be influenced by its size. Small-size tablets leave the stomach during the

digestive phase while the large-size tablets are emptied during the housekeeping waves.

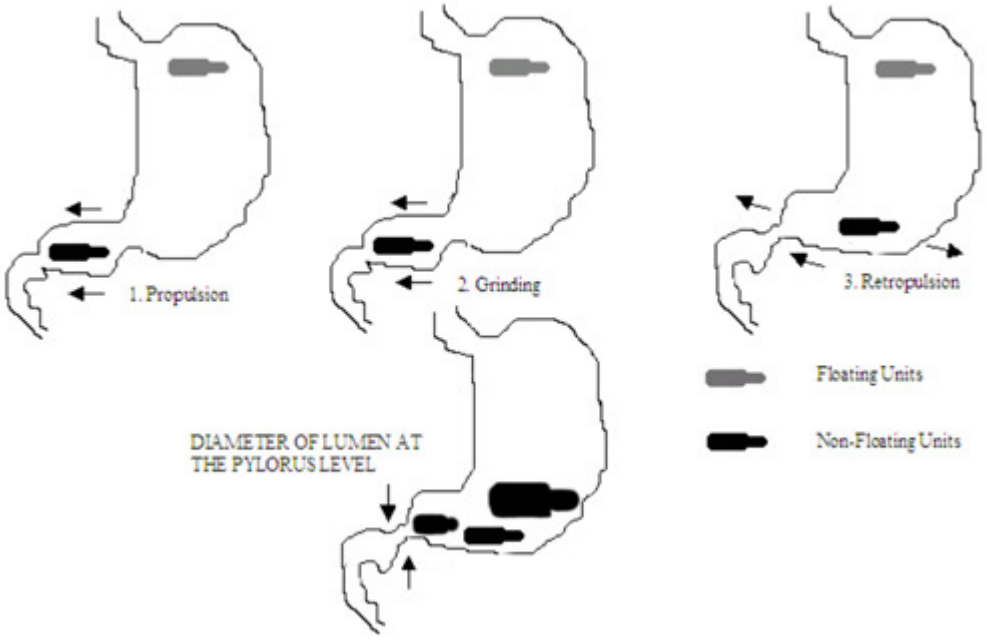
Timmermans & Andre[25] studied the effect of size of floating and nonfloating dosage forms on gastric emptying and concluded that the floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the non floating units, which lie in the antrum region and are propelled by the peristaltic waves.

It has been demonstrated using radiolabeled technique that there was 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 interdigestive migrating myoelectric complex. When liquid and digestible solids are present at stomach, it contracts 3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time {GRT} can be significantly increased under the fed conditions since the MMC is delayed.

Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multi particulate formulations as compared with single unit formulations, which suffer from “all or none concept.” As the units of multi particulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of

food compared with single unit formulation. Size and shape of dosage unit also affect the gastric emptying.

Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase**.** It was also observed that of the floating and non floating units, the floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms.



Intragastric residence positions of floating and nonfloating units.

When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

A comparison was made to study the affect of fed and non-fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals.

It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) [11][12]

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.

A. EFFERVESCENT SYSTEM: -

Effervescent systems include use of gas generating agents, carbonates (eg. sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

I Gas Generating systems

II Volatile Liquid/Vacuum Containing Systems

I. Gas – Generating Systems:

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):

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 unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6 and containing two layer i.e., Immediate release layer and Sustained release layer.

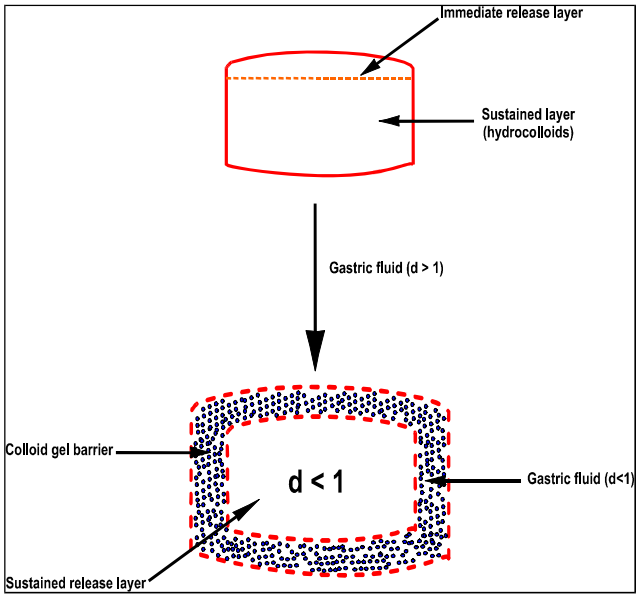


Figure 2. **Intra gastric bilayer floating tablet**.

3. Multiple Unit type floating pills:

These systems consist 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.

II. Volatile Liquid / Vacuum Containing Systems:

1. Intragastric Floating Gastrointestinal Drug Delivery System:[13]

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment.

2. 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, then 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 is continuously released from the reservoir into the gastric fluid.

3. Intragastric 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 intragastric osmotically controlled drug delivery device. 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 vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

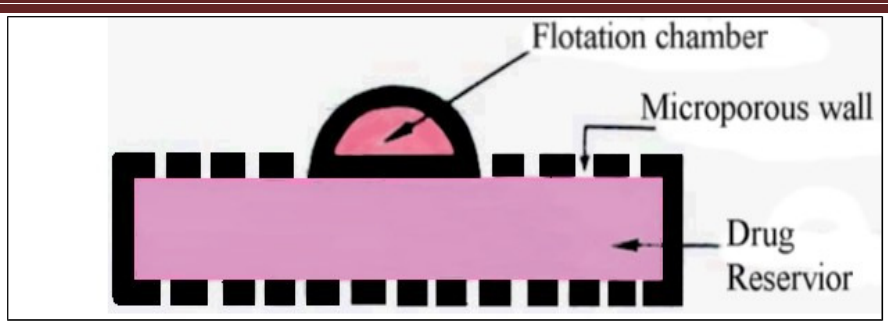


Fig 4. Intragastric osmotically controlled drug delivery system.

B. NON EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

1. Single Layer Floating Tablets: [14] [15].

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the 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.

3. Alginate Beads: [16]

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 a 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. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microspheres of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

Advantages of Floating Delivery System.[17].

- Enhanced bioavailability enhanced first pass biotransformation.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuation of drug concentration.
- Improved receptor activation selectivity.
- Reduced counter-activity of the body.

- Extended time over critical (effective) concentration.
- Minimized adverse activity at the colon.
- Site specific drug delivery 1.

Disadvantages of floating drug delivery system [17].

- Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

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

1. **Sustained Drug Delivery:** HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CK formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg: Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using

rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) [26].

2. Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g.: Riboflavin and furosemide. E.g.:- Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets[27].

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

1.7 Factors Controlling Gastric Retention Time of Dosage Form:

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

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.
- Size – Dosage form units with a diameter of more than 9.5 mm are reported to have an increased GRT.

- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

- Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

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

- Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

- Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

- Gender – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

- Age – Elderly people, especially those over 70, have a significantly longer GRT.

- Posture – GRT can vary between supine and upright ambulatory states of the patient.

- Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.

- Biological factors – Diabetes and Crohn's disease.

In general, the drugs best suited for incorporation into an external product have the following properties

Definition of Angina pectoris and types of Angina [9]:

Angina pectoris is a symptom of an underlying heart condition. It means that the heart is not getting enough blood and as a result, not enough oxygen. This decrease of oxygen being delivered to the muscle of the heart happens if one or more coronary arteries are narrowed or blocked, a condition called **atherosclerosis.**

Blood enters the heart through two blood vessels. These are known as the coronary arteries and they supply the heart muscle with the blood, oxygen and nutrients it needs to keep beating. Normally, the coronary arteries deliver enough blood so that the heart muscle gets the amount of oxygen it needs to work properly. However, in coronary heart disease these arteries become narrowed which reduces the

amount of blood that can pass through arteries causes blood can't get to the heart muscle fast enough and the heart complains with pain. This pain is known as angina. It is more likely to occur during exertion (for example, walking or climbing stairs) when the heart muscle needs more blood and oxygen as it works harder.

An episode of angina is not a heart attack. Angina is due to a temporary reduction in the flow of blood to part of the heart muscle and does not damage the heart itself. A heart attack occurs when the blood supply to part of the heart is cut off and results in permanent damage to the heart muscle. However, angina does indicate an increased risk of a heart attack. Angina is common. It is more common in men than women and the likelihood of it occurring increases with age.

1.1.2. Types of Angina

Anginas are categorized in to several ways:

- **Stable Angina:**

This is the most common type of angina occurring due to physical exertion such as walking up stairs, running to catch a bus, mental or emotional stress and physical exercise that causes strain with the pain being predictable. Stable angina follows a regular pattern and the pain/discomfort subsides on taking rest and slowing down, but returns with the resumption of activity.

- **Unstable Angina:**

With unstable angina, chest pain is unexpected and occurs with little physical effort or when the patient is at rest and the pain may be severe, prolonged and more frequent as compared to stable angina. Sometimes, stable angina can progress to unstable angina or an unstable angina can also develop from inflammation, infection,

abnormal constriction of the artery or partial blockade of the artery due to a blood clot. Unstable angina does not follow a regular pattern and can prove to be fatal if there is not immediate medical attention.

- **Variant Angina or Prinzmetal's Angina:**

  It often occurs while someone is resting (usually between midnight and 8:00 in the morning), and it has no predictable pattern—that is, it is not brought on by exercise or emotion. This kind of angina may cause severe pain, and is usually the result of a spasm in a coronary artery. Most people who have variant angina have severe atherosclerosis (hardening of the arteries), and the spasm is most likely to occur near a buildup of fatty plaque in an artery.

- **Microvascular Angina:**

  In this type, chest pain occurs but without any blockage in a coronary artery. The pain is due to improper functioning of the tiny arteries supplying blood to the heart. This condition is referred to as Syndrome X.

- **Atypical Angina:**

  Typical symptoms of angina may not be experienced in this type and the patient may experience a mild chest discomfort, shortness of breath, fatigue, nausea, back or neck pain, or burning indigestion. Women are more prone to experience symptoms of atypical angina.

1.1.3. Classes of Drugs Used to Treat Angina.[10]

Classes of drugs used in the treatment of angina and myocardial infarction are given below.

1. **Vasodilators** (dilate arteries and veins)

   - Calcium-channel blockers (Verapamil)

   - Nitro dilators (Nitroglycerin)

1. **Cardioinhibitory drugs** (reduce heart rate and contractility)
   - Beta-blockers(Metoprolol)
   - Calcium-channel blockers

2. **Blocker of late sodium currents** (FDA approved 1/06)

   - **Ranolazine**

3. **Anti-thrombotic drugs** (prevent thrombus formation)
   - anticoagulants(Warfarin)
   - anti-platelet drugs(Aspirin)

LITERATURE REVIEW

1. **M Vanaja kumari et al (2012)** prepared and characterized the Sustained release matrix tablets of Ranolazine using Kollidon SR. Three different strengths i.e. 375mg, 500mg and 750mg of Ranolazine SR tablets were prepared by direct compression method and by using common blend. The influence of compression force was studied on the dissolution release profile of Ranolazine SR tablets. In vitro release studies were performed for all the formulations using USP type II apparatus (paddle method) in 900 ml of 0.1N hydrochloric acid at 50 rpm for 24 hours and analyzed by UV spectrophotometer at 272nm. Further, in-vitro release pattern of drug from the optimized formulation was compared with innovator formulation and it was found to be super imposable with the Innovator product RANEXA based on dissimilarity and similarity factors.
2. **Anilkumar J. Shinde et al (2010)** formulated an oral floating tablet of cephalexin (CEF) using the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. The granules were prepared by wet granulation method and evaluated for their granules properties. Tablets were compressed by KBr press and evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, in vitro buoyancy study, swelling characteristics, scanning electron microscopy, kinetic release data.
3. **M. Ranga Priya et al (2011)** developed sustained-release drug delivery system containing Ranolazine (an anti-anginal drug) with different ratios of pH dependent polymer; Eudragit L100-55 was designed by wet granulation method. The physicochemical compatibility of the drug and polymers were studied by FTIR spectrophotometer and found to be compatible. The promising formulation with concentration of Eudragit L100-55 polymer 12.5% showed better release of 99.78±0.99% after 24 hours. It showed Zero-order release with linearity (r=0.9447 to

0.9895). The similarity factor (f2 values) was used for the comparison of in vitro release study of the best formulation of SR tablets and marketed ER product of Ranolazine.

4. **Jagdish Bidada et al (2011)** incorporated Ranolazine into monolithic matrices whose excipients were mixtures at different ratios of a acrylic resin (Carbopol 971 P) hydrophilic & pHdependent nature and an ethylcellulose (Ethocel N20/N50), water-insoluble and pH-independent polymers. Technological characterization (drug particle morphology, mean weight, diameter, thickness, hardness and friability of tablets) was carried out and in vitro drug release behavior was measured using the USP Type II (Paddle) apparatus. The effect of varying the Carbopol–Ethocel ratio, as well as the drug–polymeric matrix ratio, was evaluated by simple factorial design using two independent factors. The results showed the suitability of Carbopol–Ethocel mixtures as matrix-forming material for Ranolazine Extended release formulations. Combination of the swelling properties of Carbopol 971 P with the plastic properties of the more hydrophobic Ethocel N20/N50 allowed suitable modulation of Ranolazine release.

5. **A. K. Srivastava *et.al*. (2005)** developed floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (K15M, K4M), guar gum and sodium carboxymethylcellulose, alone or in combination.

6. **Aisha Khanum *et.al.* (2009)** developed bilayer tablets of propanolol hydrochloride the result of these was bilayer tablet it is possible to have a fast releasing layer and sustaining layer so as to have a zero order of water soluble drugs like propanolol can be achieved.

7. **Dave B. S. *et.al*. (2004)** developed a floating drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum and hydroxypropyl methylcellulose were evaluated for gel-forming properties. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated by using full factorial design. The results indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastro retentive formulation. No significant difference was observed between the desired release profile and optimized batches. These studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile.

8. **Dhumal R.S. et.al. (2006)** developed bilayer floating tablets of cefuroxime axetil for bimodal release using hydroxypropyl cellulose, hydroxypropyl methylcellulose and tulsion T-339 to providing sustained release upto 24 h. The result showed that oral solid dosage form based on bilayer floating drug delivery is promising to achieve bimodal drug release. After an immediate drug release from first layer, controlled release can be achieved from second layer in an area that could maximize drug reaching its absorption site.

9. **Jagadeesh Nadigoti *et.al.* (2009)** review the floating drug delivery system and concluded that the growing impact of GIT physiology on drug delivery and increasing sophistication of drug delivery technology will ensure development of an increasing number of GRDDs to optimize drug delivery of molecules exhibiting regional variability in drug absorption.

10. **Narendra C. *et.al.* (2006)** developed an optimized gastric floating drug delivery system containing metoprolol tartarate as a model drug by the optimization technique.

They studied effect of hydroxypropyl methylcellulose (K4M and K100M) on release and floating characteristics of metoprolol tartarate tablets. The effect of different viscosity grades of hydroxypropyl methylcellulose (K4M and K100M) was nonsignificant. Fickian release transport was confirmed as the release mechanism from the optimized formulation.

11. **Nitin G. Sampat *et.al.* (2009)** developed once daily baclofen sustained release or gastro-retentive systems which are acceptable alternatives to thrice daily baclofen immediate release at the same daily dosage in patients. The result showed that once-daily baclofen sustained are efficacious, convenient, and better alternatives to baclofen immediate release in patients with neurogenic spasticity. Considering the entire parameters evaluated baclofen sustained release is superior in safety to baclofen immediate release.

12. **Ozdemir *et.al.* (2000)** developed floating bilayer tablets with controlled release for furosemide. This study was designed to enhance the bioavailability of furosemide by prolonging its duration in the stomach via the floating dosage forms with controlled release. All formulations were prepared as two-layer tablets. The first layer provided floating and contained the mixture of sodium bicarbonate and citric acid to form air bubbles and HPMC K4M as a matrix material to retain the air bubbles. The second layer (release layer) provided controlled release of active material. It contained active material and HPMC K100M as hydrophilic matrix material.

13. **Prajapati S. T. *et.al*. (2008)** developed an optimized gastric floating drug delivery system containing domperidone as a model drug. Box-Behnken design was employed in formulating the GFDDS with three polymers: hydroxypropyl methylcellulose K4M

(HPMC K4M), Carbopol 934P and sodium alginate. The study showed that HPMC K4M, Carbopol 934P and SA significantly affect TFT of the formulated GFDDS.[37]

14. **Manoj N. Gambhire et al (2008)** developed floating matrix tablets of DTZ to prolong gastric residence time and increase its bioavailability.. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO, Sodium bicarbonate.. A 32 factorial design was applied to systematically optimize the drug release profile.The amounts of Methocel K100M CR (X1) and Compritol 888 ATO (X2) were selected as independent variables. The time required for 50% (t50) and 85% (t85) drug dissolution were selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR (X1) and Compritol 888 ATO (X2) favors the preparation of floating controlled release of DTZ tablets.

15. **Shailesh T. Prajapati et al (2005)** studied to develop an optimized gastric floating drug delivery system (GFDDS) containing domperidone. Box-Behnken design was employed in formulating the GFDDS with three polymers: hydroxypropyl methylcellulose K4M (HPMC K4M) (X1), Carbopol 934P (X2) and sodium alginate (X3), as independent variables. Floating lag time (FLT), total floating time (TFT), time required to release 50% of the drug (t50) and diffusion exponent (n) were selected as dependent variables, dissolution data obtained was fitted to the power law and floating profiles were analyzed. HPMC loading was found to be significant for floating propertiesand desired release.

16. **Shawky Tous S. et al (2003)** developed Nitrofurantoin floating matrix tablets, Hydroxypropyl methylcellulose (HPMC) of different viscosity grades together with a

gas generating agent (sodium bicarbonate) and other optional additives were examined to optimize the floating characters of the prepared tablets. The in vitro study of the floating behavior in simulated gastric fluid (pH 1.2, enzyme free) at 37°C showed that tablets eroded upon contact with the release medium. The results also showed that tablet composition had profound effect on the floating behavior and drug release. All formulations showed suitable floating lag time (20 s), with duration of floating more than 8 h. The drug release from those tablets was sustained over 8 hr.

17. **N.M. Patel et al (2008)** studied the influence of content of polyethylene oxide and ratio of lactose to starch 1500 on Dipyridamole release from self correcting flouting matrix tablets using 3" full factorial design. Tablets were evaluated for in vitro floating ability and drug release study using USP 24 type II apparatus using 0.1 N HCI at 100 rpm and temperature of 37±0,5". Multiple regression analysis and two way analysis of variance followed by Tukey test were performed for dependent variables. All formulations floated within 2 min regardless of factors studied and had total floating time of more than 12 h and follows zero order release.

18. **Leopoldo Villafuerte-Robles et al (2009)** developed a controlled release formulation of Captopril, floating tablets, and studied the in vitro sustained release of captoprill varying the proportions of Metolose SH400 and bicarbonate, Floating behavior studying at two different compaction pressures at (155Mpa&165Mpa). Other studied variables include the kinetics of the hydration volume, the matrices floating time and the matrix density. The results show that matrices compacted at 55 MPa float in the dissolution medium for more than 8 h while those compacted at 165 MPa. The matrix density is lower when compacted at 155 MPa. The drug release constant (k) decreases and the exponent indicative of the release mechanism (n) increases with increasing polymer contents.

19. **Subhabrata Ray et al (2008)** formulated Metformin hydrochloride floating microspheres. by non-aqueous emulsification solvent evaporation technique using Ethyl cellulose as the rate controlling polymer and Evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of floatation and drug release pattern to match target release profile was investigated in vitro floatation and release studies. floating time (> 8 hr) and the best results were obtained at the ratio of drug: polymer: solvent (250:750:12 and 250:146.45:9 [mg : mg : ml]), when both the batches were mixed in equal proportions.

20. **Javed Ali et al (2006)** formulated hydro dynamically balanced system for celecoxib as single-unit floating capsules. Various grades of low-density polymers were used. The capsules were prepared by physical blending of celecoxib and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). Capsules prepared with polyethylene oxide 60K and Eudragit RL100 gave the best in vitro percentage release and were used as the optimized formulation. By fitting the data into zero-order, first-order, and Higuchi models, we concluded that the release followed zero-order kinetics.

21. **D.M. Patel et al (2003)** developed carbamazepine Floating tablets using melt granulation technique. Bees wax, Hydroxy propyl Methyl cellulose, sodium bicarbonate and ethyl cellulose were used as matrixing agent, gas-generating agent and floating enhancer, respectively. A simplex lattice design was applied to investigate the formulation variables i.e. amount of hydroxypropyl methylcellulose (X_1), ethyl cellulose (X_2) and sodium bicarbonate (X_3). The floating lag time (F_{lag}), time required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were taken as responses. Results of multiple regression analysis indicated that, low level of X_1, and X_2 and high

level of X_3 should be used to manufacture the tablet formulation with desired in-vitro floating time and dissolution.

22. **Mukesh C. Gohel et al (2003)** prepared gastroretentive tablets of rifampicin (150 mg) by the wet granulation method using hydroxypropyl methylcellulose, calcium carbonate, and polyethylene glycol 4000. to minimize degradation of rilampicin in acidic medium and to modulate the release of rifampicin in the stomach and isoniazid in the intestine.. The in vitro drug release and in vitro drug degradation studies were performed. Rifampicin was released over 4 hours by zero-order kinetics from the novel dosage form. More than 90% of isoniazid was released in alkaline medium in 30 minutes

23. **Shashi Kiran Mishra et al (2005)** formulated gastro retentive controlled release system of loratadine was to increase the residence time in stomach and to modulate the release behaviour of the drug. Oil entrapped floating microbeads prepared by the emulsion gelation method were optimized by 23 factorial design and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (*m*/*V*) of oil (mineral oil or castor oil) and 0.45 mol L–1 calcium chloride solution as the optimized processing conditions for the desired buoyancy and physical stability. *In vitro* drug release in the fed state conditions demonstrated sustained release of loratadine for 8 h, which best fitted the Peppas model with $n < 0.45$. The ethyl cellulose coating on microbeads optimized by22 factorial design resulted in a controlled release formulation of loratadine that provided zero-order release for 8 h.

3. AIM AND PLAN OF WORK

The proposed formulation is developed by considering the drawbacks associated with the conventional controlled drug delivery system.

The formulation may remained in the stomach and / or upper part of GIT for prolonged period of time thereby giving sufficient time for drug candidate to achieve maximum bioavailability and reduce unwanted side effects by minimizing or avoiding drug release at unfavorable site.

The aim of the present dissertation work is to sustain the release of drug due to floating in stomach at acidic pH 1.2 up to 12 hrs.

3.1. PLAN OF WORK

1. Literature survey
2. Preformulation studies
    - Selection of drug.
    - Compatibility study using Fourier Transform Infrared Spectrophotometer.
    - Analytical characterization of the drug.
    - Selection of the excipients.
    - Characterization of the excipients.
3. Standard calibration curve of drug
4. Formulation development
    - Formulation of the floating tablet.
    - Effect of the formulation variables on the drug release, swelling and floating properties.

4. Evaluation of tablets
    - Tablet characteristics.
    - *In vitro* Buoyancy study.
    - Water uptake.
    - *In vitro* drug release studies of tablets.

5. Study of release kinetics.
6. Stability study of the optimized batch.

7. *In vivo* confirmation of Buoyancy.

4. MATERIALS AND METHODS

4.1. Materials:

Table No.1: List of Chemicals Used

SR.NO.	MATERIAL USED	SUPPLIER
1.	RANOLAZINE	MICRO LABS Ltd.
2.	HYDROXY PROPYL METHYL CELLULOSE	YARROW CHEM PRODUCTS MUMBAI, INDIA.
3.	CARBOPOL 934P	YARROW CHEM PRODUCTS MUMBAI, INDIA.
4.	CHITOSAN	COCHIN FISHERIES DEPT, KERALA.
5.	SODIUM BICARBONATE	THOMAS BAKER Pvt Ltd, MUMBAI.
6.	MICROCRYSTALLINE CELLULOSE	THOMAS BAKER Pvt Ltd, MUMBAI.
7.	MAGNESIUM STEARATE	THOMAS BAKER Pvt Ltd, MUMBAI.
8.	TALC	THOMAS BAKER Pvt Ltd, MUMBAI.

4.2. Equipments:

Table No.2: List of Instruments Used

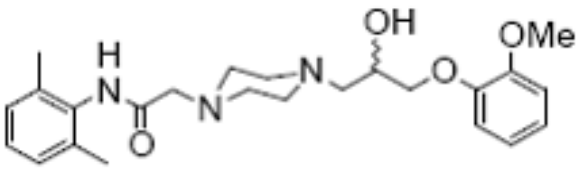
Instrument Used	Model No.	Make
FTIR Spectrophotometer	8400S	Shimadzu, Japan
UV–Visible Spectrophotometer	UV – 3000^{+}	LAB INDIA
Tablet Compression Machine	Mini Press	Rimek
Tablet Dissolution Tester USP (XXIII)	DS-8000	LAB INDIA
Environmental test chamber	JRIC – 11A	Oswald
Electronic Balance	AGN-303EC	AXIS
Tablet hardness tester	N.S	Monsanto
Roche's friabilator	N.S	Scientific
Hot air oven	PYROCON	York Scientific Ind., Mumbai
Digital pH meter	PHAN	LAB INDIA
Melting Point apparatus	N.S	Biotech India Ltd.

4.3. DRUG PROFILE

4.3.1 Ranolazine

Ranolazine is an anti-ischemic and anti-anginal drug, designed to act without reducing heart rate or blood pressure indicated for the treatment of chronic angina in patients who have failed to respond to prior angina therapies.

4.3.2 Structure of Ranolazine:



4.3.3 Molecular formula: $C_{24}H_{33}N_3O_4$

4.3.4 Relative Molecular Mass: 427.54

4.3.5 Chemical Name: N-(2, 6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl] piperazin-1yl] acetamide.

4.3.6 Appearance: Ranolazine is a white to off-white solid.

It is odourless.

4.3.7 Physical Properties of Ranolazine: Below is a table of some of the physical properties of Ranolazine.

Table No. 3: Physical Properties of Ranolazine

Melting Point	117-122°C
Dissociation Constant (pK_a)	14.25 at 24°C
Partition Coefficent (Log P (octanol))	2.08
Solubility	
Water	Very Slightly Soluble
Ethanol/Methanol	Soluble
Ether	Practically Insoluble

4.3.8 Pharmacokinetics:

Pharmacokinetic data of Ranolazine is given below:

Table No. 4: Pharmacokinetic Data of Ranolazine

Parameters	Value
Availability (oral) %	73%
Urinary excretion (%)	75%
Bound in plasma (%)	62%
Clearance (ml. min^{-1}. kg^{-1})	5.33ml/min/kg
Volume of distribution (liter / kg)	1.57L/kg
Half life (hr.)	1.4 - 1.9hrs
Effective concentration	2 – 6µmol/l

Absorption and distribution:

After oral administration, a peak plasma concentration of Ranolazine is reached between 2 and 5 hours. After oral administration of ^{14}C-Ranolazine as a solution, 73% of the dose is systemically available as Ranolazine or metabolites. The bioavailability of Ranolazine from the extended dosage form relative to that from a solution of Ranolazine is 76%. Because Ranolazine is a substrate of P-glycoprotein (P-gp), inhibitors of P-gp may increase the absorption of Ranolazine.

Food especially high fat breakfast has no important effect on the Cmax and AUC of Ranolazine. Therefore, Ranolazine may be taken without regard to meals. Over the concentration range of 0.25 to 10 µg/mL, Ranolazine is approximately 62% bound to human plasma proteins.

Protein binding:

Over the concentration range of 0.25 to 10 µg/mL, Ranolazine is approximately 62% bound to human plasma proteins.

Metabolism:

Ranolazine is metabolized rapidly and extensively in the liver and intestine. The pharmacological activity of the metabolites has not been well characterized. After dosing to steady-state with 500 mg to 1500 mg twice a day the four most abundant metabolites in plasma have AUC values ranging from about 5 to 33% that of Ranolazine.

Ranolazine is metabolized mainly by CYP3A and to a lesser extent by CYP2D6.

Elimination:

Approximately 75% of the dose is excreted in urine and 25% in feces. Less than 5% is excreted unchanged in urine and feces.[29]

Half-life:

Half-life of Ranolazine was found to be 1.4 -1.9 hours. [28]

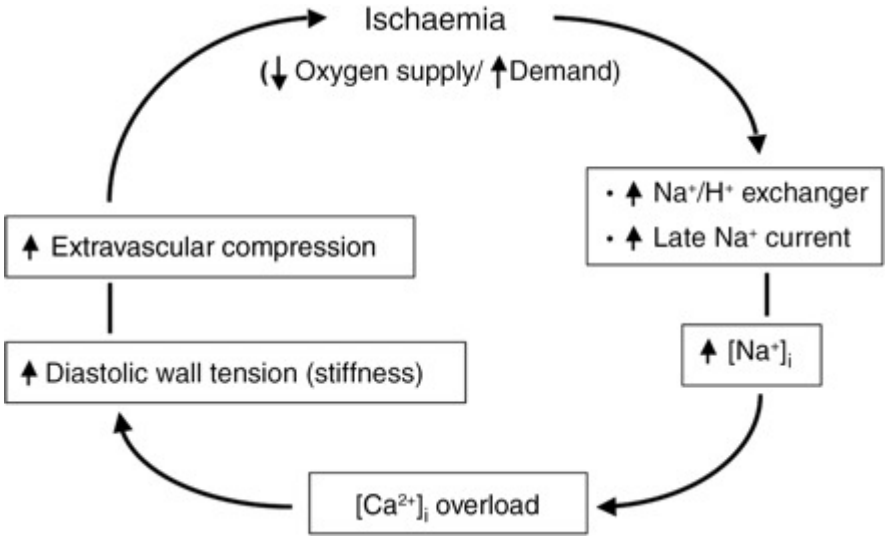
Mechanism of action:

The mechanism of action of Ranolazine is unknown. Initially, Ranolazine was thought to exert its therapeutic efficacy primarily through partial inhibition of

fatty acid oxidation. These pharmacological effects, however, were generally observed at concentrations in excess of therapeutic plasma concentrations in human clinical trials (>10 µmol/L). More recent evidence suggests that Ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I_{Na}). Myocardial ischemia produces a cascade of complex ionic exchanges that can result in intracellular acidosis, excess cytosolic Ca^{2+}, myocardial cellular dysfunction, and, if sustained, cell injury and death Thus, Ranolazine is a relatively selective inhibitor for late I_{Na}. In isolated ventricular myocytes in which the late I_{Na} was pathologically augmented, Ranolazine prevented or reversed the induced mechanical dysfunction, as well as ameliorated abnormalities of ventricular repolarization.

Ranolazine inhibition of late I_{Na} is discernible at therapeutic plasma concentrations in healthy cells, particularly in M cells and Purkinje fibers, where this current is most prominent. However, in healthy nonischemic, nonfailing myocytes, where the contribution of late I_{Na} is small, the drug does not have a measurable effect on cardiovascular performance at therapeutic plasma concentrations. In patients with chronic angina and demand-induced ischemia, Ranolazine has the potential to partially disrupt the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late Na^+ influx, thereby reducing calcium overload and ultimately reducing the concomitant increase in left ventricular wall tension. Reduction in diastolic left ventricular wall tension would decrease myocardial oxygen requirements in marginally ischemic myocytes and has the potential to reduce vascular compression, allowing more coronary blood flow to the affected area. Additional research is necessary to confirm this latter hypothesis. [30][31]

Fig.3.1.1. Positive feedback during ischaemia



Precautions:

Co-administration of Ranolazine and Digoxin increases the plasma concentrations of Digoxin by approximately 1.5-fold and the dose of Digoxin may have to be reduced accordingly. The dose of other P-gp substrates may have to be reduced as well when Ranolazine is co-administered. Ranolazine can inhibit the activity of CYP2D6 and thus the metabolism of drugs that are mainly metabolized by this enzyme may be impaired like tricyclic antidepressants and some antipsychotics, and exposure to these drugs increased. The dose of such drugs may have to be reduced when Ranolazine is co-administered.

Side effects:

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse events occurring more often with Ranolazine than

placebo, were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). In open-label, long-term treatment studies, a similar adverse event profile were observed in patients treated with Ranolazine.

About 6% of patients discontinued treatment with Ranolazine due to an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on Ranolazine than placebo were dizziness (1.3% versus 0.1%), and nausea (1% versus 0%), asthenia, constipation and headache (each about 0.5% versus 0%).

Cardiac disorders – palpitation

Ear and labyrinth disorders – tinnitus, vertigo

Gastrointestinal disorders- abdominal pain, dry mouth, vomiting

Respiratory, thoracic and mediastinal disorders- dyspnea

Drug interaction:

Pharmacokinetic Interactions: Effects of Other Drugs on Ranolazine:

Ketoconazole:

As a potent inhibitor of CYP3A, Ketoconazole 200 mg b.i.d. increases average steady-state plasma concentrations of Ranolazine 3.2-fold. Ranolazine should not be used during treatment with Ketoconazole.

Diltiazem:

As a moderate inhibitor of CYP3A, Diltiazem 180 to 360 mg daily causes dose-dependent mean increases in average Ranolazine steady-state concentrations of about 1.8- to 2.3-fold.

Verapamil:

Verapamil 120 mg t.i.d. increases Ranolazine steady-state plasma concentrations about 2-fold.

Cimetidine:

Co-administration of Cimetidine does not increase the plasma concentrations of Ranolazine. No dose adjustment of Ranolazine is required in patients treated with Cimetidine.

Rifampin:

Rifampin 600 mg q.d. decreases the plasma concentration of Ranolazine by approximately 95%. Co-administration of Ranolazine and Rifampin should be avoided.

Digoxin:

Co-administration of Digoxin does not increase the plasma concentration of Ranolazine. No dose adjustment of Ranolazine is required in patients treated with Digoxin.

Paroxetine:

Paroxetine, a potent inhibitor of CYP2D6, increased average steady-state plasma concentrations of Ranolazine 1.2-fold. No dose adjustment of Ranolazine is required in patients treated with Paroxetine or other CYP2D6 inhibitors.

Pharmacodynamic Interactions: Effects of Ranolazine on Other Drugs

Digoxin:

As a result of an interaction at the P-gp level, co-administration of Ranolazine and Digoxin results in a 1.5-fold elevation of Digoxin plasma concentrations. The dose of Digoxin may have to be adjusted when Ranolazine is co-administered with Digoxin.

Simvastatin:

Co-administration of Ranolazine and Simvastatin results in about a 2-fold increase in plasma concentrations of Simvastatin, and its active metabolite.

Warnings:

QT Prolongation:

Ranolazine has been shown to prolong the QTc interval in a dose-related manner. While the clinical significance of the QTc prolongation in the case of Ranolazine is unknown, other drugs with this potential have been associated with torsades de pointes-type arrhythmias and sudden death.

Tumor Promotion:

A published study reported that Ranolazine promoted tumor formation and progression to malignancy when given to transgenic APC(min/+) mice at a dose of 30 mg/kg twice daily.

Indication:

Ranolazine is indicated for the treatment of chronic angina. Because Ranolazine prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs. Ranolazine should be

used in combination with Amlodipine, beta- blockers or nitrates. The effect on angina rate or exercise tolerance appeared to be smaller in women than men.

Dosage and Administration:

Ranolazine dosing should be initiated at 500 mg b.i.d. and increased to 1000 mg b.i.d., as needed, based on clinical symptoms. The maximum recommended daily dose of Ranolazine is 1000 mg b.i.d. Baseline and follow-up ECGs should be obtained to evaluate effects on QT interval.

The concomitant use of Ranolazine with other commonly administered cardiovascular medications like Amlodipine, beta-blockers, nitrates, anti-hypertensive agents is well-tolerated. If a dose of Ranolazine is missed, the prescribed dose should be taken at the next scheduled time. The next dose should not be doubled. Ranolazine may be taken with or without meals. Ranolazine tablets should be swallowed whole and not crushed, broken, or chewed.

Over dosage:

No cases of intentional or accidental overdose with Ranolazine have been reported. In the event of overdose, the expected symptoms would be dizziness, nausea/vomiting, diplopia, paresthesia, and confusion. Syncope with prolonged loss of consciousness may develop. Because the QTc interval increases with Ranolazine plasma concentration, continuous ECG monitoring may be warranted in the event of overdose. If required, general supportive measures should be initiated.[32]

4.4 POLYMER PROFILE

HYDROXY PROPYL METHYL CELLULOSE [33]

Chemical Name: Cellulose 2- hydroxy propyl methyl ether

Synonym: Cellulose, Hypromellose, 2 – Hydroxypropylmethyl ether, Methyl hydroxy propyl cellulose, Methocel, Pharmacoat, Metolose.

Structure:

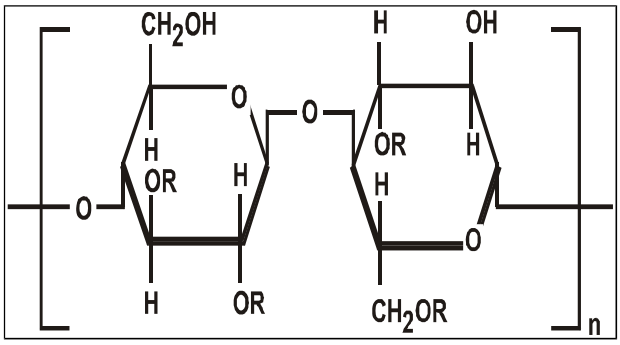


Figure 6. Hydroxypropyl methylcellulose.

Mixed ether of cellulose with some of the hydroxy groups in the form of methyl ether and some in the form of the 2-hydroxy propyl ether. Several grades of hydroxypropyl methylcellulose are distinguished by appending a number indicative of the apparent viscosity, in millipascal, of a 2% w/w solution measured at 20°C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of hydroxypropoxy group [OCH_2 CH C (OH) CH_3], calculated on a dried basis. Molecular weight is approximately 10,000 – 15, 00,000.

Description: It is a white, yellowish white or greyish white, practically odorless, fibrous powder or granules.

Physical Properties

Solubility: Soluble in cold water, forming a colloidal solution; practically insoluble in hot water, dehydrated alcohol, chloroform and ether.

pH: A 1% w/w solution has a pH of 5.5 to 8.0.

Melting Point: Browns at 190-200°C; chars at 225-230°C; Tg is at 170-180°C.

Bulk Density: 0.341 g/cm^3

Tapped Density: 0.557 g/cm^3

Enzyme Resistance: Comparatively enzyme resistant

Gel Formation: Undergoes a reversible transformation from solution to gel upon heating and cooling respectively.

Gel Point: 50 – 90°C depending upon the grade

Ash Value: 1.5 – 3 % depending upon the grade

Specific Gravity: 1.3

Surface Activity: Provides some surfactant activity in solutions, surface tension for such solutions range from 42 – 56 dynes/cm.

Storage: Store in well-closed containers.

Drug Excipients Interactions: Hydroxypropyl methylcellulose is incompatible with some oxidizing agents.

Safety: Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.

Pharmaceutical Uses:

HPMC is widely used in oral and topical pharmaceutical formulations. It is used as tablet binder, for film coating and in sustained release preparations.

Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. It is also used as an emulsifier, suspending agent and stabilizing agent in topical gel and ointments.

CARBOPOL

Nonproprietary Names

- BP: Carbomers
- PhEur: Carbomers
- USP-NF: Carbomer

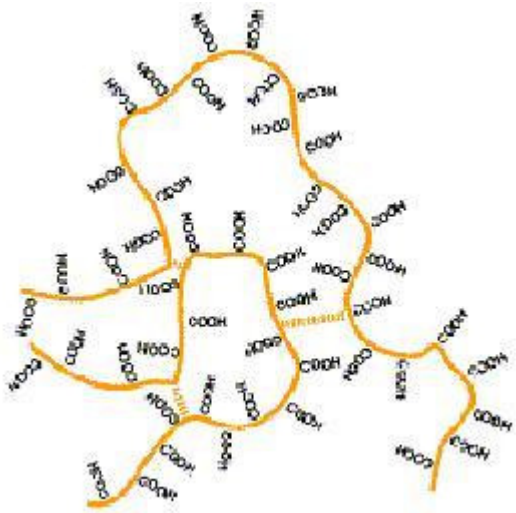
Synonyms

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

Functional Category

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

Structure:



Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor. A granular carbomer is also available.

Typical Properties

- **Acidity/alkalinity:**
- pH = 2.5–4.0 for a 0.2% w/v aqueous dispersion;
- pH = 2.5–3.0 for Acrypol 1% w/v aqueous dispersion.
- **Density (bulk):** 0.2 g/cm3 (powder); 0.4 g/cm3 (granular).
- **Density (tapped):** 0.3 g/cm3 (powder); 0.4 g/cm3 (granular).
- **Dissociation constant:** pKa = 6.0_0.5
- **Glass transition temperature:** 100–1058C
- **Melting point:** Decomposition occurs within 30 minutes at 2608C.
- **Moisture content:** Typical water content is up to 2% w/w.
- **Solubility:** Swellable in water and glycerin and, after neutralization, in ethanol (95%). Carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels.
- **Specific gravity:** 1.41

Applications in Pharmaceutical Formulation or Technology

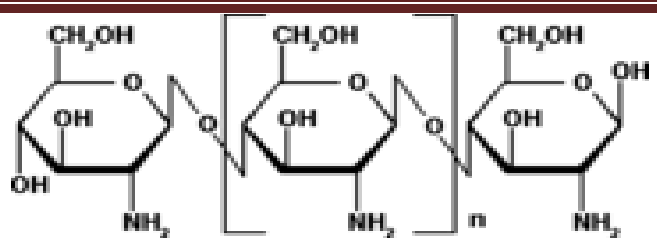
Carbomers are used in liquid or semisolid pharmaceutical formulations as rheology modifiers. Formulations include creams, gels, lotions and ointments for use in ophthalmic, rectal, topical and vaginal preparations.

CHITOSAN

Chitosan is a hydrophilic cationic polyelectrolyte obtained by alkaline N-deacetylation of chitin. Chitin is the most abundant natural polymer next to cellulose and is obtained from crab and shrimp shells.

Molecular formula: $(C_6H_{11}NO_4)_n$

Chemical structure:



Chemical name: Poly-(1-4)-2-Amino-2-deoxy-ß-D-Glucan

Description:

Chitosan is a chitin molecule obtained in the presence of NaOH. Cationic character, along with the presence of reactive functional groups in chitosan, has given it particular possibilities for utilization in controlled release technologies.

Presence of free amino groups, allow its conjugation with some drugs. Chitosan, a linear polyelectrolyte at acidic pH is soluble in variety of acids and interact with poly anionic counter ions. It forms gels with a number of multivalent anions and also with glutaraldehyde. It has a high charged density, i.e. one charge per glucosamine unit.

Chitin is a high molecular weight linear polymer of N-acetyl-D-glucosamine (N-acetyl-2-amino-2-dioxy-D-glucopyranose) units linked by β-D (1, 4) bonds. It is highly insoluble in common solvents, resembling cellulose in its solubility and low chemical reactivity. Like cellulose, it naturally functions as a structural polysaccharide. It is most abundant in crustaceans, insects and Fungi. The skeletal shells of these crustaceans contain approximately 75% calcium carbonate and 15 - 20 % chitin.

Chitosan is non-toxic and easily bio absorbable with gel forming ability at low pH. Also, chitosan matrix formulations appear to float and gradually swell in acidic medium.

Solubility:

a. Chitosan is soluble in acidic solutions, soluble to a limited extent in dilute inorganic acids except phosphoric and sulphuric acids.

b. Soluble at pH values less than 7.0 but mainly in dilute acid. Preferably below pH 6.0 and often in formic, acetic, tartaric, citric, lactic acids of 0.25 – 1 % concentration. Dissolve readily in dilute solutions of most organic acids.

c. Insoluble in water, alkaline solutions at pH levels above 6.5 organic solvents.

d. It has gel forming properties in low pH range.

Important characteristics of Chitosan to be considered in the pharmaceutical formulations

a. **Molecular weight**

Low molecular weight – 150,000

High molecular weight – 600,000

b. **Degree of deacetylation**

Commercial deacetylated chitin is approximately 80 – 85 % deacetylated.

Degree of deacetylation necessary to obtain a soluble product must be 80 – 85 % (or) higher i.e., acetyl content of the chitosan product must be < 4 – 4.5%.

c. **Viscosity**

At concentration of 1.25 % in dilute acetic acid has a viscosity of

1200 cps – good quality

160 cps – medium quality

161 cps – low quality

d. Crystallinity index, number of monomeric units (n), water retention value, pKa, energy of hydration.

Pharmaceutical requirements of chitosan:

- Particle size - < 30 µm
- Density - between 1.35 and 1.40 g/cc
- pH - 6.5 – 7.5

Chitosan can also be characterized in terms of its quality, intrinsic properties and physical forms. The quality characteristics of Chitosan are:-

- Levels of heavy metals and proteins
- Pyrogenicity
- Bio-burden
- Cytotoxicity
- Clarity.

Biological properties:

- Biocompatibility (non-toxic, biodegradable, natural well tolerated by living tissues)
- Bioactivity
- Wound healing acceleration
- Reduces blood cholesterol level
- Immune system stimulant
- Bacteriostatic
- Haemostatic
- Fungistatic
- Spermicidal
- Anti-carcinogenic
- Anti-cholesteromic

Chemical properties:

Deacetylation	**:**	40%-98%
Ash	**:**	Less than 1.5%
Loss on drying	**:**	Less than 10%
Inherent viscosity	**:**	< 200 mPas
Molecular weight	**:**	50 kDa-2000 kDa

Crystallinity index : ~70%

pKa *:* 5.5 - 6.5

Other properties:

- Cationic polyamine
- High charged density at pH < 6.5
- Adheres to negatively charged surfaces forms gels with poly-anions
- High molecular weight linear polyelectrolyte, viscosity, high to low
- Chelates certain transitional metals
- Amiable to chemical modification
- Reactive amino / hydroxyl groups

Storage conditions:

10kg net in plastic woven bags, or corrugated paper carton with plastic liners**.**

Chitosan and drug delivery:

Drug release characterized by an initial burst effect probably due to the release of the drug which is adsorbed on the surface of the microspheres or nanoparticles.

Injectable route:

Since chitosan is well tolerated by living tissues and is biodegradable, it has been recently envisaged for the controlled release or drugs administered parenterally in the form of cross-linked microspheres and nanoparticles. It has been shown that drug diffusion from a chitosan matrix could be effectively controlled using a cross-linking agent such glutaraldehyde, which leads to a diminished susceptibility of the polymer to lysozyme.

4.5 EXCIPIENT PROFILE

SODIUM BICARBONATE [34][35]

Synonyms:

Baking soda; monosodium carbonate; sodium hydrogen carbonate; sodium acid carbonate

IUPAC Name:

Carbonic acid monosodium salt

Empirical Formula: $NaHCO_3$

Molecular Weight: 84.01

Pharmaceutical Application:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain alkaline pH in preparation. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and tartaric acid combinations of citric and tartaric acid often preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone granules lose firmness. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anaesthetic solutions. In some parenteral formulations (e.g. niacin), sodium bicarbonate is used to produce sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze drying stabilizer and in toothpastes.

Recently, sodium bicarbonate has been used as a gas forming agent in alginate raft systems and in floating, controlled release oral dosage forms of furosemide and cisapride. Therapeutically, sodium bicarbonate may be used as an antacid, and as the source of bicarbonate anion in a treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

Description:

Sodium bicarbonate occurs as an odourless, white, crystalline powder with saline, slightly alkaline taste.

Typical Properties:

Density (bulk): 0.869 g/cm^3

Density (tapped): 1.369g/cm^3

Melting point: 270°C

Moisture content:

Below 80 % relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity sodium bicarbonate rapidly absorbs water and may start to decompose with loss of carbon dioxide.

Incompabilities:

Sodium bicarbonate reacts with acids, acidic salt and many alkaloidal salts, with the evolution of carbon dioxide. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of bismuth salt. In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine and levofloxacin.

MICROCRYSTALLINE CELLULOSE

Nonproprietary Names:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Chemical Name:

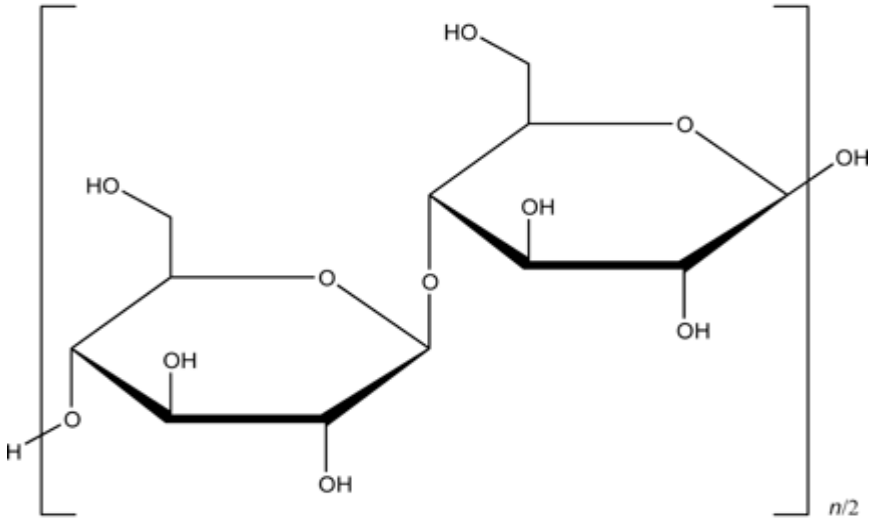
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$ _36 000

where n is 220.

Structural Formula:



Functional Category:

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

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrantproperties that make it useful in tableting.

MAGNESIUM STEARATE [34]

Non-Proprietary Names

BP: Magnesium stearate; IP: Magnesium stearate

PhEur: Magnesii stearas; USPNF: Magnesium stearate

Synonyms: Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name and CAS Registry Number: Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula: $C_{36}H_{70}MgO_4$

Molecular Weight: 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula

$[CH_3 (CH_2)_{16}COO]_2Mg$

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Physical Properties :

Crystalline Forms: High-purity magnesium stearate has been isolated as a trihydrate, a dehydrate and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flash point: 250°C

Flowability: Poorly flowing, cohesive powder.

Melting Range: 117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific Surface Area: 1.6–14.8 m^2/g

Stability and Storage Conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Pharmaceutical Application

Magnesium stearate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

TALC[33]

Synonyms	**:**	Purified French Chalk, Purtalc, Soapstone.
Description	**:**	It is very fine, white to grayish-white colored odorless, impalpable, unctuous, crystalline powder.
Functional categories	**:**	Glidant and lubricant in tablets and capsules.
Solubility	**:**	Insoluble in water, organic solvent, dilute acid & alkalis.

pH	**:**	7.0 – 10.0 for a 20 % aqueous dispersion.
Loss on drying	**:**	< 1.0 %
Hygroscopicity	**:**	It absorbs insignificant amount of water at & relative humidities upto about 90 %.
Stability and storage		
Conditions	**:**	It is a stable material. It should be stored in a Well-closed container in a cool, dry place.
Incompatibilities	**:**	Incompatible with quaternary ammonium Compounds
Applications	**:**	It is widely used in oral solid dosage forms as a Lubricant & diluents. It is used as a dusting powder in topical use. Additionally used to clarify liquids and mainly used in food and cosmetics products because of its lubricant properties.

4.5 PREFORMULATION STUDIES:

4.5.1. Determination of Melting Point.

Melting point of Ranolazine was determined by capillary method. Fine powder of Ranolazine was filled in glass capillary tube (previously sealed on one

end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt by using the thermometer which was already immersed into the liquid paraffin in the apparatus.

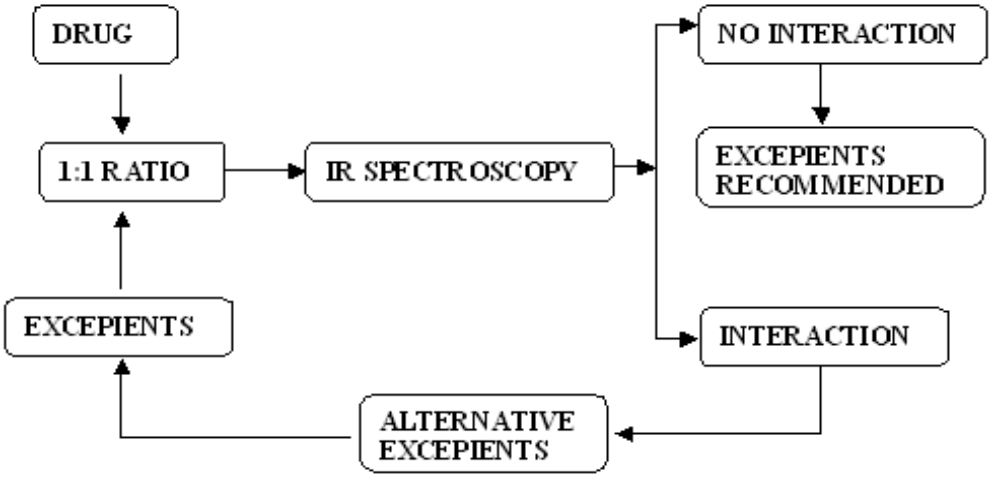
4.5.2. Compatibility study:

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

FT-IR:

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

Schematic representation of compatibility studies



Procedure:

Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50ºC). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.

4.5.3 Drug–Polymer Interaction/Compatibility study using FTIR

Fourier Transfer Infrared Spectroscopy

IR has been the method of choice to probe the nature and extent of interaction in polymer blends. IR was used in the study because mixing of the two components at molecular level will cause changes in oscillating dipoles of the molecules. If the drug and polymer interact then functional groups in FTIR spectra will show band shift and broadening compared to that of pure compounds.

Method

Potassium Bromide disc containing drug, polymer and their physical mixture were prepared to record the spectrum by using Shimadzu 8400S FTIR.

4.5.4 Total Ash Value

Silica crucible was heated to red hot for 30 minutes, allowed to cool in a dessicator and weighed. Accurately weighed 1.0 g of each polymer was transferred and distributed in crucible, dried at 100-105ºC for 1 h and ignited to constant weight in a muffle furnace at 600±25ºC. The crucible was allowed to cool in a dessicator and weighed till constant weight has been attained. Total ash value was calculated with reference to the air dried sample.

4.5.5. Sulfated Ash

Silica crucible was heated to red hot for 10 minutes allowed to cool in a dessicator and weighed. Accurately weighed 1.0 g of sample was transferred and distributed in a crucible, and ignited until the substance was thoroughly charred. The crucible was allowed to cool, the residue was moistened with 1.00 ml of 0.2 M sulfuric acid and ignited at about 600±25ºC, until the white fumes were no longer evolved and ignited until all black particles has been disappeared. Then the crucible was allowed to cool and weighed till constant weight has been attained.

4.5.6 Loss on Drying

A glass stoppered shallow weighing bottle dried at 105ºC was taken and accurately weighed sample was transferred to the bottle. The sample was evenly distributed by gentle sidewise shaking. The loaded bottle was placed in an oven. The stopper was removed and left in the chamber and the sample was dried at 105ºC. The sample was dried to constant weight. After drying was completed, the bottle was closed properly and allowed to cool at room temperature in a dessicator. The weight of content was calculated.

4.5.7 pH of the solution:

A 1% W/V solution of different polymers and excipients were prepared and pH of the solution was determined by pH meter.

4.5.8. Acid Insoluble Ash:

The ash was boiled with 25 ml of 2 M HCl for 5 min., and the insoluble matter was collected on an ashless filter paper, washed with hot water, ignited, cooled in a desiccator and weighed.

4.6 The Standard Calibration Curve of Ranolazine

Ranolazine was quantitatively analyzed by various techniques. In the present study, Ranolazine was estimated by UV spectrophotometry method.

4.6.1. Determination of λ_{max} for: Ranolazine

Two different stock solutions of drug sample were prepared by dissolving 100.0 mg of drug in 100.0 ml of 0.1 N HCl and in 100.0 ml of phosphate buffer solution pH (6.8), solutions were further diluted and analyzed spectrophotometrically to determine λ_{max}.

Observation:

The λ_{max} was found to be 272 nm.

4.6.2 Preparation of standard calibration curve of Ranolazine

4.6.3 In 0.1 N HCl

A. Preparation of 0.1 N HCl: 85 ml of conc. hydrochloric acid was diluted upto 1000 ml with distilled water, gives 1N solution. 10 ml of resulting solution was further diluted up to 100 ml with distilled water gives 0.1 N HCl.

B. Preparation of dilutions for standard curve: Stock solution was prepared by dissolving 100.0 mg of Ranolazine in 100.0 ml of 0.1 N HCl solutions, which was further diluted to give the solutions of concentration 5, 10, 15, 20 and 25 µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at 272 nm and plotted against the concentration to give the standard curve.

C. Changes in the height of solid and liquid layers were measured after every 24 hours.

4.6.5. In 6.8 pH Phosphate Buffer

A. Preparation of Phosphate Buffer pH 6.8 : Accurately weighed quantity of 27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and diluted with distilled water upto 1000 ml. 50ml of above solution was taken in a 200 ml volumetric flask, 22.4 ml of 0.2 M NaOH was added to the solution and then diluted with distilled water upto volume.

B. Preparation of dilutions for standard curve: Stock solution was prepared by dissolving 100.0 mg of Ranolazine in 100.0 ml of 6.8 pH Phosphate buffer solutions, which was further diluted to give the solutions of concentration 5, 10, 15, 20 and 25 µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at 272 nm and plotted against the concentration to give the standard curve.

4.7 Formulation of Floating Tablets of Ranolazine [37]

Fig. No. 16.Steps involved

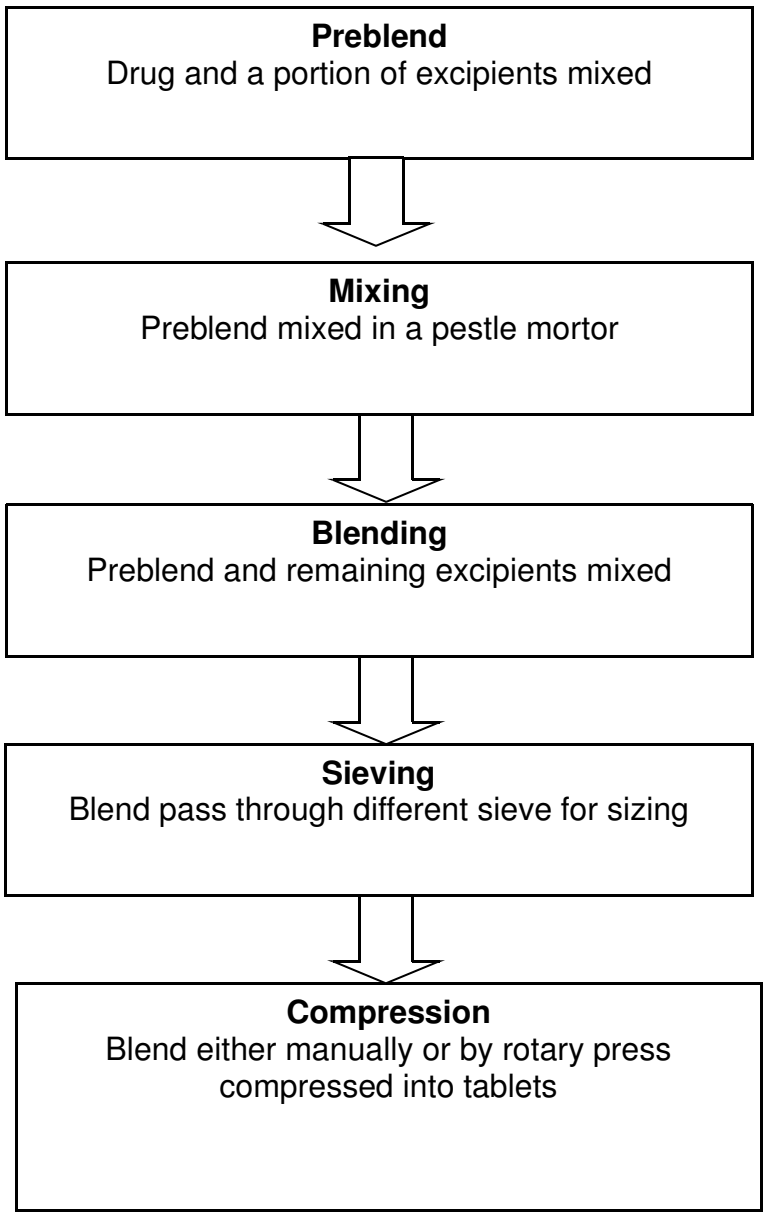


Table No. 5: Composition of Ranolazine Floating Tablet

Batch Code	Drug (mg)	HPMC K 4 M (mg)	HPMC K 15 M (mg)	HPMC K 100 M (mg)	Carbopol 934 P (mg)	Chitosan (mg)	Sodium bicarbonate (mg)	Micro crystalline cellulose (mg)
RF1	500	300	-	-	-	-	30	10
RF2	500	-	300	-	-	-	30	10
RF3	500	-	-	300	-	-	30	10
RF4	500	150	-	-	150	-	30	10
RF5	500	-	150	-	150	-	30	10
RF6	500	-	-	150	150	-	30	10
RF7	500	150	-	-	-	150	30	10
RF8	500	-	150	-	-	150	30	10
RF9	500	-	-	150	-	150	30	10
RF10	500	-	-	-	-	300	30	10

HPMC- Hydroxy propyl methyl cellulose. All the formulations contained 1% of Magnesium stereate and 1% Talc.

* Quantities are in milligrams.

4.7.1. Preparation Floating Tablets of Ranolazine

Technology Applied: Direct compression.

The key ingredients included in the formulations are:

- Hydrophilic Polymers: HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 934P and Chitosan to modify the pattern of Ranolazine release from matrix.
- Effervescent agent: Sodium bicarbonate
- Filler: Micro Crystalline Cellulose
- Antiadherant: Talc
- Lubricant: Magnesium Stearate.

Procedure:

Accurately weighed quantities of polymer and MCC for each batch were taken (in a mortar and mixed geometrically, to this required quantity of Ranolazine was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the Ranolazine blend which was also passed through sieve no 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and mixed for minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 850mg was compressed into tablets with 13.5mm capsulate punches (A total weight of 170g powder blend was required in each batch containing 100 tablets). The composition of various formulations was given in Table 5.

4.8 Evaluation of powder characteristics [35][36]

A) Pre-Compression Parameters:

4.8.1. Angle of Repose

Angle of response is the angle of inclination, formed to the flat surface by the bulk of granules when it is allowed to flow under gravitational force from a fixed height. It is a characteristic of granule flow properties and is calculated by using the formula.

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

Where

θ - Angle of repose

h - Height of granule above flat surface

r - Radius of circle formed by the granule pile

4.8.2. Compressibility Index

It is also a characteristic of granule flow properties. The bulk density and tapped density was measured and compressibility index was calculated using the formula,

$$C.I. = \{ (P_t - P_0) / P_t \} \times 100$$

Where, P_t = tapped density

P_0 = bulk density

4.8.3. Hausner Ratio

Tapped density and bulk density were measured and the hausner ratio was calculated using the formula,

Hausner ratio = P_t / P_0

Where, P_t = tapped density

P_0 = bulk density

A) Post-Compression Parameters:

4.9 Evaluation of Tablets [40]

4.9.1. Hardness

Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester (Monsanto type), force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded.

4.9.2. Thickness

The tablet thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The thickness of the tablets was measured using vernier caliper. It is expressed in mm. 5 tablets of each batch were picked randomly and its thickness were measured individually. The thickness of the tablet is mostly related to the tablet hardness

4.9.3. Friability

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Preweighed tablet samples (20 tablets) were placed in the friabilator, which

was then operated for 100 revolutions, dropping the tablets a distance of 6 inches with each revolution. The percentage friability was calculated using the formula.

$$\% \text{ friability} = \frac{\text{initial wt} - \text{final wt}}{\text{initial wt}} \times 100$$

4.9.4. Weight variation test

20 tablets were selected at random and weighted individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablets weighed over 100 mg, I.P. specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

4.9.5. Drug content

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, ten tablets from each batch were weighed and powdered. Powder equivalent to the average weigh of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of distilled water. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer at 272 nm.

4.9.6. *In vitro* Buoyancy Study:

The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) and duration of time by which the dosage form constantly emerge on surface of medium called total floating time.(TFT).

Procedure

One tablet from each formulation batch was placed in USP type II dissolution apparatus containing 900 ml of 0.1N HCl using paddle at a rotational speed of 50 rpm. The temperature of medium was maintained at 37±2 °C. the time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium was noted.

Fig. 18: Floating behavior of Ranolazine Floating Tablet (RF_8)

At initial time **After 30 sec**

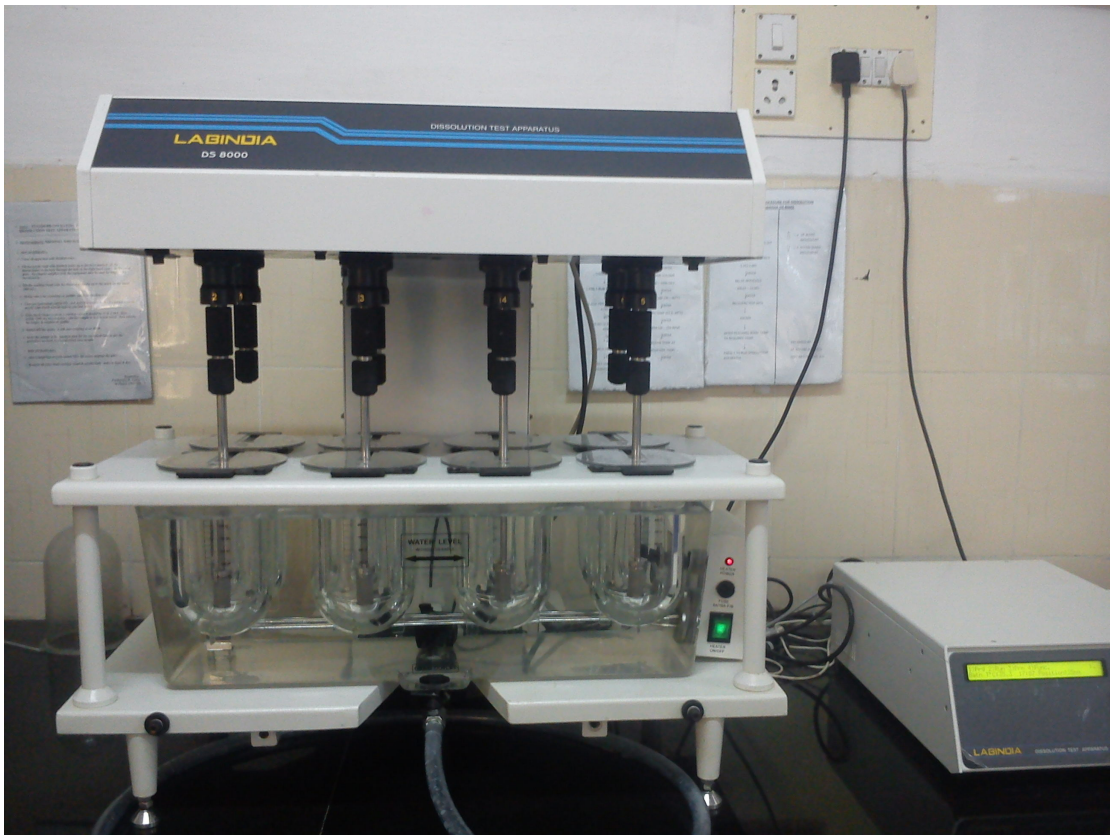
4.10 Water Uptake Studies:

4.10.1. Study of Swelling behaviour

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.

4.11. In-Vitro Dissolution Study [30]:

Dissolution of the tablet of each batch was carried out using USP type I apparatus (Basket type).



Procedure

Nine hundred ml of 0.1 N HCl was filled in a dissolution vessel and the temperature of the medium was set at 37±2°C.[106] Tablet was placed in each dissolution vessel and rotational speed of paddle was set at 50 rpm. The 5 ml of sample was withdrawn at predetermined time interval for 24 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1 N HCl as blank at λ_{max} of 272 nm using double beam UV visible spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The % cumulative drug release was calculated.

4.12. Study of drug release kinetics [29]:

For finding out the mechanism of drug release from floating tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations.

Zero order release equation

$$Q = K_0 t \quad \text{_____} \quad (1)$$

First order equation

$$\text{In } Q = K_f t \quad \text{_____} \quad (2)$$

Higuchi's square root of time equation

$$Q = K_H t^{½} \quad \text{_____} \quad (3)$$

Korsmeyer and Peppas equation

$$F = (M_t / M) = K_m t^n \quad \text{_____} \quad (4)$$

Where,

Q = amount of drug release at time t.

M_t = drug release at time t.

M = total amount of drug in dosage form

F = fraction of drug release at time t.

K_0 = zero order release rate constant.

K_f = first order release rate constant.

K_H = Higuchi square root of time release rate constant.

K_m = constant depend on geometry of dosage form.

N = diffusion exponent indicating the mechanism of drug release, where for cylinder value of n is 0.45 indicate fickian diffusion, between 0.45 and 0.89 indicate anomalous transport and 0.89 indicate case – II transport.

In order to study the drug release kinetics of the examined tablets, the dissolution profiles of formulations were analyzed according to zero-order, first order, Higuchi's square root and Peppas korsmeyer's equations.

4.13. Stability Studies:[29]

Stability testing is an integral part of formulation development. It generates information on which to base proposals for the shelf lives of drug substances and products and their recommended storage conditions. Stability data also are a part of the dossier submission to regulatory agencies for licensing approval.

Stability testing ensures that a drug substance will be safe and effective throughout the shelf life of the product. However, meeting the potency and purity profiles established in the compendia can be challenging as pharmaceutical products become increasingly complex and diverse.

The optimized formulation RF8 packed in PVC blister pack then, they were stored at three different temperatures $4^0C\pm2^0C$, $27^0C\pm2^0C$ and $45^0C\pm2^0C$ for 45 days at RH 75±5%. At 15 days intervals, the tablets were evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

4.14. In-vivo confirmation of buoyancy by using radiographic studies[36]

In-vivo study was performed in albino rabbits using X-Ray imaging technique. Prior permission was taken from institutional animal ethical board (Reg.No. JKKMMRFCP/IAEC/2012/010). For this study the tablets of optimized batch (RF8) was prepared by replacing half of the amount of drug with barium sulfate. Animals were fasted for 12 hrs before study apart from drinking water. Tablets were administered orally. Radiographs were obtained at predetermined time intervals (30mins, 60 mins, 120 mins, 180 mins and 300mins)

5. RESULTS AND DISCUSSION

5.1 Preformulation study:

Table No. 6: Analysis Report of Ranolazine

Test	Specification of IP	Results
Character	White or almost white powder.	White granular powder
Solubility	Soluble in ethanol; sparingly soluble in water; slightly soluble in dichloromethane; practically insoluble in ether	Insoluble in hot water, in acetone, in ethanol, in ether and in toluene.
IR Spectra	The potassium bromide disc contain drug was prepared to record the spectrum by using FTIR spectrophotometer	The spectrum showed all prominent peaks of Ranolazine
Melting Point	117^0C – 122^0C	119^0C
Loss on Drying	1.0%	0.68%
Sulphated Ash	0.1%	0.1%
Bulk Density	N.S.	0.51
Tapped Density	N.S.	0.327
Compressibility Index	N.S.	15.84
Hausner Ratio	N.S.	1.163

N.S. Not Specified

Discussion:

Preformulation studies indicate that the drug (Ranolazine) passes the identification test specified in IP. The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablet by direct compression technique. The value of Carr's Index from 5 – 16 indicates excellent to good flow of powder. Similarly value of Hausner ratio (< 1.25) and Angle of repose (< 25°) indicates good flow properties of drug.

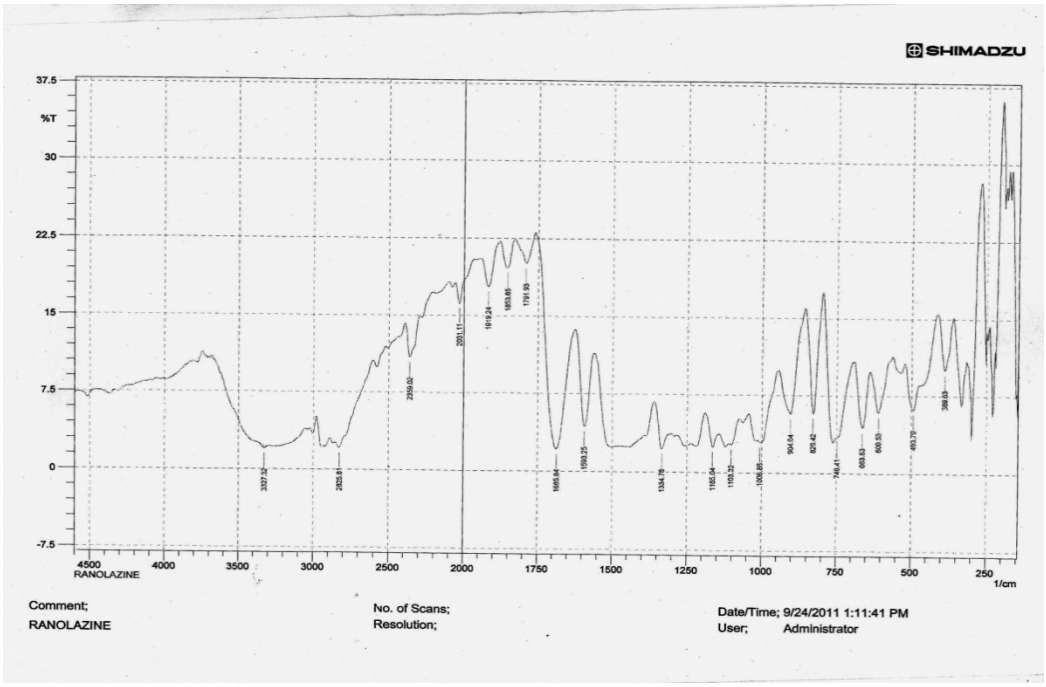
5.1.1. Drug–Polymer Interaction/Compatibility study using FTIR

Table No. 7: FTIR Spectral Analysis

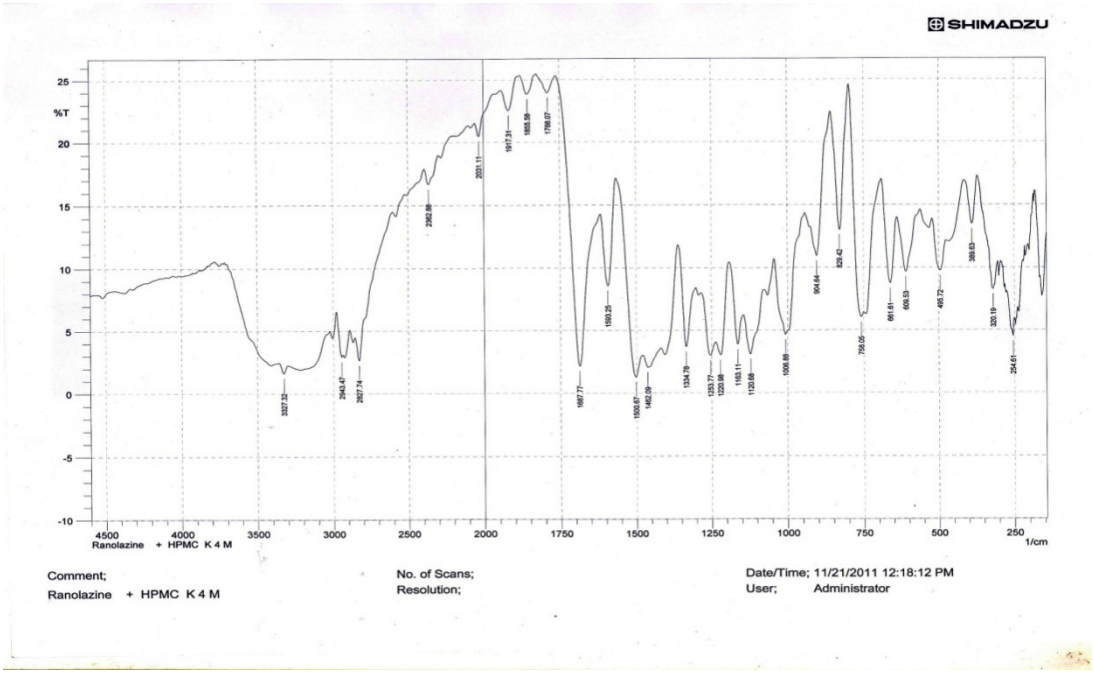
S. No	Functional groups	Characteristic peaks (nm)		Observed peaks(nm)	
		Stretching	Bending	Stretching	Bending
1	N–H	3500 – 3100	Near 800	3327.32	829.82
2	C=O	1680 – 1630	-	1685.84	-
3	O–H	1440–1220	-	1334.78	-
4	–O–	1250–1040	-	1103.32	-

The different peaks of drug, polymer and their physical mixture indicate all groups and characteristics of the drug were not altered. There is no significant interaction in drug and polymer.

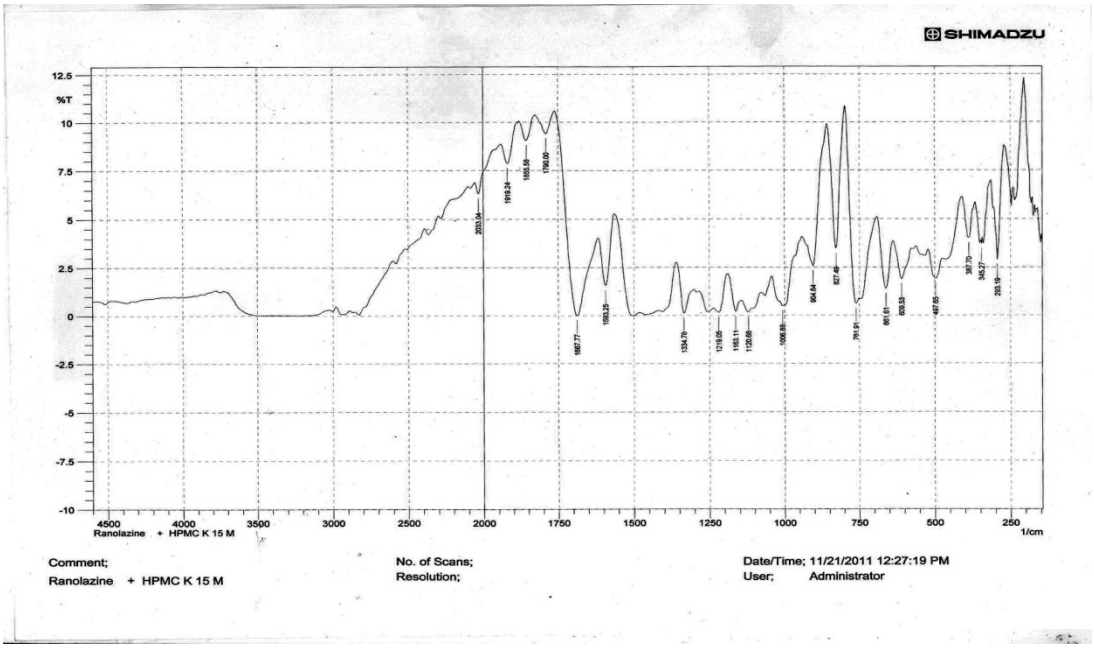
Graph No.1: FTIR Spectral Analysis of Ranolazine



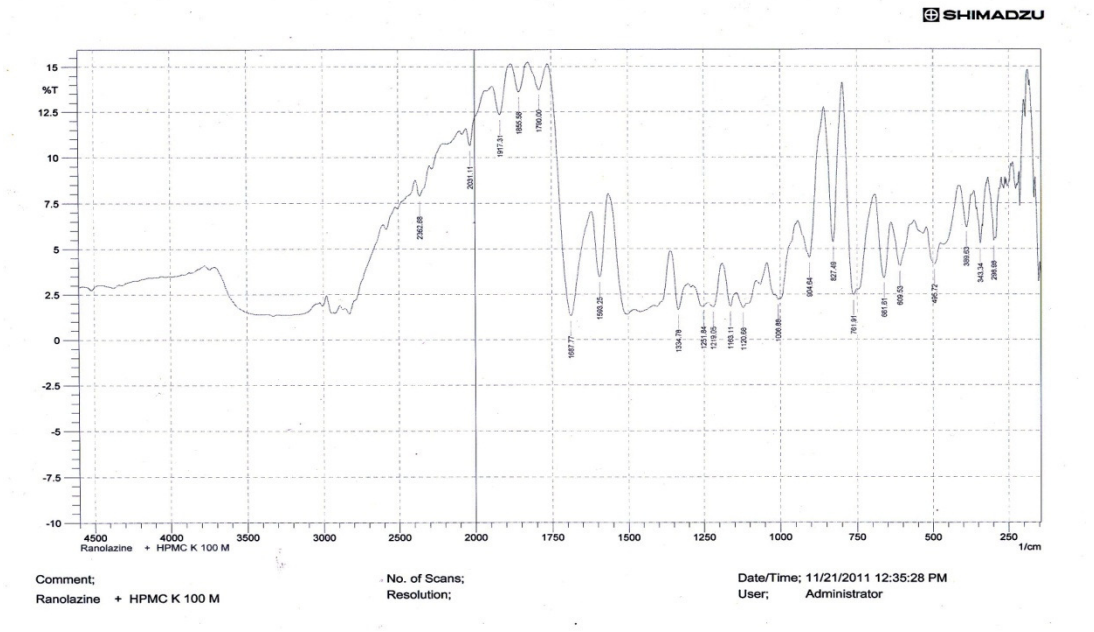
Graph No.2: FTIR spectral analysis of Physical mixture of Drug and polymer (Ranolazine +HPMC K4M)



Graph No.3: FTIR spectral analysis of Physical mixture of Drug and polymer (Ranolazine +HPMC K15M)

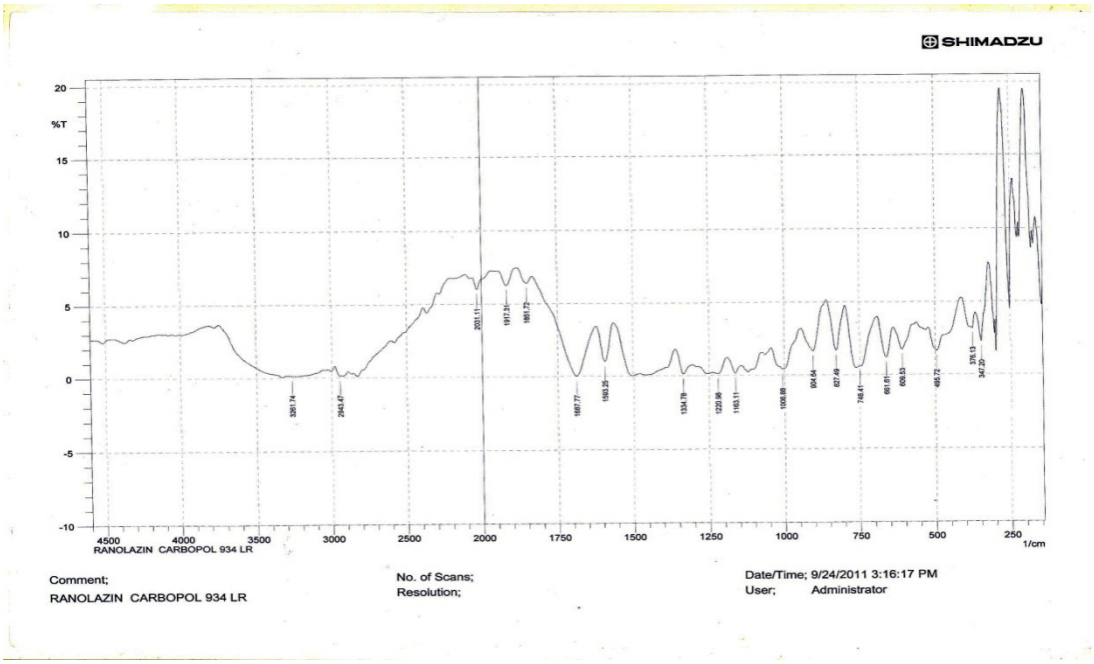


Graph No.4: FTIR spectral analysis of Physical mixture of Drug and polymer (Ranolazine +HPMC K100M)



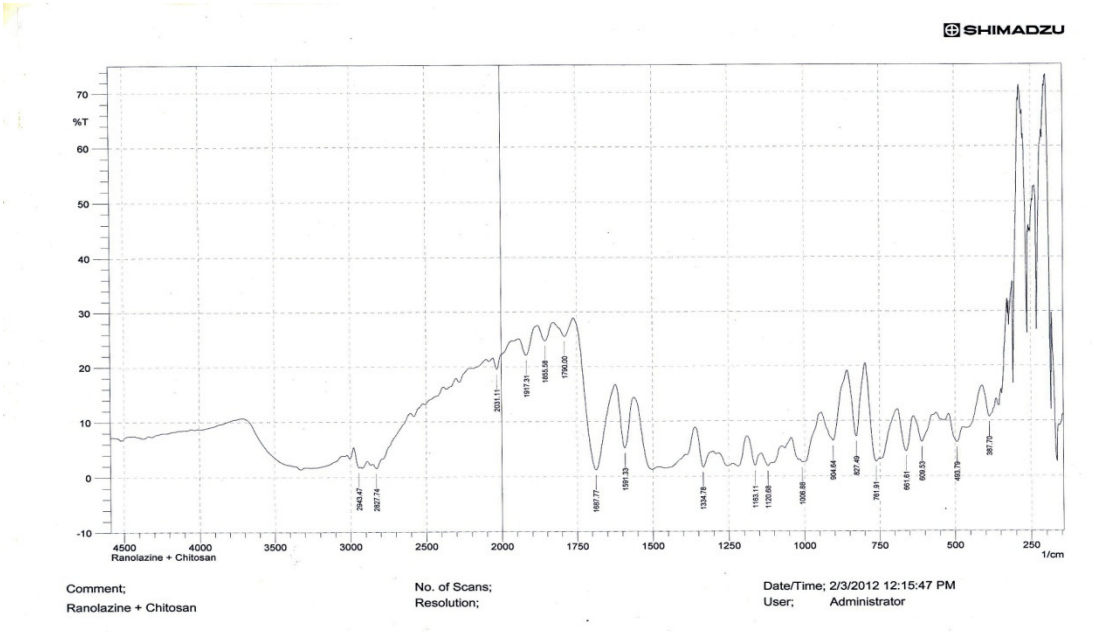
Graph No.5: FTIR spectral analysis of Physical mixture of Drug and polymer

(Ranolazine +Carbopol 934 P)



Graph No.6: FTIR spectral analysis of Physical mixture of Drug and polymer

(Ranolazine +Chitosan)

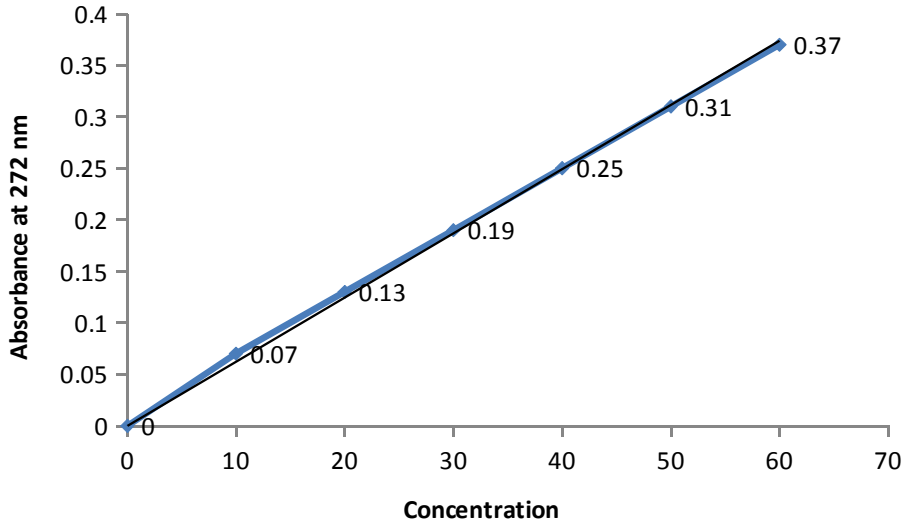


Discussion:

Physical mixture of drug and polymer was characterized by FTIR spectral analysis (Graph 1, 2, 3, 4, 5, and 6) for any physical as well as chemical alteration of drug characteristics. From results, it was concluded that there was no interference in the functional group as the principle peaks of *Ranolazine* were found to be unaltered in the drug polymer physical mixture.

5.2 Standard Calibration Curve of Ranolazine

Graph 7: Calibration curve of *Ranolazine* in 0.1 N HCl



Discussion:

From the scanning of drug in 0.01 N HCl, it was concluded that the drug had λ_{max} of 272.0 nm and which was exactly similar as reported. From the standard curve of 0.1 N HCl

it was observed that the drug obeys Beer – Lambert's law in concentration range of 0 – 60µg / ml in the medium.

5.3 Pre-Compression Parameters:

Formulations	**Angle of repose (θ)**	**Compressibility Index or Carr's Index (%)**	**Hausner's ratio**
RF_1	$26^0.86'$	14.16	1.152
RF_2	$23^0.48'$	14.10	1.127
RF_3	$24^0.49'$	15.50	1.154
RF_4	$27^0.39'$	15.92	1.165
RF_5	$22^0.77'$	14.34	1.152
RF_6	$25^0.15'$	15.01	1.176
RF_7	$24^0.12'$	14.18	1.125
RF_8	$25^0.52'$	15.04	1.177
RF9	$22^0.35'$	14.35	1.152
RF10	$24^0.65'$	15.45	1.185

Table No. 8: Characteristics of Final blend

Discussion:

Table 8 indicates the powder characteristics of various batches of floating tablets. Various formulations show good flow properties. Results of Angle of repose ($22^0.77'$ –

$27^0.39'$), Carr's index (14.34 – 15.92), Hausner's ratio (1.165-1.177) shows satisfactory results, which is required for better bioavailability

5.4.1. Physical Properties

Table No. 10: Physical Properties of each Batch of Ranolazine Floating Tablets

Batch code	Weight variation (mg)	Thickness (mm)	Hardness(kg/cm^2)	Friability (%)	Drug uniformity (%)
RF1	848±1.81	4.2	7.5	0.52	98.45
RF2	850±1.53	4.5	7.72	0.54	98.41
RF3	849±1.70	4.12	7.89	0.57	98.57
RF4	852±2.35	4.75	7.56	0.56	97.74
RF5	848±1.84	4.2	7.34	0.6	98.12
RF6	851±2.02	4.71	7.62	0.63	97.43
RF7	849±1.67	4.32	7.1	0.54	99.21
RF8	850±1.58	4.19	7.23	0.57	99.14
RF9	848±1.86	4.72	7.55	0.61	98.65
RF10	851±2.11	4.31	7.37	0.64	98.15

Discussion:

From the physical parameters (Table 10) of each batch, it was concluded that the tablets of all batches had desirable physical characteristics. Results of Hardness of various batches of prepared formulations (7.1 –7.89 kg / sq cm.) and Friability (0.52 – 0.64 %) indicates that the tablets having sufficient strength to withstand physical abrasion. Tablets of all batches pass the weight variation test as per the limits prescribed in IP. (5% deviation is allowed for average weight of tablet X ≥ 250 mg).

5.4.2. *In-vitro* Buoyancy study:

Table 11: *In-vitro* Buoyancy study of Ranolazine Floating Tablets

Batch Code	Floating Lag Time(Sec)	Total Floating Time (Hours)
RF1	53	>10
RF2	41	>12
RF3	62	>12
RF4	364	>08
RF5	333	>10
RF6	431	>10
RF7	42	>12
RF8	32	>12
RF9	53	>12
RF10	40	>12

Discussion:

Results of floating properties (Table 11) study reveal that all batches had good floating capability. This might be due to the presence of gas generating agent, i.e., sodium bicarbonate. Incorporation of sodium bicarbonate helps to improve floating property by reacting with gastric fluid, when dosage form comes in contact and produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float. It was also observed that as the total concentration of the polymers increases in final formulation, floating lag time increases. The floating lag time results were in the range of 32 Sec to 431 Sec. Formulations from RF1 to RF3 which are formulated by using HPMC (K4M, K15M, K100M) showed satisfactory total floating time. Formulations from RF4 to RF6 which are formulated by the combination of HPMC and Carbopol 934P showed decreased total floating time which may be due to high affinity of Carbopol towards water, which promotes water penetration into tablet matrices, leading to increased density. Formulations from RF7 to RF9 showed increased total floating time which may be due to the good natural gel strength of Chitosan.

5.4.3. Water Uptake Studies

Table No. 12: Study of swelling characteristics of floating tablets of Ranolazine

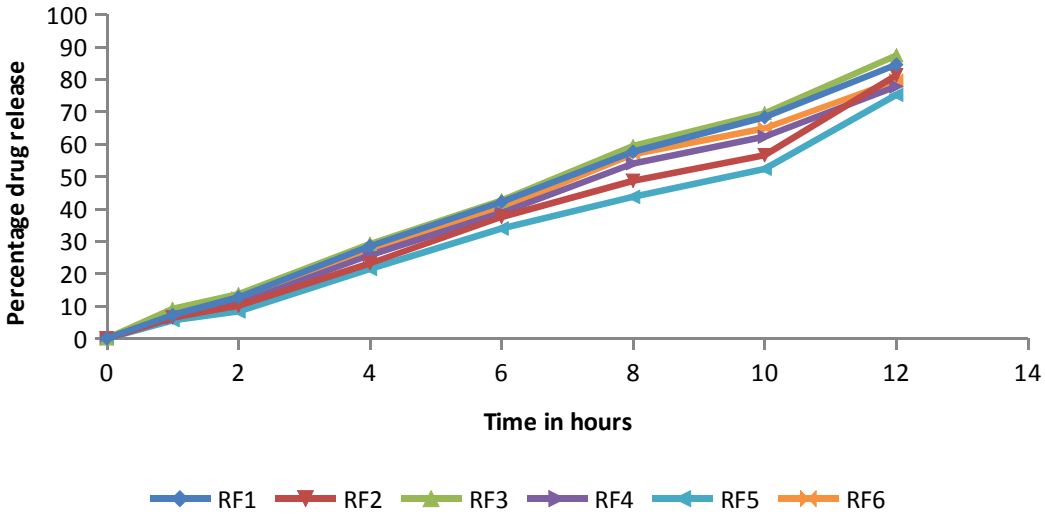
Batch Code	Time in hrs. (% Swelling)			
	2	**4**	**6**	**8**
RF_1	75.25	102.48	67.14	59.45
RF_2	117.45	176.37	184.46	107.24
RF_3	68.17	97.34	61.48	53.75
RF_4	87.19	119.72	78.49	72.19
RF_5	127.35	194.62	181.15	113.45
RF_6	82.15	113.75	70.17	65.73
RF_7	66.65	93.41	55.48	47.84
RF_8	105.24	169.82	161.75	94.19
RF_9	58.19	89.73	51.79	42.65
RF_{10}	54.97	82.43	47.19	40.64

Discussion:

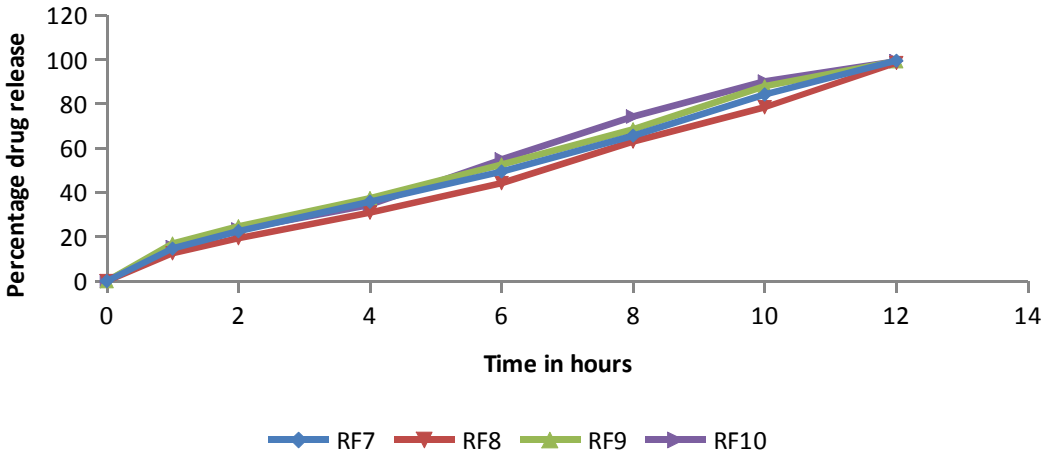
Water uptake (swelling) study Table No. 12 cleared that order of swelling observed in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymers were achieved after 4-6 hrs. The swelling index was calculated with respect to time. As the time increases, the swelling

index was increased, because weight gain by the tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. A direct relationship was observed between swelling index and nature of polymer.

Graph No. 10: In-Vitro Dissolution Profile of F1-F6



Graph No. 11: In-Vitro Dissolution Profile of F7-F10



Discussion:

Table 13 indicates the dissolution data of various batches of floating tablets. The percentage drug release from batch RF1 to RF10 vary from 77.87 to 98.37%. For the formulation batch from RF1 to RF3, TFT was sufficient but showed relatively less drug release as higher level of HPMC K4M, K15M, and K100M (300 mg each) were used in these formulations. The formulation batch from RF4 to RF6 showed decreased TFT and drug release was more retarded as combination of HPMC and Carbopol 934P were used in these formulations. But the formulation batch from RF7 to RF9, showed satisfactory results both in case of Total floating time and percentage drug release. The formulation RF10 which contain Chitosan (300 mg) showed drug release to the extent of 90.06 % within 10 hours. But the optimized formulation RF8 (combination of HPMC K15M + Chitosan) showed satisfactory drug release (98.37%) during the final period of study.

5.5 Study of drug release kinetics:

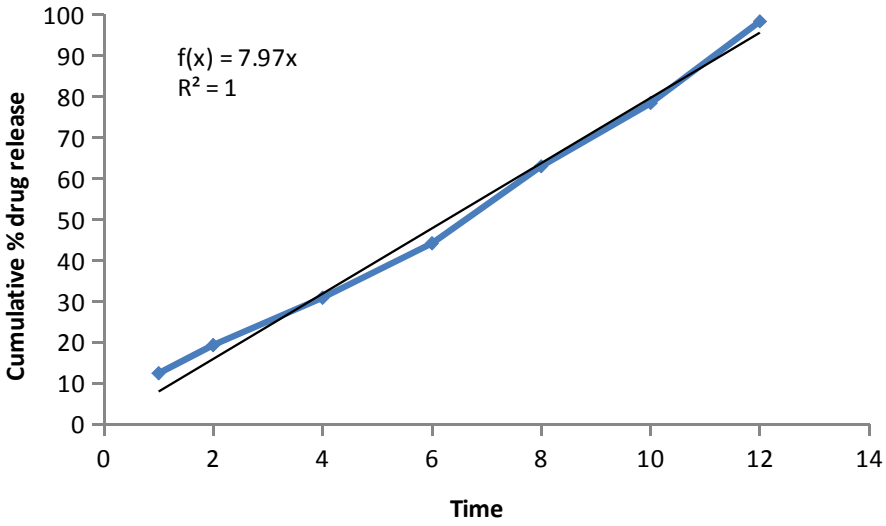
Table No. 14: Dissolution Kinetics of *Ranolazine* Floating Tablets

Code	Zero order	First order	Higuchi	Krosmeyer-peppas	
	R^2	R^2	R^2	R^2	N
RF7	0.997	0.980	0.861	0.989	0.771
RF8	0.990	0.992	0.826	0.975	0.806
RF9	0.996	0.989	0.866	0.985	0.724
RF10	0.991	0.932	0.869	0.983	0.780

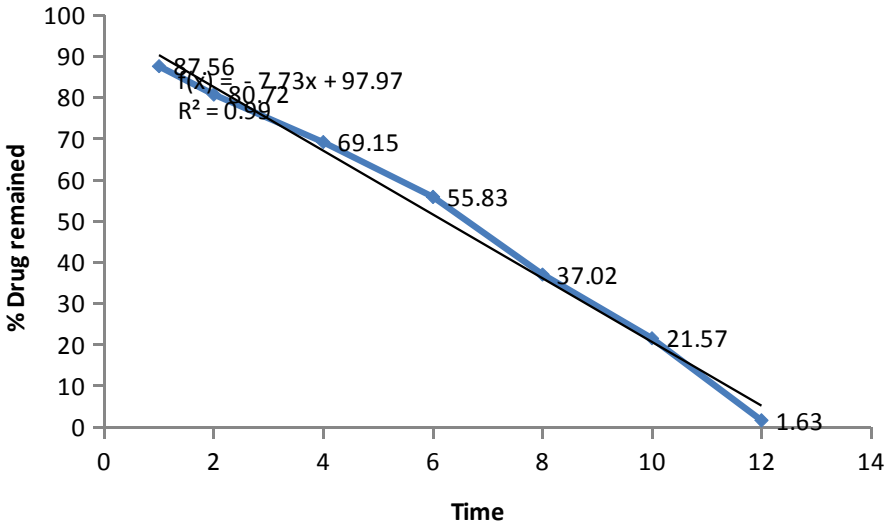
Discussion:

Table 14 indicates the release kinetics of floating tablets of *Ranolazine.* Dissolution data of the tablet of batch RF_8 were subjected to treatment with different kinetics equations, which showed that release patterns .

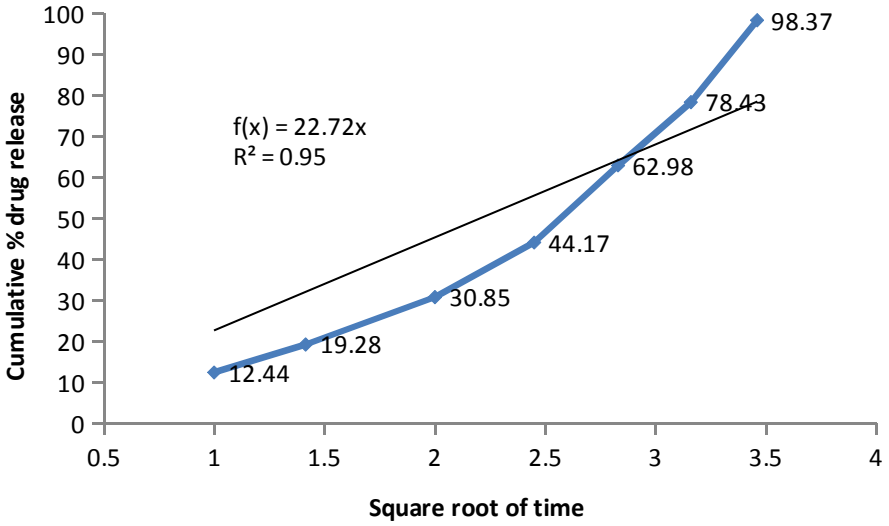
Graph No. 12: Zero Order Plot



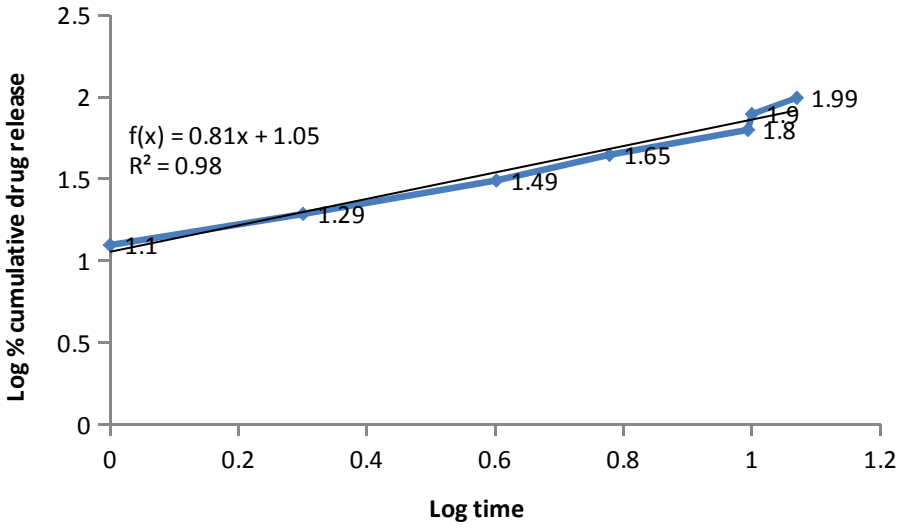
Graph No. 12: First Order Plot



Graph No. 13: Higuchi ' s Plot



Graph No: 14 Peppas Koresmeyer's plot



Discussion:

Regression co-efficient value (R^2) and n values for all formulation were shown in table 14. The release profile of the optimized formula RF8 fitted best to Korsmeyer-Peppas model with R^2 value of 0.975. As the n value for the Korsmeyer-Peppas model was found to be less than 0.89, it follows case-2 transport.

5.6 Determination of stability study of product:

Table 15. Stability studies of Ranolazine floating tablets.

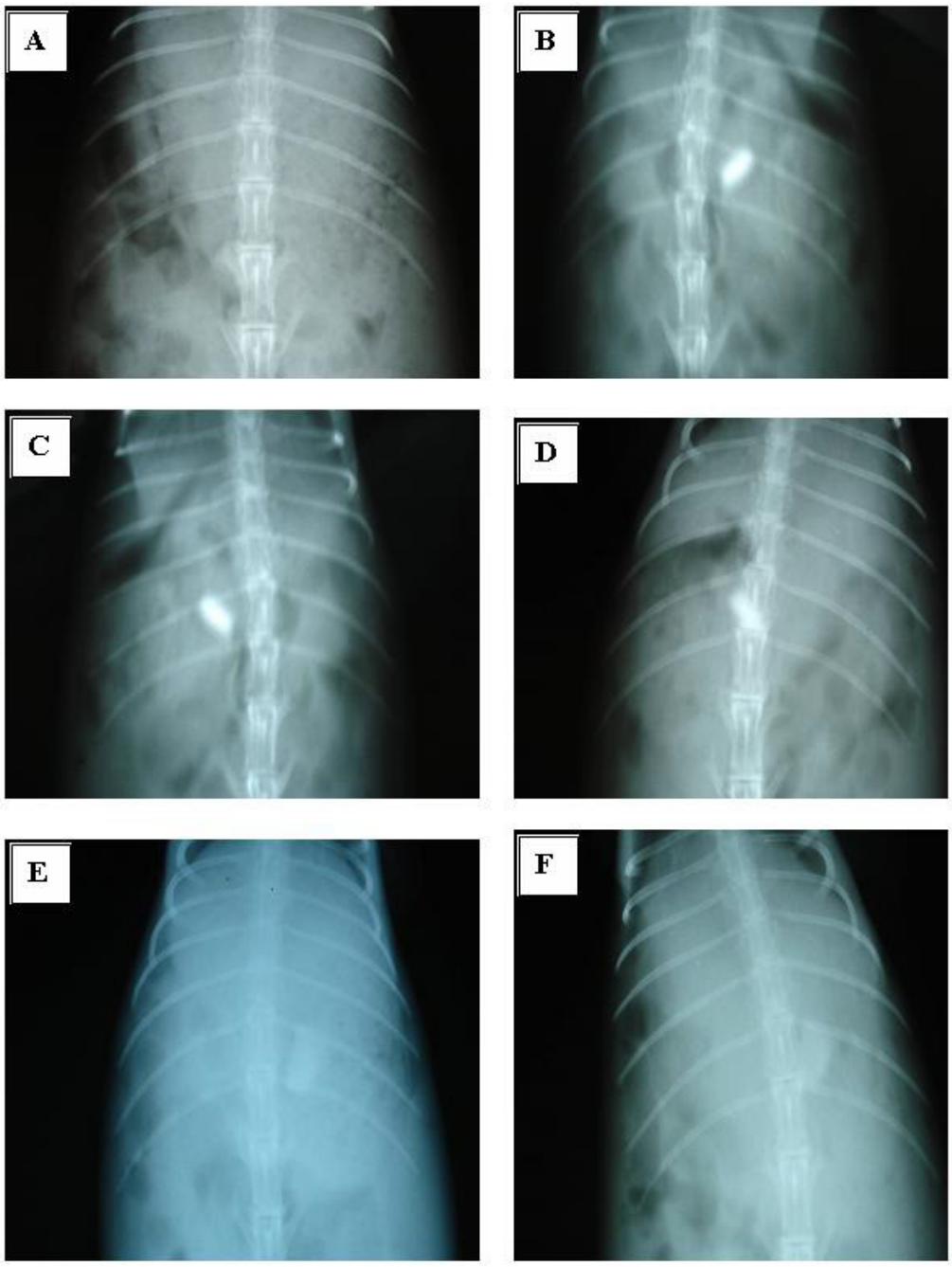
Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	850±1.6	850±2.70	849±1.30
Thickness (mm)	4.19±1.87	4.21±2.86	4.23±3.98
Hardness (kg/cm^2)	7.24±0.23	7.20±0.64	7.20±0.99
Friability (%)	0.56±0.05	0.57±0.08	0.57±0.06
Drug content (mg/Tab)	98.34±0.34	98.21±0.29	98.01±0.87
Buoyancy lag time (Sec)	32±1.60	33±2.8	33±3.10
Duration of Buoyancy (Hours)	>12	>12	>12

Discussion:

According to ICH guidelines, 45 days stability study at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% of optimized formulation (RF8) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content

between initial and formulations stored at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% for 45 days.

5.7 Fig 3. *In-vivo* confirmation of buoyancy by using radiographic studies:



Radiographic images showing the presence of floating tablet in the stomach at different time intervals. Images were taken after: A) Without tablet, B) 30 Mins, C) 60 Mins, D) 120 Mins, E) 180 Mins and F) 300 Mins of tablet administration.

Discussion:

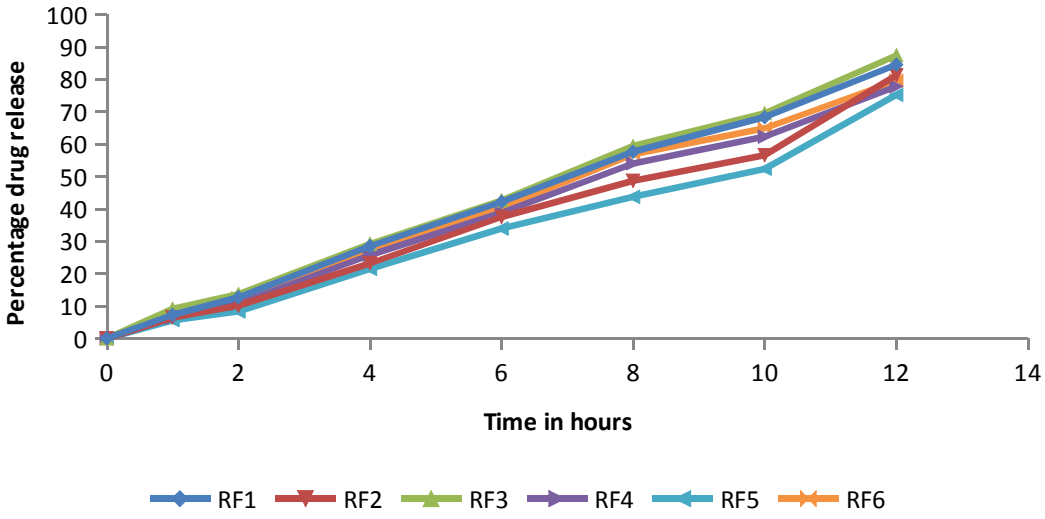
In-vivo studies were conducted on albino rabbits to find out the gastric residence time of the optimized formulation (RF8). The studies were based on X-Ray radiography. Images were taken at different time intervals to find the location of the tablet shown in figure 3. The tablet was found to be floating on the gastric content for about 300±10 mins.

5.4.4. *In-Vitro* Dissolution Study

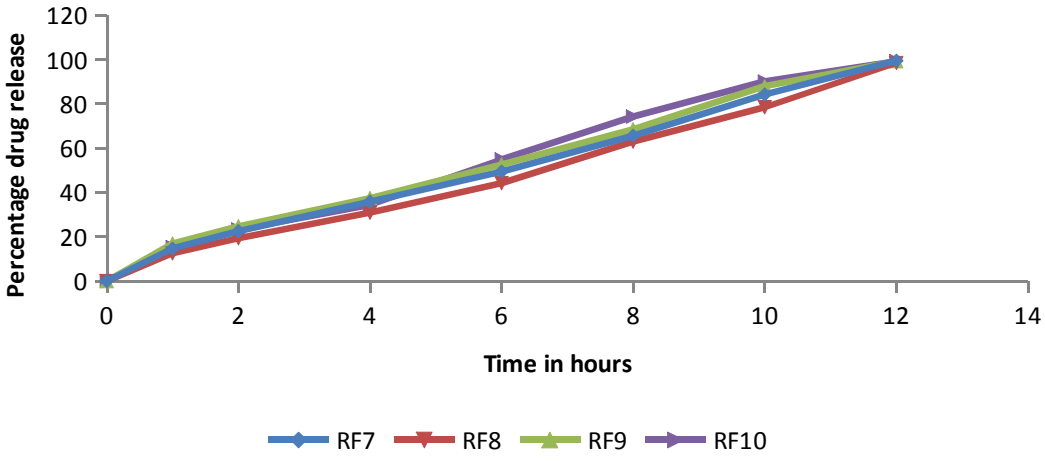
Table No. 13: *In-Vitro* Dissolution Data of Ranolazine Floating Tablet

S.NO	TIME (hr)	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9	RF10
1	1	7.19	6.4	9.1	6.35	5.57	7.15	14.57	12.44	16.85	15.32
2	2	12.64	10.08	13.61	10.79	8.29	12.31	22.47	19.28	24.66	23.19
3	4	28.52	23.16	29.2	25.76	21.44	26.96	35.74	30.85	37.45	34.32
4	6	42.17	37.47	42.67	38.78	33.96	40.23	49.42	44.17	52.56	54.81
5	8	57.65	48.67	59.43	54.05	43.76	56.86	65.57	62.98	68.43	74.18
6	10	68.31	56.54	69.54	62.26	52.38	64.93	84.11	78.43	87.86	90.06
7	12	84.58	81.29	87.42	77.87	75.19	79.58	96.44	98.37	95.21	94.19

Graph No. 10: In-Vitro Dissolution Profile of F1-F6



Graph No. 11: In-Vitro Dissolution Profile of F7-F10



Discussion:

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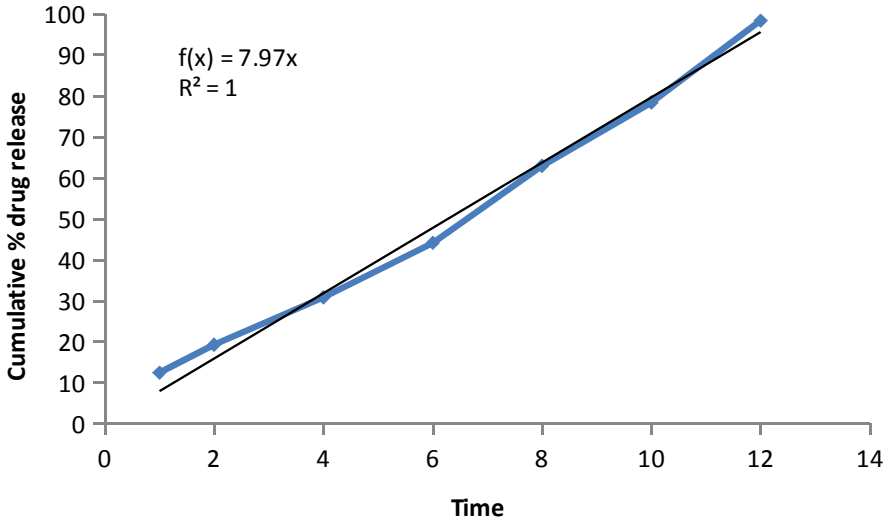
RF7	0.997	0.980	0.861	0.989	0.771
RF8	0.990	0.992	0.826	0.975	0.806
RF9	0.996	0.989	0.866	0.985	0.724
RF10	0.991	0.932	0.869	0.983	0.780

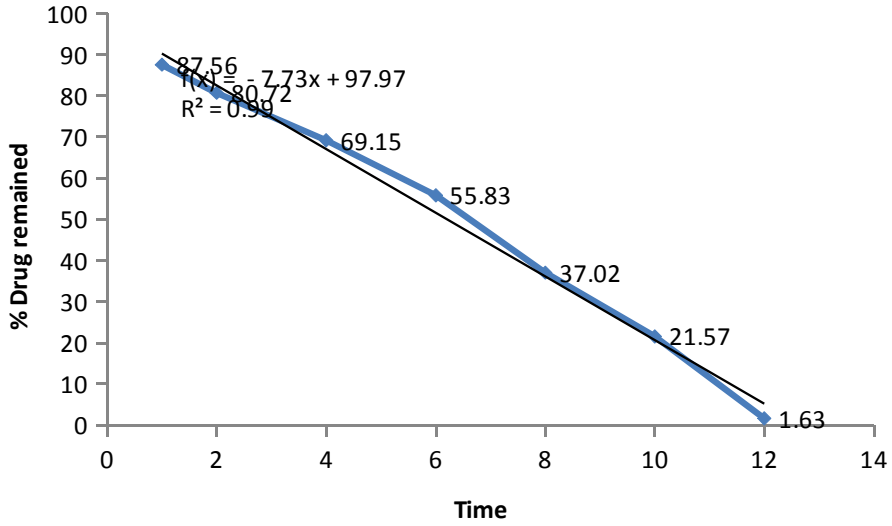
Discussion:

Table 14 indicates the release kinetics of floating tablets of *Ranolazine.* Dissolution data of the tablet of batch RF_8 were subjected to treatment with different kinetics equations, which showed that release patterns .

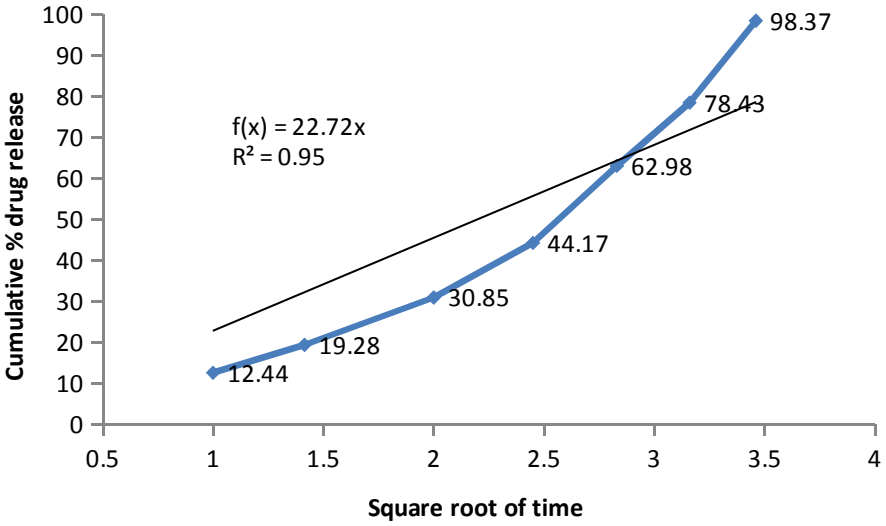
Graph No. 12: Zero Order Plot



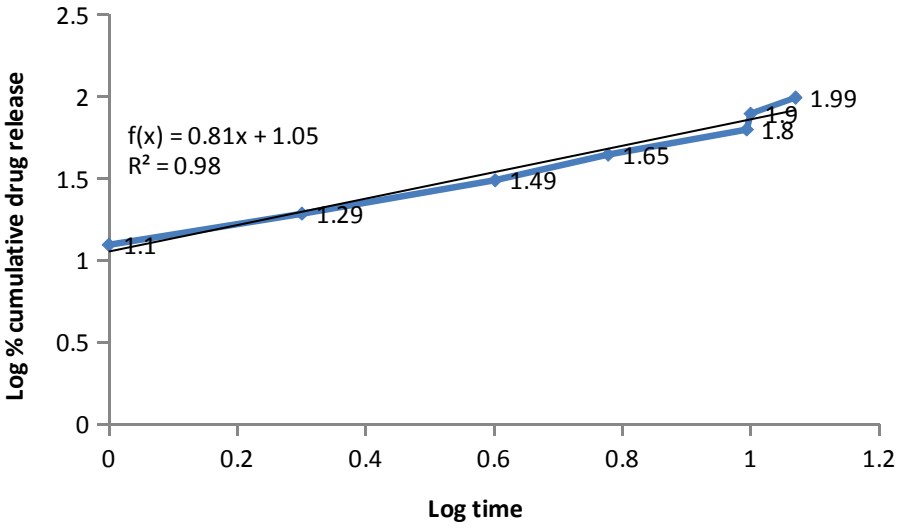
Graph No. 12: First Order Plot



Graph No. 13: Higuchi ‘ s Plot



Graph No: 14 Peppas Koresmeyer‘s plot



Discussion:

Regression co-efficient value (R^2) and n values for all formulation were shown in table 14. The release profile of the optimized formula RF8 fitted best to Korsmeyer-Peppas model with R^2 value of 0.975. As the n value for the Korsmeyer-Peppas model was found to be less than 0.89, it follows case-2 transport.

5.6 Determination of stability study of product:

Table 15. Stability studies of Ranolazine floating tablets.

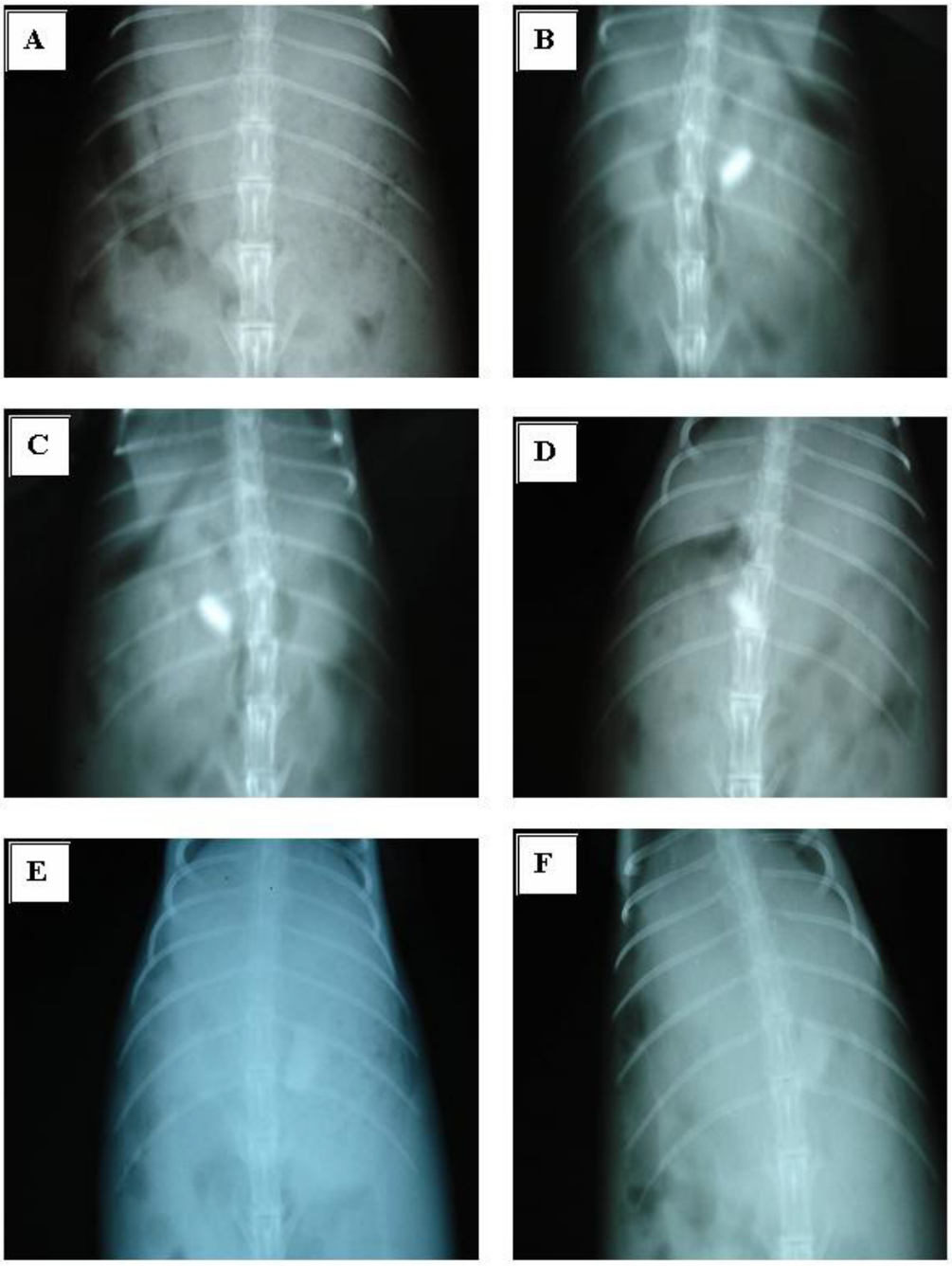
Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	850±1.6	850±2.70	849±1.30

Thickness (mm)	4.19±1.87	4.21±2.86	4.23±3.98
Hardness (kg/cm^2)	7.24±0.23	7.20±0.64	7.20±0.99
Friability (%)	0.56±0.05	0.57±0.08	0.57±0.06
Drug content (mg/Tab)	98.34±0.34	98.21±0.29	98.01±0.87
Buoyancy lag time (Sec)	32±1.60	33±2.8	33±3.10
Duration of Buoyancy (Hours)	>12	>12	>12

Discussion:

According to ICH guidelines, 45 days stability study at 4^{0}C ±2^{0}C, 27^{0}C ±2^{0}C and 45^{0}C ±2^{0}C for 45 days at RH 75±5% of optimized formulation (RF8) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 4^{0}C ±2^{0}C, 27^{0}C ±2^{0}C and 45^{0}C ±2^{0}C for 45 days at RH 75±5% for 45 days.

5.7 Fig 3. *In-vivo* confirmation of buoyancy by using radiographic studies:



Radiographic images showing the presence of floating tablet in the stomach at different time intervals. Images were taken after: A) Without tablet, B) 30 Mins, C) 60 Mins, D) 120 Mins, E) 180 Mins and F) 300 Mins of tablet administration.

Discussion:

In-vivo studies were conducted on albino rabbits to find out the gastric residence time of the optimized formulation (RF8). The studies were based on X-Ray radiography. Images were taken at different time intervals to find the location of the tablet shown in figure 3. The tablet was found to be floating on the gastric content for about 300±10 mins.

SUMMARY

Ranolazine is used for the treatment of Angina pectoris, which has a short elimination half-life of 1.4-1.9 hours. Its dose is 500 to 1000 mg daily in divided doses. Because of frequent administration and short elimination half-life, Ranolazine is considered as an ideal drug for designing a sustained release formulation.

- Floating tablets were developed to prolong the gastric residence time and increase drug bioavailability.
- Ranolazine was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract.
- FTIR studies concluded that there were no interaction in drug and polymer.
- Tablets were prepared by direct compression technique, using polymers such as HPMC different grades, Carbopol 934P, Chitosan alone and in combination, and other standard excipients. According to this formulation codes RF1, RF2, RF3, RF4, RF5, RF6, RF7, RF8, RF9 and RF10 were prepared.
- Tablets were evaluated for physical properties, viz. hardness, friability, weight variation, *in vitro* Buoyancy and swelling studies etc. Further, tablets were evaluated for *in vitro* release characteristics for 12 hrs. Drug release kinetics was studied for zero order, first order, Higuchi order and Korsmeyer-Peppas order.
- *In vivo* confirmation of Buoyancy was performed.

CONCLUSION

From the above study it can be concluded that promising controlled release by gastro retentive floating tablets of Ranolazine was developed using a combination of HPMC K15M and Chitosan.

- The floating tablet of Ranolazine was capable of maintaining plasma drug concentration through 12 hrs.
- The release rate of the drug from the floating tablets was significantly influenced by the proportion as well as viscosity of the polymer used.
- The formulation RF8 was selected as an optimized formulation because it gave the best result in terms of the required *in-vitro* buoyancy study, good floating integrity and drug release in sustained release manner.
- The release profile of the optimized formula, fitted best to Korsmeyer-Peppas model with R^2 value of 0.975.
- As the n value for the Korsmeyer-Peppas model was found to be less than 0.89, it follows case-2 transport.
- In-vivo radiographic studies revealed that the tablets remain in the stomach for 300±10 mins which indicates the increase in the gastric residence time.
- Short-term stability studies indicated no appreciable changes in the drug content and *In-vitro* drug release rates of formulation RF8.

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