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Formulation and Characterization of Gastroretentive Beads of Anti-Hypertensive Agent

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Abstract : Extended release gastroretentive beads of amlodipine besylate was prepared by an ionotropic external gelation method in ratios of 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5 using sodium alginate in the presence of calcium chloride using a syringe 20 gauze. As Amlodipine besylate has maximum solubility in acidic pH and thus most suitable to prolong release of drug. Prepared beads were evaluated for various parameters such as drug content and entrapment efficiency, size and shape and swelling index. Surface morphology of the beads was studied using stage microscope while in-vitro drug release studies showed show sustained release property for 7 h with very good spherical geometry with mean diameter in the range of 3.21 – 4.74 mm. The drug loading efficiency, around 24.63±0.04 %, 98.51±0.001 % entrapment efficiency and good floating characteristics comprising short onset (around 5 minutes) and the long duration of buoyancy (more than 7 hours). The release of amlodipine besylate from the formulation F6 was found to be controlled by the swelling of polymer followed by drug diffusion through the swelled polymer and slow erosion of the beads with swelling Index 176±0.33. Further, short term stability study of optimized formulation for three months period has undergone to check significant changes in physical characteristics and in-vitro release.

Keywords: Gastroretentive, beads, amlodipine besylate, ionotropic gelation, swelling index.

I. INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. (Nayak AK. et al., 2010)

1.1 Classification of Different Modes of Gastric Retention

1.1.1 Low-density (Floating) systems
1.1.2 High-density (Sinking) systems
1.1.3 Expandable systems
1.1.4 Superporous hydrogel systems
1.1.5 Mucoadhesive systems
1.1.6 Magnetic systems

1.1.1. Floating drug delivery systems (FDDS)
FDDS are invented to retain the drug in the stomach as presented in Figure 1A and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them. FDDS are hydro-dynamically controlled low-density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. (Mirmeera NG. et al., 2018)
1.1.2. High-density (Sinking) systems

High-density systems have a density greater than that of gastric fluid (Figure 1B). Commonly used excipients of these systems include barium sulfate, zinc oxide, iron powder, and titanium dioxide. In 1930, Hoelzel first discovered the effects of dosage form density on the GRT of several animal species. The densities of the tested dosage forms ranged from 0.9 to 10.5 g/cm3. (Tripathi J. et al., 2019)

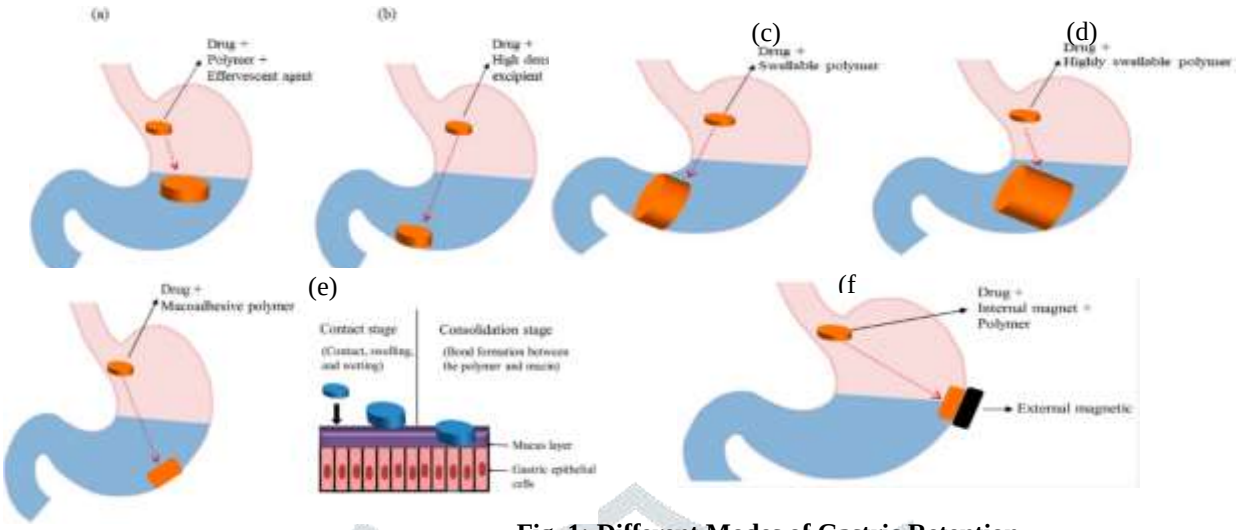

Fig. 1: Different Modes of Gastric Retention

1.1.3 Expandable systems

Expandable drug delivery systems are designed to have a longer GRT through an increase in their volume or shape (Figure 1C). Initially, they were used for veterinary purposes and, subsequently, their applications were extended to humans. Three general configurations need to be considered for the proper functioning of the system: small size for easy oral intake, expanded form in the stomach to prevent passage through the pyloric sphincter, and size reduction of the system after complete drug release to enable evacuation. This system is also termed as a "plug type system" because it has the ability to block the pyloric sphincter. Expansion of the system occurs by two methods, swelling and unfolding, which allow for volume and shape modification, respectively. The main mechanism for swelling and drug release from the system is diffusion. These systems utilize hydrophilic polymers (e.g., HPMC, polyethylene oxide, and carbopol) that can absorb water from the gastric fluids and increase the volume of the system. Likewise, in unfolding systems, the polymer and drug are in a folded/compressed state inside the gelatin capsule. When they come into contact with the gastric fluid, gelatin is dissolved and releases the mechanically preferred expanded configuration. (Tripathi J. et al., 2019)

1.1.4. Superporous hydrogel systems

In 1998, the super porous hydrogel was presented as a different category of water-absorbent polymer system. This system has gained popularity in the controlled-release formulation due to its high mechanical strength and elastic properties. It has a pore size greater than 100 µm, and as a result, it swells rapidly to an equilibrium size due to water uptake by capillary wetting through numerous pores. Figure 1D depicts the schematic concept of the super porous hydrogel system. The conventional hydrogel system is a slow process and takes several hours to reach equilibrium; thus, the dosage form can be easily evacuated from the stomach. On the contrary, the super porous hydrogel systems swell up to 100 times or more, and gain enough mechanical strength to withstand pressure by gastric contraction, thereby increasing the GRT. Highly swellable polymers, such as croscarmellose sodium and sodium alginate are used in these systems. However, these systems can be highly sensitive to pH, and swelling can be reversible due to changes in pH and poor mechanical strength of the structure. (Tripathi J. et al., 2019)

1.1.5. Mucoadhesive systems

The mucoadhesive/bio adhesive system was first introduced by Park and Robinson in 1984. It was designed to adhere to the gastric epithelial cell surface and prolong the GRT of drug compounds. Figure 1E illustrates the concept of this system. In this approach, drugs are incorporated in a mucoadhesive agent, which can be either natural or synthetic polymers. Bonding established between the polymer and mucosal surface facilitates the mucoadhesion process, which generally involves two steps: the contact stage and the consolidation stage (Figure 1e). Commonly used mucoadhesive polymers include carbopol, chitosan, sodium alginate, HPMC, polyethylene glycol, and poly(acrylic acid). Mucoadhesive polymers assist in binding drug substances to the mucosal surfaces and prolonging the drug residence time at the application site. (Tripathi J. et al., 2019)

1.1.6. Magnetic systems

In magnetic systems, a dosage form consists of active pharmaceutical ingredient, excipients and also a small amount of internal magnet. An extracorporeal magnet is placed over the stomach to control the position of the dosage form containing internal magnet as presented in Figure 1F. The position and the magnetic field intensity of the extracorporeal magnet can affect the GRT. (Tripathi J. et al., 2019)

1.2 Classification Of Floating Drug Delivery System (FDDS) (Mirmeera NG. et al., 2018)

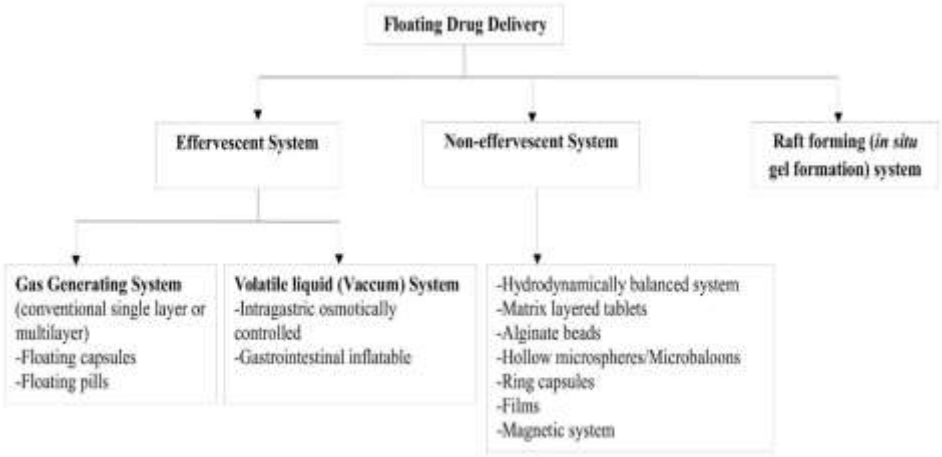

Fig. 2: Classification of floating drug delivery system (FDDS)

1.2.1. Effervescent system floating drug delivery system

These are particular drug delivery system made up of matrix type and a swellable polymer such as methylcellulose and chitosan along with effervescent compounds viz. sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a specific way as once it comes in contact with gastric juice; CO2 gets liberated with entrapment in swollen hydrocolloid to provide buoyancy for dosage form. The basis of the delivery system is on swellable asymmetric triple layer tablet approach design.

1.2.1.1. Gas generating systems

Low-density FDDS is based on the release of CO2 upon contact with gastric fluids after oral administration. The materials are formulated in such a way that after entering in the stomach, CO2 is librated due to reaction with acidic gastric content and which get entrapped in the gel-based hydrocolloid (fig. 3). It produces an upward motion of the dosage form and maintains its buoyancy. Ultimately it causes a decrease in specific gravity of dosage form and hence resulting into a float on the chime. The CO2 generating components are mixed within the tablet matrix in a single layer or multi-layered form to produce gas generating mechanism in hydrocolloid layer, and the drug in the other layer results into a sustained release effect.

1.2.1.2. Volatile liquid containing systems (Osmotically controlled drug delivery system)

This is an osmotically controlled floating system in which a device comprised of a hollow deformable unit in convertible collapsed form. Housing would be attached to its deformable unit and internally divided into a first and second chamber separated by an impermeable, pressure sensitive movable unit. The first chamber usually contains an active drug, while the second a volatile liquid, such as cyclopentane or ether get vaporized at a physiological temperature to produce a gas, enabling the drug reservoir to float. The unit gets expelled from the stomach, with the help of bioerodible plug that allowed the vapour to escape.

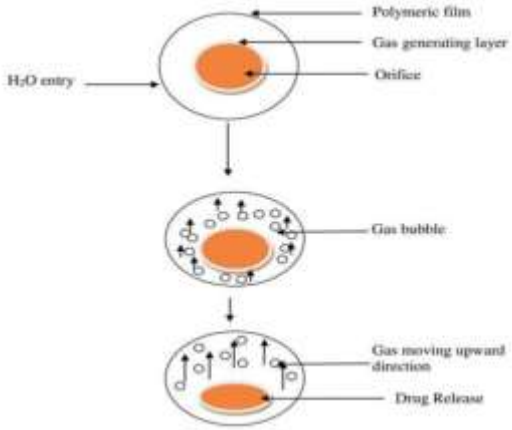

Fig. 3: Mechanism of floatation via CO_2 liberation

1.2.2. Non-effervescent FDDS

Non-Effervescent Floating Drug Delivery Systems comprises a gel-forming (or) swellable cellulose type of hydrocolloids made up of polysaccharide along with matrix forming polymers like polycarbonate, polymethacrylate, and polystyrene. The routine formulation method involves the mixing of the drug with gel forming hydrocolloids that swell in contact with gastric fluid upon oral administration and maintains the integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms.

1.2.2.1. Colloidal gel barrier systems (Hydrodynamic balanced systems)

This system prolongs gastric retention time and maximizes the amount of drug that reaches its absorption site in the solution form. It essentially contains drug with gel-forming hydrocolloids to remain buoyant on the stomach content. Such a system incorporates one or more gel-forming cellulose type hydrocolloid e. g. hydroxypropyl methylcellulose (HPMC), polysaccharides and matrix forming

polymers such as polycarbophil, polystyrene, and polyacrylate. Upon contact with gastro-Intestinal (GI) fluid, the hydrocolloid in the system hydrates to generate a colloid gel barrier to its surrounding.

1.2.2.2. Microporous compartment systems

This technology incorporates the encapsulation technique of a drug reservoir inside a microporous compartment along with pores at top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach, the floatation chamber composed of entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, to the extent that it prevents theirs exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption.

1.2.2.3. Floating Microspheres/Micro balloons

Hallow microspheres also are known as micro balloons are considered as a most efficient buoyant system. It is composed of central hallow space inside the microsphere. Hallow microsphere is loaded with a drug in their outer polymer shelf are fabricated by a novel solvent Diffusion method for emulsion.

1.2.2.4. Alginate beads/Floating beads

Multi-unit floating dosage forms have been developed from calcium alginate spherical beads of about 2.5 mm in diameter and can be fabricated by adding sodium alginate solution into aqueous solution of calcium chloride, resulting in the precipitation of calcium alginate, the beads are further separated, snap-frozen in liquid nitrogen and freeze-dried at 400 °C for 24 h, leads to generation of a porous system. This fabricated system would maintain a floating force for over 12 h and these floating beads provide a longer residence time of more than 5.5 h.

1.2.3. Raft-forming systems

Raft-forming systems are in much attention for the delivery of antacid and drug delivery for gastro infection and disorders. On contact with gastric fluid, a gel-forming solution swells and forms a viscous cohesive gel entrapped with CO2bubbles which generate raft layer on top of gastric fluid, thus facilitates releases drug slowly in the stomach.

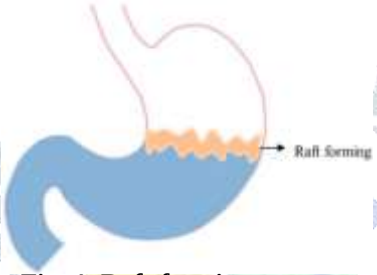

Fig. 4: Raft-forming systems

1.3. Objectives

General Objective

- Formulation andCharacterization of Gastroretentive Beads of Anti-Hypertensive Agent.

Specific Objective

- To retain the drug to specific part of body.
- To reduce dose, dose frequency which ultimately archive patient compliance.
- To increase bioavailability.

1.4. Potential Drug Candidates for Gastroretentive Drug Delivery Systems (Nayak AK. *et al.*, 2010)

- Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
- Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para amino benzoic acid, furosemide, riboflavin etc.
- Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
- Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
- Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

1.5. Drugs those are Unsuitable for Gastroretentive Drug Delivery Systems (Nayak AK. *et al.*, 2010)

- Drugs that have very limited acid solubility e.g. phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

1.6. Factors Affecting Gastric Retention (Rathod HJ. *et al.*, 2016)

1.6.1. Density: Gastric retention time (GRT) is a function of dosage form buoyancy which is dependent on the density. The density of the dosage form must be lower than the gastric contents (1.004 gm/ml).

1.6.2. Size: Dosage form units having a diameter of greater than 7.50 mm are stated to have an improved GRT related with those having a diameter of 9.90 mm.

1.6.3. Shape of the dosage form: Tetrahedron and ring shaped devices having a flexural modulus of 48 and 22.50 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

1.6.4. Single or Multiple unit formulation: Multiple unit formulations show a more expectable release profile and insignificant damaging of performance because of failure of units, allow co-administration of units that have dissimilar release profiles related with single unit dosage forms.

1.6.5. Fed/Unfed state: In fasting conditions, gastrointestinal motility is categorized by periods of strong motor activity that occurs every 1.5 to 2h and if timing of administration of the formulation overlaps with that of the MMC, the gastric retention time of unit can be anticipated to be very short. However, in fed state, MMC is postponed and gastric retention time is significantly longer.

1.6.6. Nature of meal: Feeding of fatty acid salts or indigestible polymers can modify the motility pattern of stomach to a fed state, hence reducing the gastric emptying rate.

1.6.7. Caloric content: GRT can be improved by 4 to 10 h with a meal which is high in proteins and fats.

1.6.8. Age: Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.

1.6.9. Frequency of feed: Gastric retention time can rise by over 400 minutes, when consecutive meals are given related with a single meal because of the low frequency of MMC.

1.6.10. Gender: Mean ambulatory gastric retention time in males (3.4 ± 0.6 hours) is less correlated with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, body surface and height.

1.6.11. Posture: Gastric retention time can be differing between supine and upright ambulatory states of patients.

1.6.12. Concomitant drug administration: Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and Cisapride decrease GRT.

1.6.13. Disease state: Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

1.7. Advantages of floating drug delivery system (Mirmeera NG. et al., 2018)

- Simple and conventional technique for formulation.
- Site-specific drug delivery.
- Controlled delivery of drugs.
- Delivery of drugs for residual action at a specific site in the stomach.
- Improved drug absorption with increased GRT and excess duration of contact of dosage regimen at its target site.
- Minimizing irritation of GIT mucosa by the drugs with slow release rate. Acidic drug substances like aspirin cause irritation to gastric mucosa as it comes in contact. Hence HBS formulation would be beneficial in administration of aspirin and other similar drugs. Administration of prolonged release floating dosage forms, tablet or capsules, causes dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid before getting absorbed in the small intestine with emptying stomach contents. Hence it is expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- When there would be vigorous intestinal movement with short transit time, it might result in a certain type of diarrhea hence poor absorption is expected. Under such conditions, it is advantageous to maintain the drug in floating condition in the stomach for better efficacy.
- In treating gastroesophageal reflux disorders (GERD).
- Ease of administration with higher patient compliance.

1.8. Disadvantages of floating drug delivery system (Mirmeera NG. et al., 2018)

- The major disadvantage of a floating system is due to the necessity of a sufficient level of gastric fluids to float without a sink. However, this limitation can be overcome by coating the dosage form with bio adhesive polymers that easily adhere to gastric mucosa.
- The drugs those get significantly absorbed throughout gastrointestinal tract, with significant first-pass metabolism, are desirable candidate predominantly.
- Certain drugs present in the floating system may causes irritation to gastric mucosal linings.
- Gastric emptying of floating systems may occur at random and highly dependent on its dimensions. Therefore patients should not have dosage prior going to bed.

1.9 Application of floating drug delivery system (Mirmeera NG. et al., 2018)

- FDDS are claimed for the increased efficacy of drugs as recent studies show that the administration of Diltiazem floating tablets twice a day would be more effective compared to normal tablets in hypertensive patients.

- In case of Parkinson patient, FDDS is effective in absorption of the drug over a period of 6-8 h and maintained substantial plasma concentration.
- FDDS is site-specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine, e. g., Riboflavin and Furosemide.
- FDDS served as an excellent drug delivery system in the eradication of Helicobacter pylori, blamed for chronic gastritis and peptic ulcers.
- FDDS are perfect HBS dosage form to provide better delivery of drugs and reduced its GI side effects.

II. DRUG PROFILE OF AMLODIPINE BESYLATE

Amlodipine besylate is the besylate salt of amlodipine, a long-acting calcium channel blocker.

- **Chemical formula:** Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]- 4-(2chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate
- **Empirical formula:** C26H31CLN2O8S
- **Chemical structure:**

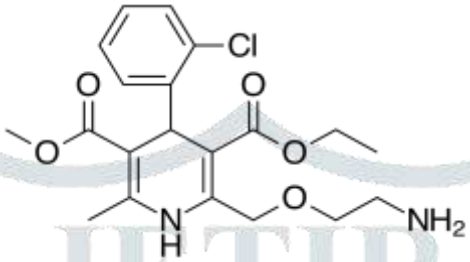

Fig. 5: Amlodipine besylate

- **Molecular weight:** 567.1
- **Description:** White or almost white powder
- **Melting point:** 195-204°
- **Solubility:** Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.
- **Therapeutic category:** Anti –anginal, Anti-hypertensive
- **Half-life:** 30 – 35 hours

- **Mechanism of action (Bulsara KG. et al., 2023)**

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

- Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.
- Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

- **Pharmacokinetics:**

Absorption: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6–12-hour post dose. Absolute bioavailability has been estimated to be between 60 and 80 %.

Distribution: In-vitro studies have shown that approximate 97.5% of circulating amlodipine is bound to plasma proteins.

Metabolism: Amlodipine is extensively metabolized by the liver to inactive metabolites.

Excretion: 10% of the parent compound and 60% of metabolites excreted in the urine.

- **Indications:** Hypertension and prophylaxis of angina

- **Dosage and administration:** Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. Small, fragile, or elderly patients or patients with hepatic insufficiency may be started on 2.5 mg once daily. Pediatric staring dose: 2.5 mg to 5 mg once daily.
- **Side effects**: Amlodipine besylate may cause the following side effects. Most side effects are mild or moderate
  - Headache
  - Swelling of legs or ankles
  - Tiredness, extreme sleepiness
  - Stomach pain, nausea
  - Dizziness
  - Flushing (hot or warm feeling in your face)
  - Arrhythmia (irregular heartbeat)
  - Heart palpitation (very fast heartbeat)

III. MATERIALS & EQUIPMENTS

Table No. 1: List of Material's

Sr. No	CHEMICAL/MATERIAL	SOURCE
1	Amlodipine besylate	Kopalle Pharma Chemicals Pvt. Ltd. CAS No. [9005-38-3]
2	Sodium alginate	Ozone International, Mumbai Batch No: AB-50220520
3	Calcium chloride	OXFORD lab Fine Chem LLP
4	Calcium carbonate	Samar Chemicals

Table No. 2: List of Equipment's

Sr. No	NAME OF THE INSTRUMENT	COMPANY NAME
1	Mechanical stirrer	Remi Elctrotechnik Limited
2	UV spectrophotometer	UV-1800 Shimadzu Spectrophotometer
3	Optical microscope	Samar Optik
4	FT-IR Spectrophotometer	Alpha II E-ATR (OPUS Version 8.5), Lab India Analytical Instruments Pvt.Ltd.
5	Magnetic stirrer	HICON Magnetic Stirrer
6	Dissolution apparatus	ELECTROLAB Tablet Dissolution tester
7	Hot Air Oven	HICON Hot Air Oven

IV. EXPERIMENTAL WORK

4.1. SOLUBILITY PROFILE: Determination of solubility profile of amlodipine besylate. The solubility profile of the selected drug (Amlodipine besylate) was determined.
Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

4.2. PREPARATION OF STANDARD GRAPH OF AMLODIPINE BESYLATE:
4.2.1. Preparation of stock solution: 20 mg of Amlodipine besylate was accurately weighed and dissolved in 10 ml of methanol in 10 ml volumetric flask and the volume was made up to the mark using methanol, to make (2000 µg/ml) standard stock solution (I).
4.2.2. Preparation of sample solution: 1 ml stock solution (I) was taken in another 100 ml volumetric flask and further dilute in 100 ml of methanol to make (20 µg/ml) standard stock solution (II), then final concentrations were prepared 02, 04, 06, 08, 10, 12, 14, 16, 18 and 20µg/ml with 0.1N HCL. The absorbance of standard solution was determined using UV/ Visible spectrophotometer at 236nm. A standard curve was plotted with concentration on X-axis and absorbance on Y-axis.
4.3. Fourier transform Infra-red (FTIR) spectroscopy Study
I.R. spectroscopy can be used to investigate and predict any physiochemical interactions between difference components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients. The aim of the present study was to find out the possible interaction between selected polymer and the drug Amlodipine besylate and also identify the compatibility between the drug and polymer. 10 mg of sample and 40 mg of KBr was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet marker and was compressed at 10 kg/cm2 using hydraulic press. The pellet was kept in a sample holder and scanned from 4000 cm-1 in Alpha II E-ATR (OPUS Version 8.5) FT-IR spectrophotometer. Samples were prepared for pure polymer, pure drug, physical mixture of drug and polymer and drug loaded microparticles. The spectra obtained for these samples were compared and interpreted for the shifting of major functional peaks and disappearance of functional peaks if any.

4.4. Formulation of Amlodipine Besylate Floating Gastroretentive Beads
Sodium alginate solutions of different concentrations were prepared by dissolving required amount of alginate (Table No. 3) in 100 ml of deionized water under gentle agitation. Amlodipine Besylate and calcium carbonate (as gas forming agent) were dispersed in alginate solution under constant stirring for uniform mixing. The dispersion was sonicated for 30 minutes to remove any air bubbles.

The resultant dispersion was dropped through an 18-gauge syringe needle into 100 ml of 1% (w/v) calcium chloride solution containing 10% (v/v) acetic acid at room temperature. Then the beads formed were allowed to remain in the stirred solution for 10 min. The beads were filtered and subsequently oven-dried at 50ºC for 4 hours.

4.5.

Table No. 3: Formulation of Amlodipine Besylate Beads

Sr. No	Formulation code	Sodium alginate (gm)	Drug (gm)	$CaCO_3$(gm)	$CaCl_2$ solution (%)
1	F1	0.25 g	0.5 g	0.5 g	1 %
2	F2	0.5 g	0.5 g	0.5 g	1 %
3	F3	1.0 g	0.5 g	0.5 g	1 %
4	F4	1.5 g	0.5 g	0.5 g	1 %
5	F5	2.0 g	0.5 g	0.5 g	1 %
6	F6	2.5 g	0.5 g	0.5 g	1 %
7	F7	3.0 g	0.5 g	0.5 g	1 %
8	F8	3.5 g	0.5 g	0.5 g	1 %
9	F9	4.0 g	0.5 g	0.5 g	1 %

Evaluation of Amlodipine Besylate Beads

4.5.1. Production Yield

The prepared beads were collected and weighed. Percentage yield was obtained by dividing measured weight of floating beads by the total weight of drug and the polymer.

Percentage yield = (Weight of Beads/Weight of Polymer + drug) x 100

4.5.2. Micromeritic Properties

4.5.2.1. Angle of repose: Angle of repose is a measure to determine the flow ability of the powder or granules. The fixed funnel free standing cone method was used to determine angle of repose. Beads were passed through fixed funnel to make a heap of the predetermined height. The angle made by heap with that of base was determined. The angle of repose of the beads was determined by fixed funnel free standing cone method using the following formula. $\Theta = \tan^{-1} h/ r$ where "h" is height between the lower tip of funnel and the base of heap of beads, and "r" is radius of the base of heap formed. Relationship between angle of repose (Θ) and flow ability is represented in Table No. 4.

Table No. 4: Relationship between Flow properties and Angle of Repose

Angle of repose (Θ)	Flow ability
<20	Excellent
20-30	Good
30-40	Passable
>40	Very poor

4.5.2.2. Bulk density and tapped density: To calculate the bulk density and tapped density, the beads were weighed, and transferred to a measuring cylinder. The volume occupied by beads was noted as bulk volume and the cylinder were tapped until the constant volume was achieved, and this was noted as tapped volume. The values of bulk density and tapped density were calculated by using following equations:

Bulk density = weight of powder/ volume of the packing

Tapped density = weight of powder/ volume of the packing

4.5.2.3. Compressibility Index: Carr's compressibility index were determined from the value of bulk density and tapped density using following formulae.

Car's compressibility index = {(tapped density − bulk density)/ bulk density}x 100

4.5.2.4. Hausner's ratio: Hausner's ratio were determined from the value of bulk density and tapped density using following formulae.
Hausner's ratio = tapped density/ bulk density
The values within range 5–15% of Carr's index and values less than 1.25 of Hausner's ratio showed good compressibility of the sample.

4.5.3. Partical Size Determination
The particle sizes of the floating beads were obtained by optical microscopy method. By using stage micrometer eye piece micrometer was calibrated. The beads were mounted onto the slide and mean particle size was determined by the measuring the sizes of hundred particles.

4.5.4. Determination of Swelling Index
Beads were studied for swelling characteristics. Samples from drug-loaded beads were taken, weighed and placed in the wire basket of USP dissolution apparatus-I. The basket containing beads was put in a beaker containing 100 mL of 0.01 N HCl maintained at 37 ◦C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling Index was calculated as per the following formula:
Swelling Index = weight of wet beads/ weight of dried bead x 100

4.5.5. Percentage of Drug content/ Drug loading amount (%)
Drug content estimation was done by stirring 20 mg beads in sodium citrate solution (1%, w/v) until complete dissolution occurs. Methanol was added to the sodium citrate solution to gel the dissolved Sodium alginate and further solubilize drug. This solution was then filtered to get the drug solution. The filtrate was then suitably diluted with 0.01 N hydrochloric acid, and absorbance was taken at 236nm.
Actual drug content (%) = (Mact/Mms) x100

4.5.6. Percentage of Drug entrapment (%)
Entrapment efficiency (%) = (Mact/ Mthe) × 100
Were,
Mact is the actual drug content in weighed quantity of beads, Mms is the weighed quantity of dried beads and
Mthe is the theoretical amount of drug in beads calculated from the quantity added in the process.

4.5.7. In-vitro Buoyancy Study
In-vitro buoyancy studies were done using dissolution test apparatus USP type II (rotating paddle). 50 beads were taken and added to the dissolution flask containing 0.1 N HCl as medium (900 ml) containing 0.02% tween 80. Temperature was maintained at 37 ºC ± 0.5 ºC. Paddle maintained at 100±5 rpm. At hourly intervals stirring was stopped for 2 min and number of settled beads was counted visually. The floating and the settled portion of beads recovered separately.
Buoyancy percentage was calculated as the ratio of the number of beads that remained floating and the total number of beads taken.
Buoyancy percentage (%) = (No. of beads remained floating/ Total no. of beads) x100.

4.5.8. In-vitro Drug Release
In vitro dissolution studies were performed for all the formulations using USP apparatus II (paddle type). An accurately weighed floating alginate beads were taken into 900 ml 0.1N HCL (pH 1.2). The temperature was maintained at 37ºC and stirred at a speed of 50 rpm. At 30 minutes time intervals, a 10-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37ºC. The collected samples were filtered and analysed at 236nm using UV-visible spectrophotometer against 0.1N HCL (pH 1.2) taken as blank.

5.0. Stability Studies
The optimized formulation was weighed and wrapped in a butter paper and placed in petri-dishes. These containers were stored at 40°C±2°C at 75% RH ± 5 % for a period of three months. Then beads were withdrawn at the intervals of one month and analyzed for physical changes (such as color and texture), size, actual drug content and in vitro drug release.

V. RESULT

5.1. Preformulation Studies

5.1.1. Color and Appearance
Amlodipine besylate is an almost white powder.

5.1.2. Melting Point determination
The melting point for Amlodipine besylate was found to be 200-202°C which complies with the reported literature.

5.1.3. Solubility determination

Table No. 5: Solubility Profile of Amlodipine Besylate

Solvent	Solubility
Water	Slightly soluble
Methanol	Freely soluble
0.1 N HCL	Soluble

5.4. Fourier transform Infra-red spectroscopy (FTIR Spectroscopy)

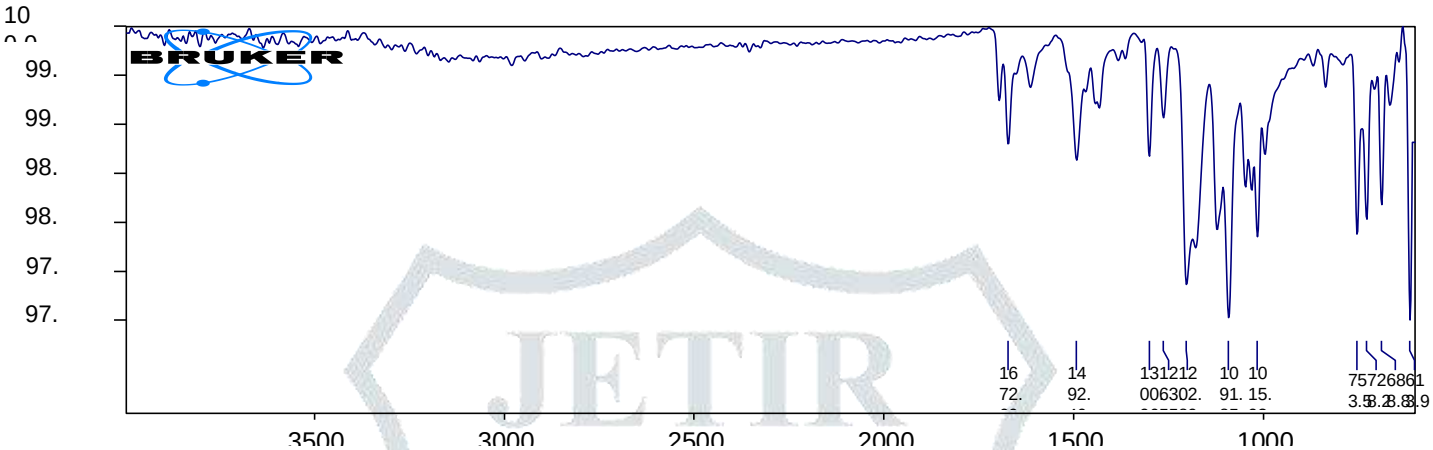

Fig. 06: FTIR spectra of Amlodipine besylate

Table No. 06: FTIR spectra of Amlodipine besylate

Sr. No.	Absorption Ranges(cm^{-1})	Observed Peaks (cm^{-1})	Type of Vibration
1	650-610	613.93	C-H Bend
2	600-800	753.53	C-Cl Stretch
3	1300-1000	1300.96	C-O Stretch
4	1550-1450	1492.46	N-H Bend
5	1675-1600	1672.60	C-C=C Symmetric Stretch

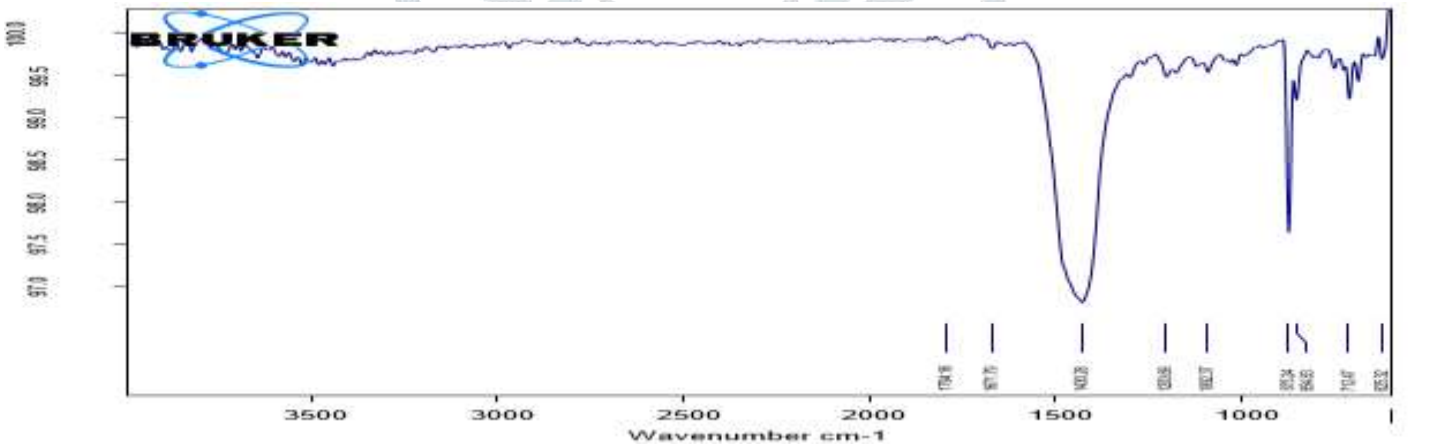

Fig. 07: FTIR spectra of Physical Mixture

Table No. 07: FTIR spectra of Physical Mixture

Sr. No.	Absorption Ranges(cm^{-1})	Observed Peaks (cm^{-1})	Type of Vibration
1	600-800	712.47	C-Cl Stretch
2	1300-800	875.24	C—C Stretch
3	1300-1000	1203.69	C-O Stretch
4	1470-1430	1430.28	N-H Bend
5	1675-1600	1671.79	C-C=C Symmetric Stretch
6	1755-1650	1794.16	C=O Stretch

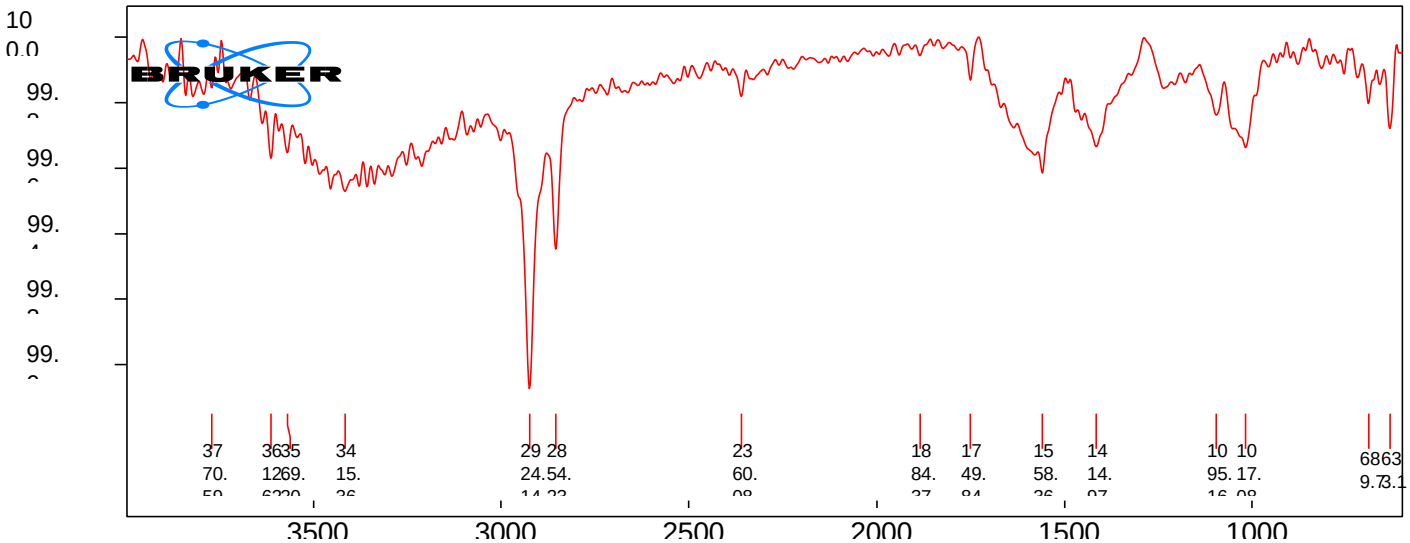

Fig. 08: FTIR spectra of Amlodipine Besylate Beads

No. 08: FTIR spectra of Amlodipine Besylate Beads

Sr. No.	Absorption Ranges(cm^{-1})	Observed Peaks (cm^{-1})	Type of Vibration
1	800-600	689.77	C—Cl Stretch
2	1300-1000	1095.16	C-O Stretch
3	1640-1550	1558.36	N-H Bend
4	1755-1650	1749.84	C=O Stretch
5	2700–2250	2360.08	N—H Stretch
6	3400-2400	2854.23	Hydrogen-bonded O-H Stretch
7	3400-2400	2924.14	Hydrogen-bonded O-H Stretch
8	3500-3100	3415.36	N-H Stretch
9	3700-3500	3569.2	O—H Stretch

5.5. Standard Calibration Curve of Amlodipine Besylate in 0.1N HCL Buffer

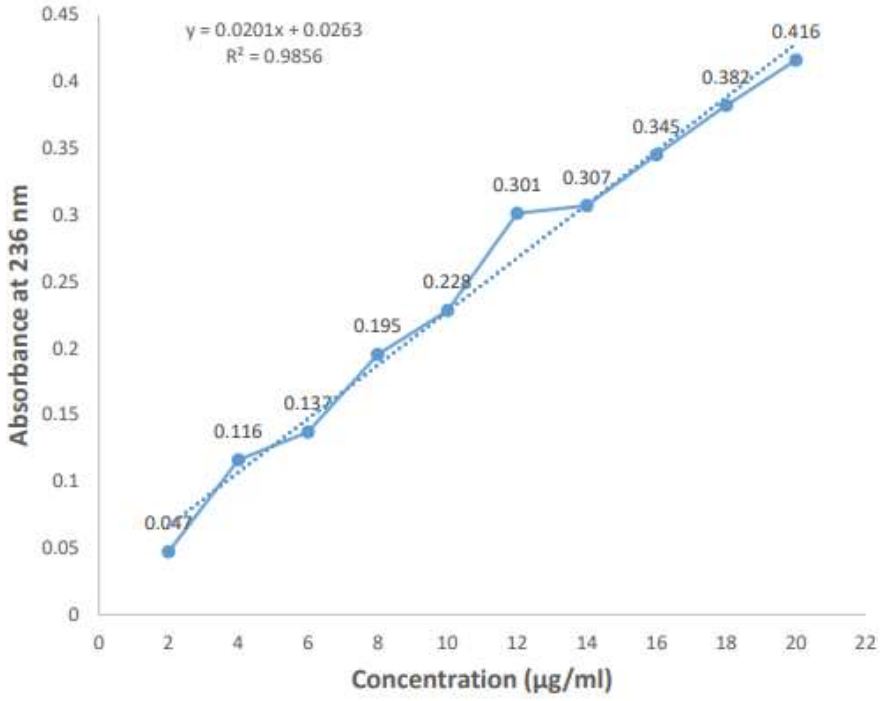

Fig. 09: Standard Calibration Curve of Amlodipine Besylate in 0.1N HCL Buffer

5.6. Evaluation Of Amlodipine Besylate Microparticles

5.6.1. Production Yield

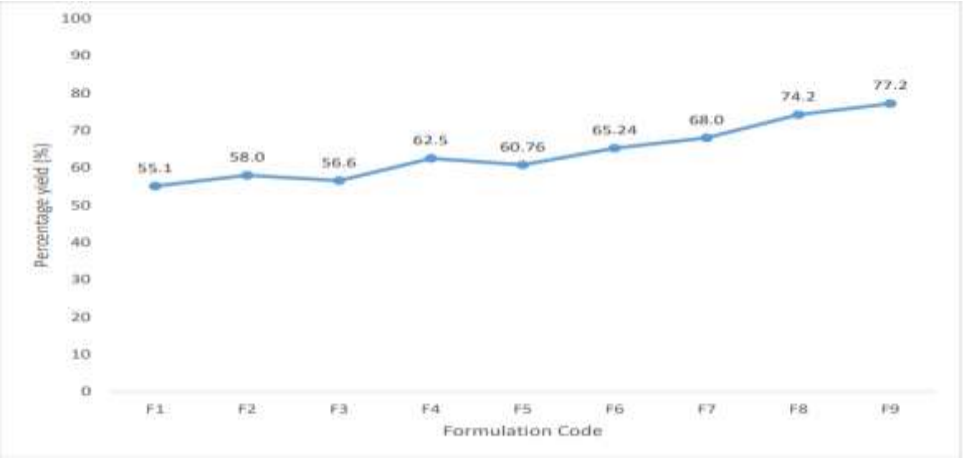

Fig. 10: Production Yield of Amlodipine Besylate Beads

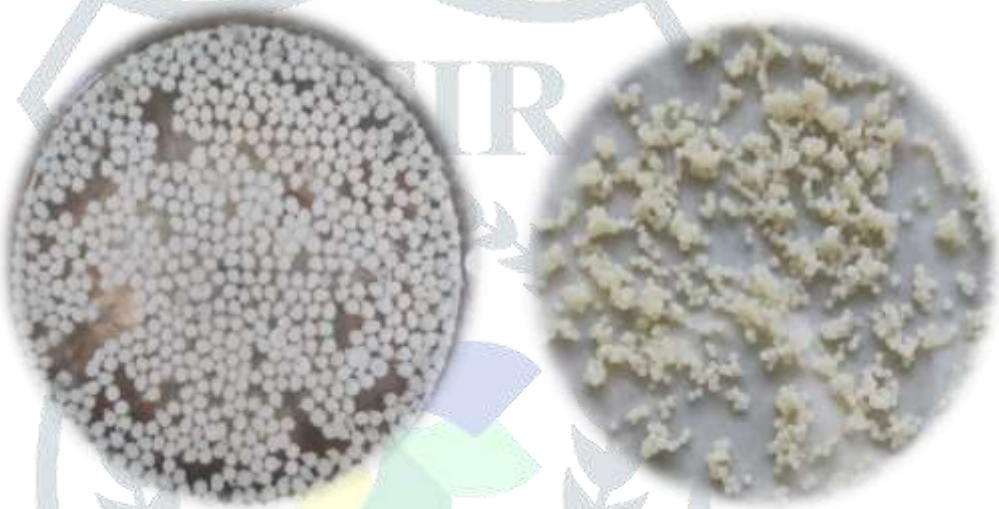

Fig. 11: Formulated Amlodipine Beads

Fig.12: Surface analysis for formulation F 5

5.6.2. Micromeritic Properties

Table No. 09: Micromeritic Properties of Amlodipine Besylate Beads

Formulation Code	BULK DENSITY	TAPPED DENSITY	CARR'S INDEX	HAUSNER'S RATIO	Angle of repose (Ɵ)
F1	0.48±0.01	0.56±0.04	14.29±0.02	1.17±0.04	19.26±0.41
F2	0.55±0.03	0.67±0.02	17.91±0.03	1.21±0.01	17.02±0.24
F3	0.62±0.04	0.71±0.06	12.68±0.08	1.15±0.04	21.28±0.12
F4	0.75±0.06	0.83±0.02	9.64±0.04	1.11±0.05	26.8±0.61
F5	0.85±0.01	0.9±0.02	5.66±0.09	1.06±0.01	35.36±0.82
F6	0.82±0.03	0.87±0.01	6.32±0.35	1.07±0.02	28.87±0.43
F7	0.79±0.02	0.86±0.02	7.9±0.06	1.09±0.06	31.51±0.52
F8	0.82±0.07	0.89±0.02	7.78±0.34	1.08±0.08	29.82±0.26
F9	0.83±0.02	0.88±0.05	5.68±2.9	1.06±0.03	29.67±0.79

Each value is average of three separate determinations ± standard deviation (SD)

5.6.3. Particle Size Determination

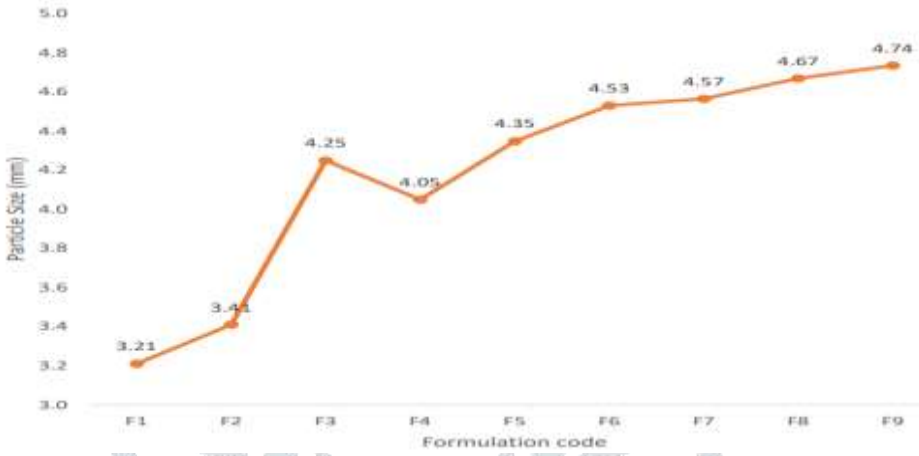

Fig. 13: Particle size Determination of Amlodipine Besylate Beads

5.6.4. Determination of Swelling Index (%)

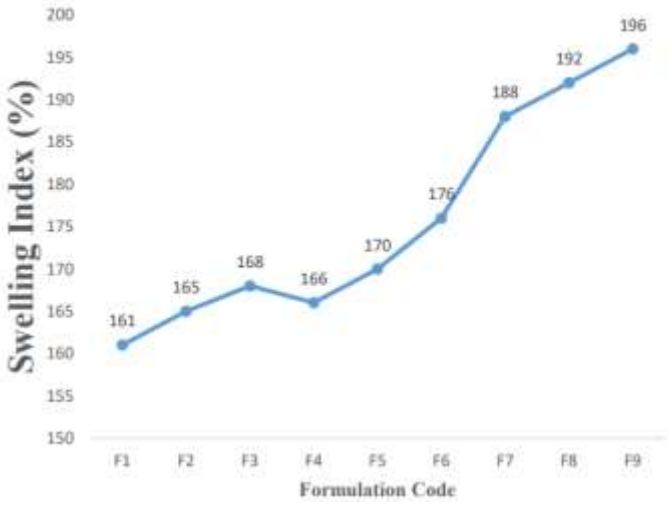

Fig. 14: Swelling Index (%) of Amlodipine Besylate Beads

5.6.5. Percentage of Drug content/ Drug loading amount (%)

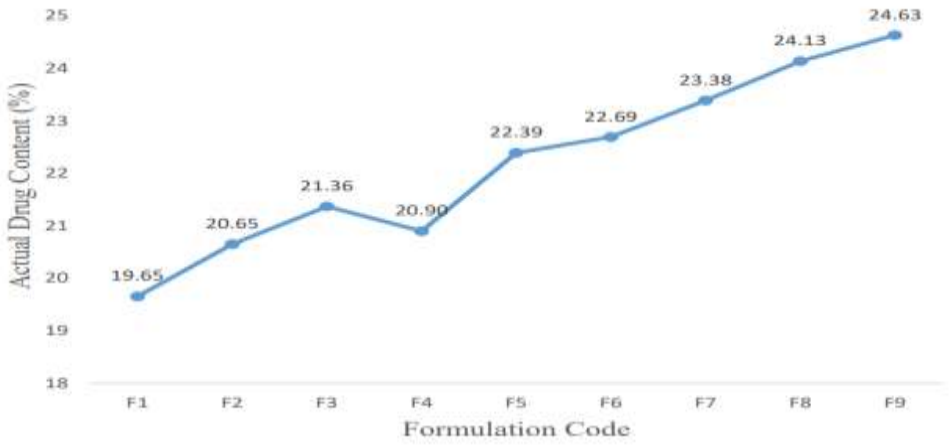

Fig. 15: Percentage Drug loading of Amlodipine Besylate Beads

5.6.6. Percentage of Drug entrapment (%)

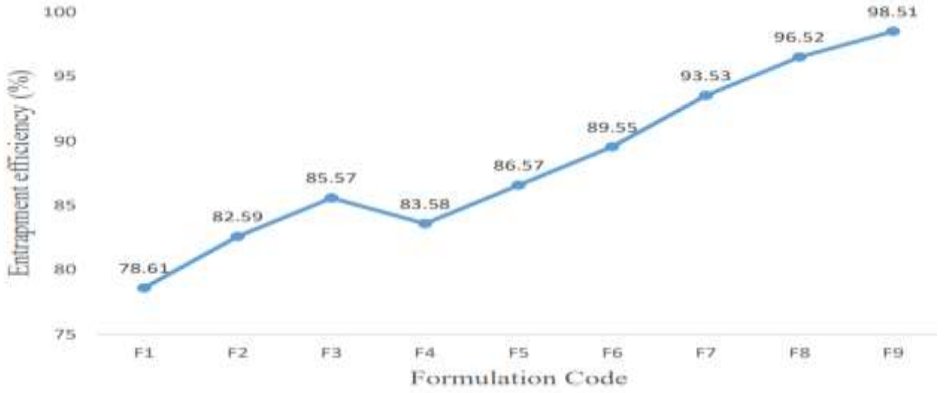

Fig. 16: Entrapment Efficiency of Amlodipine Besylate Beads

5.6.7. In-vitro Buoyancy (%) Study

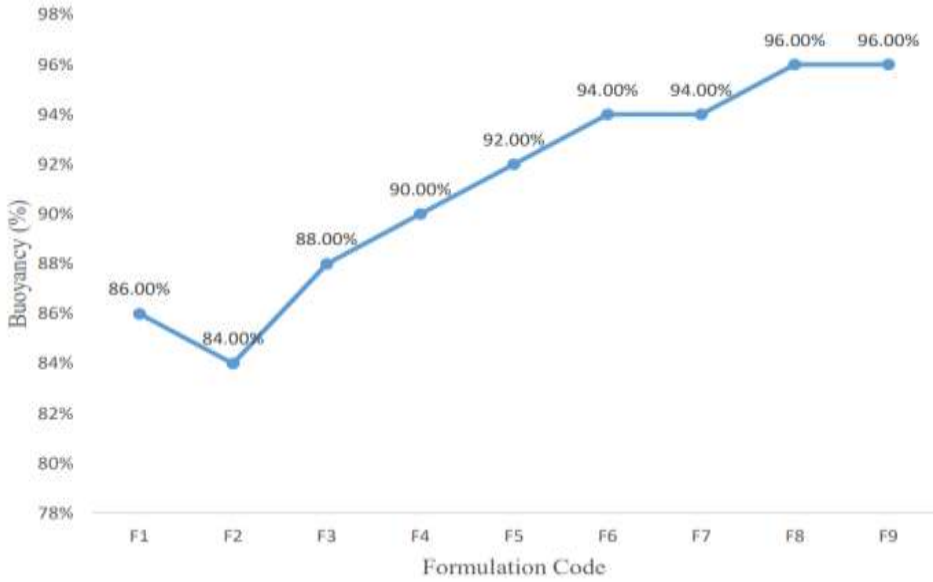

Fig. 17: Entrapment Efficiency of Amlodipine Besylate Beads

5.6.8. In-vitro Drug Release

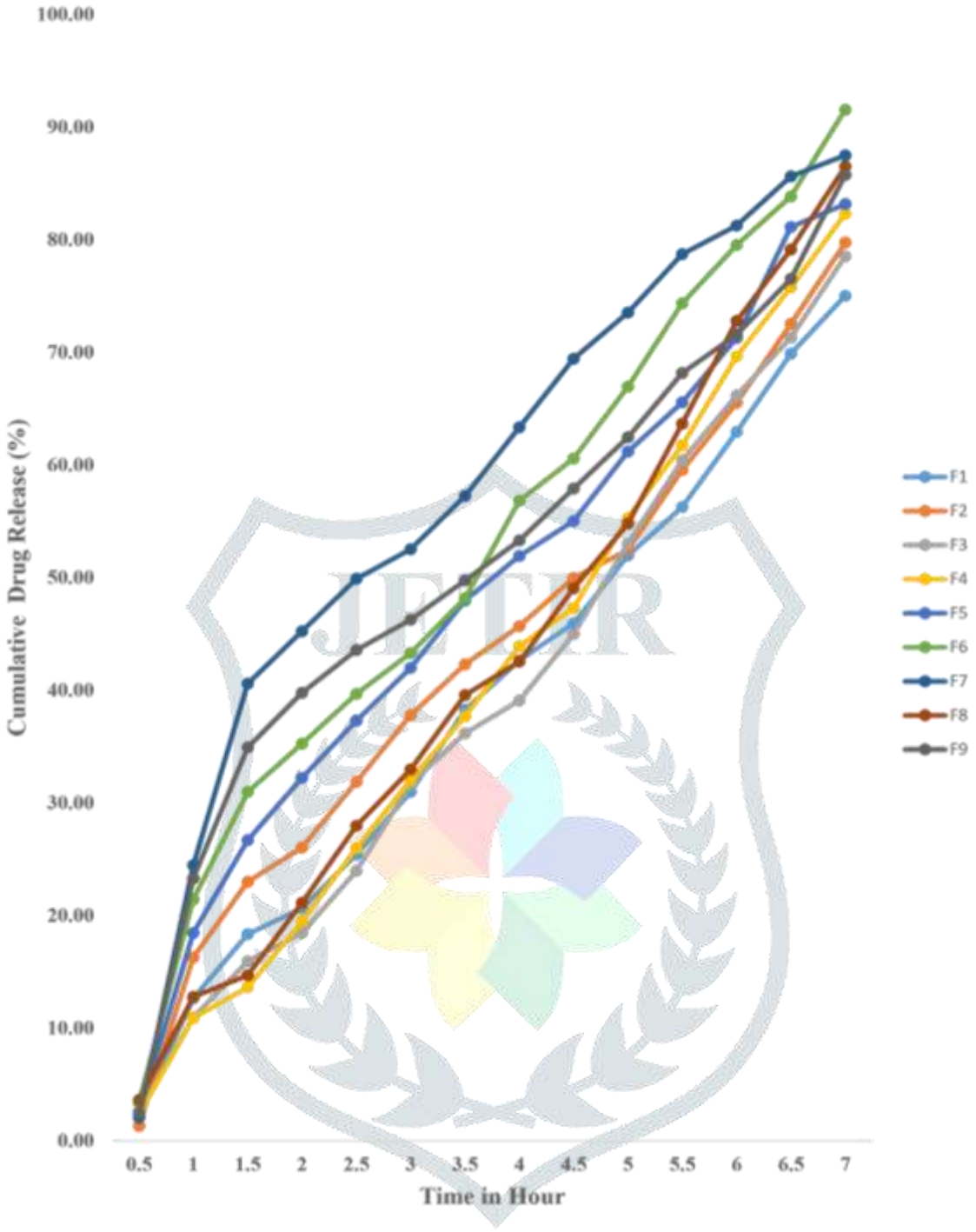

Fig. 18: In-Vitro Dissolution Profile of Amlodipine Besylate

5.6.9. In-vitro Drug Release Kinetics

Table No. 10: Correlation Coefficient and release rate of Amlodipine besylate containing Alginate beads (F6)

Formulation Code	Alginate: Drug	Correlation Coefficient (R^2)			% Drug Release after 7 hr
		Zero Order	First Order	Higuchi	
F6	2.5:1	0.9735	0.9842	0.8622	91.54

5.7. STABILITY STUDIES

The stability studies indicate the significant difference between the release patterns of beads at 40°C±2°C at 75% RH ± 5 % for 02. The stability studies were carried out at and optimized formulation, i.e, from F6 formulation. The formulation was store at 40°C±2°C at 75% RH ± 5 % for 01-02 months. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

.

Table No. 11: Stability Studies for Formulated floating Beads of Amlodipine Besylate (F6)

Characters	Initial month	After 1 month	After 2 months
Appearance	Spherical	Spherical	Spherical
Solubility	1.2 pH HCl	1.2 pH HCl	1.2 pH HCl
Colour	Half white	Half white	Half white
Particle size	4.74±0.51 mm	4.79±0.12 mm	4.82±0.12 mm
Swelling index	196	196	194

Table No. 12: In-vitro drug release under Stability Studies for 01-02 month

Time (Hr)	Initial month	After 1 month	After 2 months
0.5	3.36±0.001	4.10±0.003	3.16±0.001
1	21.40±0.001	21.11±0.001	20.76±0.003
1.5	30.97±0.001	27.96±0.003	28.18±0.002
2	35.25±0.001	35.96±0.002	36.42±0.002
2.5	39.67±0.001	39.21±0.001	40.16±0.001
3	43.29±0.015	43.57±0.001	44.12±0.002
3.5	48.17±0.001	51.63±0.02	49.35±0.02
4	56.82±0.007	58.80±0.013	57.85±0.01
4.5	60.57±0.003	61.28±0.002	60.95±0.01
5	66.95±0.008	65.87±0.007	64.96±0.004
5.5	74.35±0.001	75.34±0.005	75.74±0.002
6	79.54±0.001	80.64±0.001	80.76±0.001
6.5	83.84±0.003	84.42±0.003	84.62±0.001
7	91.54±0.001	91.72±0.001	90.65±0.003

VI. DISCUSSION

The principle objective of this research study was to formulate and characterize Gastroretentive Beads of Anti- Hypertensive Agent (Amlodipine besylate) using sodium alginate polymer. Various batches were made form batch (F1 to F9).

To achieve the above objective, sodium alginate was found to be suitable polymer due to its biocompatibility, good stability, and ease of fabrication.

The drug was received from Kopalle Pharma Chemicals Pvt. Ltd. Batch No: AB-50220520. Manufacturing Date: May-2020. Expiry Date: Apr-2024. With certificate that complies tests result.

Alginate beads were prepared by ionotropic external gelation technique using CaCl2 as crosslinking agent. The prepared Gastroretentive Beads were evaluated for percentage yield, Micromeritic properties such as Angle of repose, Bulk density, tapped density, compressibility index, Hausner's ratio, particle size, Morphology analysis, swelling index (%), Drug content (%), Drug Entrapment efficiency (%), Buoyancy studies, in-vitro drug release and finally stability studies.

FT-IR study was carried out to see whether there is any incompatibility between drug and polymer and also to know whether there is complete physical adsorption of drug on to the polymer matrix without any mutual interaction. The results obtained from the IR studies are shown in Fig No.08 Amlodipine showed prominent peaks. The same peaks were also observed in the physical mixture of drug & polymer and drug loaded Gastroretentive Beads. After interpretation through the spectra, it was confirmed that there was no major shifting of functional peaks between the spectra of drug, polymer, physical mixture of drug and polymer and drug loaded Beads.

The Drug excipients interaction was studied using (FT-IR) Fourier transformed infrared spectroscopy. The characteristic peaks of the drug (Fig No. 06) were observed at wave numbers 613.93cm-1, 753.53cm-1, 1300.96cm-1, 1492.46 cm-1, 1672.60 cm-1 in the functional group region of the pure drug spectrum. These characteristic peaks in the spectrum correspond to 712.47cm-1, 1203.69 cm-1, 1671.79 cm-1, 1794.16 -1 for stretching vibration of functional groups (C- Cl, C-O, C-C=C Symmetric Stretch, C=O). These characteristic peaks also appear in the spectrum of amlodipine beads formulation at the same range of wave numbers indicating that there was no interaction between the drug and formulation excipients.

The low percentage yield in some formulation may be due to beads lost during the washing process. Percentage yield of all formulations varies from F1 to F9 which are shown in fig No.10 and indicates that F9 shows highest percentage yield of 77.2%.

Angle of repose value of all the formulations were in the range of 17.02±0.24 to 35.36±0.82, which shows free flow nature of the prepared beads, the results were shown in Table No. 09.
It has been stated that, bulk density values less than 1.2 gm/cm3 indicate good glow and values greater than 1.5 gm/cm3 indicate poor flow characteristic. It is seen from Table No. 09 that the bulk density values are less than 1.2 gm/cm3 indicating good flow characteristics of the beads.
The Carr's index of all the formulations was less than 20, i.e from 5.66±0.09 to 17.91±0.03, which indicates good flow properties and compressibility.
Hausner's ratio was ranging from 1.06±0.01 to 1.21±0.01 i.e., all the preparation showed that they had good flow properties. The improvement in flow properties suggests that the beads can be easily handled during processing. The results were shown in Table No. 09.
In the study of Partical size, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases, viscosity increases, which influences the interaction between disperse phase and dispersion medium and affects the size concentration, there was increase in relative viscosity so as resulted in an increase in mean particle size. The particle size of drug loaded batches, ranges from 3.21±0.48 mm to 4.74±0.51 mm. The mean particle size of all the formulations was shown in fig No. 13. The surface morphology it was performed on the prepared Amlodipine besylate beads to access their surface and morphological characteristics as shown in Fig. 12 indicate that beads were spherical and discrete.
The swelling index for all F1 to F9 formulations are ranges from 161±0.30 to 196±0.35%.
Loading efficiency of drug loaded batches are found to be 19.65±0.08 % to 24.63±0.04%. The drug loading efficiency of all formulations were shown in fig. No. 15 which indicates that the highest drug loading was found to be F9 as 24.63±0.04%.
The beads exhibited an increase in drug entrapment with an increase in the proper ratio up to a particular concentration. A decrease in drug entrapment was observed after that point due to saturation capacity of the polymer. The entrapment efficiency of drug loaded batches, ranges from 78.61±0.001 to 98.51±0.001. The results were shown in fig No. 16.
The maximum drug entrapped in the F9 formulation, 98.51±0.001%. The results are shown in fig No. 16.
In the study of Buoyancy, the values range from 86.00% to 96.00%.
Cumulative percentage release of amlodipine besylate loaded Beads carried out in 1.2 pH HCl upto 7, hours. The release rate was decreased by increasing the polymer concentration and particle size. The rapid release was obtained in formulation F1 due to low concentration of polymer and size of the particle results in higher contact of dissolution medium due to increased surface area.
Drug release from all the formulations was slow and sustained over 7 hours. By the end of 7 hours the polymer/drug F6 showed better sustained release pattern and found to be most suitable among all the other formulations.
The decrease in drug release was due to simultaneous increase in alginate amount. Because the more the amount of alginate, more would be the cross-linking between sodium alginate and calcium chloride; hence more drug would remain entrapped and decrease the release. In the absence of gas-forming agent the release rate was very slow. CaCO3 is present as an insoluble dispersion in neutral pH aqueous alginate solution. However, in acidic media, the CaCO3 becomes water soluble. After studying the drug release kinetics, it was observed that the F6 formulation follow First order kinetics (Table No. 10). In-vitro release profiles of all the formulations have been shown in Fig. 18.
Stability studies of formulated Amlodipine beads was done 40°C±2°C at 75% RH ± 5 % for 01-03 months. Evaluating for month one and two, founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, in-vitro drug release. Decided to do in-vivo studies in future.

VII. SUMMARY AND CONCLUSION

Floating amlodipine besylate beads using polymer sodium alginate was developed by ionotropic gelation technique using CaCl2 as cross-linking agent and it was found to be a suitable floating oral drug delivery system in terms of particle size distribution, drug loading capacity and Sustained release. Amlodipine besylate beads obtained was spherical in shape, discrete and free flow in nature. Amlodipine besylate was the prototype of Calcium Chanel blocker used in the treatment of cardiovascular system especially hypertension. Amlodipine besylate possess the mean half-life of 30-35 hours and 97.5% of circulating amlodipine is bound to plasma proteins, Hence, it was chosen as the good candidate for the Controlled release gastroretentive beads in order to improve the bioavailability and prolong period of drug released.
Chemical compatibility study was performed using FTIR spectroscopy and FTIR studies revealed that there was no change in major peaks thus confirming no interaction between the drug and excipients.
On comparing the major criteria in evaluation such as percentage yield, drug content, entrapment efficiency and In-Vitro drug released profile, the formulation F6 was selected as the best formulation, as it showed a good Controlled drug release pattern up to 07 hrs.
Stability studies of formulated Amlodipine beads was done at 40°C±2°C at 75% RH ± 5 % for a period of three months. Then beads were withdrawn at the intervals of one month and in evaluation founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, in-vitro drug release. Decided to do in-vivo studies in future.

VIII. Acknowledgment

First and foremost I feel always deeply indebted to Bappa (Ganesh Ji) who helped me to achieve this research. I dedicate this research to my parents who implicated seeds of the success in myself and encouraged me to continue the study until to reach the specialization degree in Pharmaceutics. I would like to express my great thankful to my supervisor Professor Dr. Ram D. Bawankar and Principal Dr. D.R. Mundhada who kindly supervisd and motivated me to performance this research, thanks for their support. Also Special Thanks to Kumudini D. Selukar for amazing lectures and discussions! I learned a lot and benefited from your cours. I would like to thank all my colleagues for helping me in preparation this research. I am greatly honored to express my sincere appreciation to all who contributed to this work for devoting their precious time to help me until complete this study.

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