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Gastro retentive Ethyl Cellulose Floating Microspheres containing ATENOLOL

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Abstract
Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Incorporation of the drug in a controlled release gastro -retentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recently developments of Stomach Specific FDDS are discussed that helps to overcome physiological adversities like short gastric residence times and unpredictable gastric emptying times

1. Introduction

Oral drug delivery is the most desirable and preferred method of administering therapeutics agent for their systemic effect. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms. This system has been of limited success. Oral dosage forms have proved to be successful in achieving a plethora of controlled release objectives ranging from immediate release to site specific delivery. An although tremendous advances have been seen in oral controlled drug delivery system during last two decades. Oral formulations are being developed into different types, such as controlled release delayed release, fast dissolving and taste masking formulation and other delivery technologies are being tried to deliver already existing and new drug molecules, oral formulations still control more than 60% of the market inability to restrain and localize the DDS. Within the desired this approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility.

2. Gastro-Retentive Drug Delivery Systems

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Slowed motility of the gastrointestinal tract concomitant administration of drugs or intestine. Pharmaceutical excipients also increase gastric retention of drug.

3. Approaches to Gastro-Retentive Delivery Systems Drug

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The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, forms may be achieved by the mechanism of expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs These efforts resulted in GRDFs that were designed, in large part, based on the following. (Figure 1)

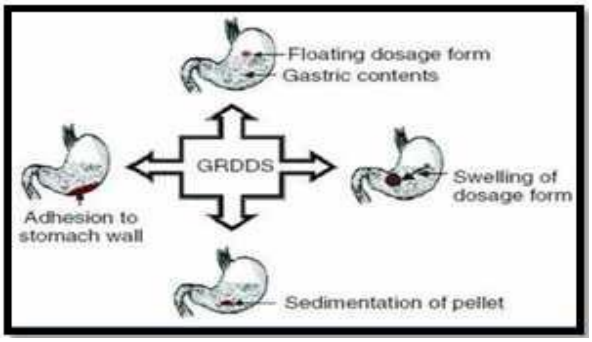


Fig: 1. Different Approaches of Gastric Retention

3.1 Floating Drug Delivery System

Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control ofluctuations in plasma drug concentration.

3.2 Basic GIT Physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus). The design and

evaluation of FDDS is based on anatomy and physiology of GIT. The stomach is J shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac regions of abdominal cavity.The Gastrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat pharynx), oesophagus, stomach, small intestine(consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum.The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region (Figure 2). The stomach is an organ with a capacity for storage and mixing. The average length of the stomach is about 0.2 meter and the apparent absorbing surface area is about 0.1 sq. meter8. The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emp-tying by propelling actions

3.3 Process of Gastric Emptying

Gastric emptying occurs in both the fasting and fed states. During the fasting and fed states. an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is or migrating myloelectric cycle (MMC) which is further divided in to four phases9, 10. After the ingestion of a mixed meal, the pattern of fcontractions changes from fasted to that of fed state which is also termed as digestive motility pattern figure 3

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles

3.4 Evaluation of Floating Drug Delivery Systems

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

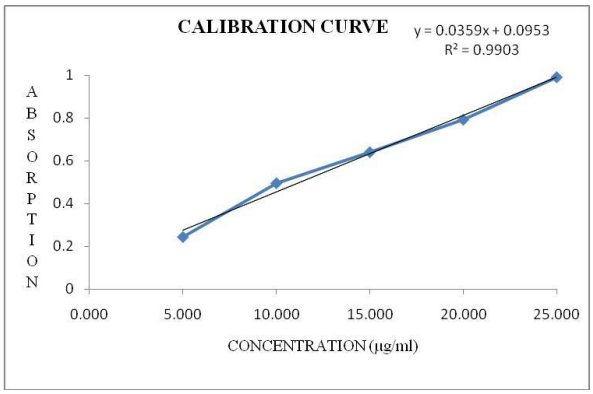
A. In Vitro Methods

Floating lag time and floating time: The test for floating time measurement is usually performed in stimulated gastric fluid or The test for floating time measurement is usually performed in stimulated gastric fluid or1 N HCl maintained at 37 0C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as dissolution medium at 37 0C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. The system to check continuous floating behaviour contains a stainless steel basket connected to a metal string and suspended from a Sartorius electronic balance. A lotus- spread sheet could automatically pick up the reading on the balances .Test medium is (maintained was 900 ml simulated gastric fluid pH 1.2) maintained at 37°C, data was collected at30 sec interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.

a. Dissolution Study

Gohel et al proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. The proposed test may show good in vitro in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device was observed with the USP dissolution apparatus. The drug release followed zero-order kinetics in the proposed method. The proposed test may show good in vitro in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

b. Standard Curve of ATENOLOL



c. Swelling Index

An in vitro measuring apparatus has been conceived to determine the real floating capabilities conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be

used to quantify its floating or no floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F bouy) and gravity (F grav) forces acting on the object as shown in the equation

F = F buoy – F grav

F = d f gV – d s gV = (d f - d s) gV

F = (df – M / V) gV

In which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d f is the fluid density, d s is the object density, M is the object mass, and V is the volume of the object. By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sinks.

B. In vivo Method

1) X-Ray method

X-Ray is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid form enables it to be visualized by Xrays.

2) Gamma-Scintigraphy

Gamma -Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastro-retentive formulation in healthy Volunteers small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of gamma - scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation radiopharmaceutical Sm, is compounded into DF during its preparation .The main drawbacks of gamma - scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radio- pharmaceuticals..

3) Gastroscopy

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation

4) Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during imaging of some abdominal organ. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

Drugs Used In the Formulations of Stomach SpecificTable1:

Types of dosages forms

1. Microspheres- Aspirin, Griseofulvin, P-nitro aniline, Ibuprofen, Ketoprofen,
2. Granules- Diclofenac sodium, Indomethacin, Prednisolone.
3. Films- Cinnarizine, Drug delivery device.
4. Capsules- Chlordiazepoxide HCl, Diazepam, Furocemide, L-Dopa and Benserazide,
5. Tablets/Pills- Acetaminophen, Aspirin, Amoxycillin trihydrate, Ampicillin, Atenolol, Captopril, Ciprofolxacin, Chlorpheniramine maleate, Cinnarizine, Furosemide, 5-Fluorouracil, Isosorbide mononitrate, Diltiazem, Isosorbide dinitrate, Nimodipine.

4. Atenolol Drug Profile

Atenolol is a beta-1 selective (Cardioselective) b adrenergic receptor blocking agent. It does not have membrane stabilizing and intrinsic sympathomimetic (partial agonist) activities. Besides being one of the most widely used b-blockersclinically, it has often been used as a reference drug in randomized controlled trials of hypertension. The present review focuses on pharmacological profile of atenolol discussing its structure, pharmacokinetics and metabolism, pharmacodynamics, dosage, administration, adverse effects and contraindications

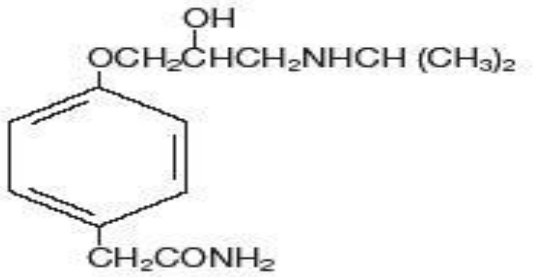
4.1 Structure

Atenolol may be chemically described as a benzene acetamide, 4-[21 – hydroxy – 31 – [(1- methyl ethyl) amino] propoxy]. The molecular and structural formula is as shown Figure 1. Atenolol (free base) has a molecular weight of 266.34. It is a relatively polar hydrophilic compound with water solubility of 26.5 mg/ml at 370C and a log partition coefficient (octanol / water) of 0.23. Lipid insoluble hydrophilic compounds (atenolol, sotalol, nadolol) are excreted only by the kidneys and have low brain penetration. Metoprolol and propranolol are more lipophilic compounds and so are more often used in migraine and have more cerebral side effects of b-blockers.

4.2 Pharmacokinetics and Metabolism

Atenolol is incompletely absorbed (about 50%), but most of the absorbed dose reaches the systemic circulation. Peak blood levels are reached between two and four hours after ingestion. Unlike propranolol or metoprolol, atenolol undergoes little or no metabolism by the liver and the absorbed portion is eliminated by renal excretion. Over 85% of intravenous dose is excreted in urine within 24 hours compared with 50% for an oral dose. Only a small amount (6-16%) is protein-bound resulting in relatively consistent plasma drug levels with about a four-fold inter-patient variation. The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration following intravenous administration peak plasma levels are reached within 5 minutes. Declines

from peak levels are rapid (5 to 10 fold) during the first 7 hours. Following oral doses of 50 mg or 100 mg both b-blocking and anti-hypertensive effects persist for at least 24 hours. The drug accumulates in patients with renal failure and dosage should be adjusted for patients whose creatinine clearance is less than 35 mL/min/1.73m2.



4.3 Pharmacodynamics

Beta -blockers are classified into three generations. Atenolol (2nd generation b-blocker) is a beta 1 selective antagonist (cardio selective); however this selectivity is not absolute and at higher doses atenolol inhibits b-2 Adrenoceptors chiefly located in bronchial and vascular musculature. It has no partial agonist and intrinsic sympathomimetic activity and so results disturbances in lipid profile (unlike acebutolol). CVS: The major therapeutic effects are on cardiovascular system (Table1). It is important to distinguish these effects in normal subjects from those in subjects with cardiovascular disease (CVD) such as hypertension or myocardial ischemia. The negative ionotropic and chronotropic effects are modest when simulation of b-receptors is low. However, in presence of activated sympathetic nervous system as during exercise or stress; atenolol attenuates the expected rise in heart rate (HR) and myocardial contractility. The exercise-induced increase in cardiac output (CO) is less affected because of an increase in stroke volume. It decreases the effects of catecholamine on determinants of myocardial oxygen consumption (heart rate; contractility and systolic pressure), hence improving the relationship between cardiac oxygen supply and demand; exercise tolerance is improved in patients with angina. The duration of action is dose-related and also bears a linear relationship to the logarithm of plasma atenolol concentration. Besides reducing HR, cardiac index and blood pressure; effects on total peripheral resistance have been documented; though less uniformly. Acute intravenous administration is usually followed by increase in total peripheral resistance of 20-30%.6 Studies during chronic oral administration of atenolol have found either no change in vascular resistance7-8 or an increase in about 5%. In long term studies, Lund Johansen10 has demonstrated that haemodynamic effects of atenolol are unchanged after 1 and 5 years of therapy.

Atenolol blunts the reflex mediated increase in heart rate that usually follows the Valsalva maneuver or abrupt tilting to the upright position. It also prolongs the sinus node recovery time and lengthens the RR interval. An increase in atrial refractory period follows administration of atenolol and atrioventricular (A-V) conduction is prolonged. Besides prolonging AV nodal refractoriness, decrease in intracellular calcium overload and After depolarization mediated automaticity is seen. The antiarrhythmic actions of atenolol are less than of sotalol and propranolol (due to less membrane stabilizing.

Atenolol has no effect on plasma volume, exchangeable sodium or potassium or total body potassium.9,11 However, block peripheral because it does not b2 receptors, it does not

Table: 2. Cardiac effects of Atenolol

1. Negative Chronotropic (decreased heart rate)
2. Negative dromotropic (decreased conduction)
3. Negative inotropic (decreased contractility)
4. Anti arrhythmic
5. Anti ischemic

Prevent fall in serum potassium levels that can occur when plasma catecholamine rises. Like other b-blocking agents, atenolol inhibits the release of renin, inhibits lipolysis13-14 and causes increased plasma triglyceride levels and a fall in HDL concentration. When administrated in large doses enough to block b-2 receptors, the resulting reduction of glucose production in response to catecholamine release can prolong hypoglycemia induced by insulin. Atenolol reduces renal vascular resistance in hypertensive patients 9. No effect on creatinine clearance, glomerular filtration rate or renal blood flow has been observed in contrast to nonselective b-blockers. Although atenolol does not pass the blood brain barrier fully, some of the compound reaches the central nervous system. The following symptoms, possibly related to CNS effect have been reported, dizziness, vertigo, lightheadedness, tiredness, fatigue, lethargy, drowsiness, depression and vivid dreams.

5. Dosage and Administration

5.1 Hypertension

The initial dose of atenolol for the treatment of hypertension usually is 50 mg per day given once daily. If an adequate therapeutic response is not evident within several weeks, the daily dose may be increased to 100 mg, Higher doses are unlikely to provide any greater anti-hypertensive effect. Young hypertensives have high renin hypertension and increasedsympathetic activity. So b-blockers are used in younger ages only now. In elderly hypertensives b- blockers specially atenolol is no longer a preferred drug.

In angina pectoris the initial dose is 50 mg once daily. If an optimal response is not achieved within one week, the dosage should be increased to 100 mg. Some patients may require a

Dose of 200 mg. In some patients with acute MI (within 6 hours) especially those with anterior infarction and sinus tachycardia but not intravenous atenolol may be given 5 mg atenolol over 5 minutes followed by another 5 mg intravenous injection 10 minutes later can be given.

The mortality benefits of early atenolol treatment persisted at one year (10.7% in atenolol group vs 12% in control $p< 0.01$). In most patients of myocardial infarction, b-blockers are used for secondary prophylaxis and a treadmill test (TMT) is required for risk stratification. However, false negative TMT can occur in patients on b-blockers. Conversion of negative or mildly positive TMT into strongly positive result after withdrawal of b-blockers has been reported19. It is suggested that b-blockers can and

should be withdrawn in post-MI patients before doing TMT figure 4

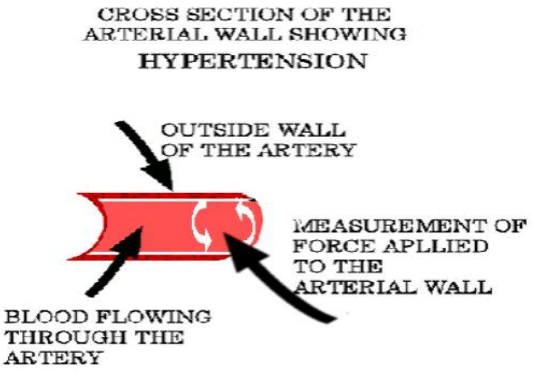


Fig: 4. Hypertension

5.2 Precaution, Adverse Effects and Contraindications

In patients with congestive heart failure some b-blockers like carvedilol, metoprolol succinate and bisoprolol are standard forms of therapy. However, there is no data on use of atenolol and hence it should be avoided in such patients specially in those with class IV symptoms.

Because b-blockers slow A-V conduction, they should not be used in patients with advanced grades of heart block such as 2nd and 3rd degree AV block because of risk of producing complete heart block.

When used in low doses it may not lower the limb blood flow in patients with peripheral vascular disease, as occurs with use of non selective b-blockers. Similarly,the incidence of cold extremities, acrocyanosis or aggravation of Raynaud's. The occurrence of bronchospastic disease, masking of tachycardia associated with hypoglycemia in diabetes, similarly is lesser with low dose atenolol as compared to non-selective agents.

5.3 Drug Interactions

Atenolol should be used with caution when used concomitantly with drugs like reserpine (Catecholamine-depleting drugs); other b-blockers (increased risk of cardiac depressant effects like enhanced bradycardia), calcium channel blockers (negative inotropic and chronotropic effects); disopyramide and amiodarone (negative chronotropic effects), clonidine withdrawal (rebound hypertension); digitalis (bradycardia).

5.4 Overdose of b-Blockers

Bradycardia may be countered by intravenous atropine. If serious, temporary transvenous pacing may be required. When an infusion is required, glucagon (2.5 to 7.5 mg/h) is the drug of choice, because it stimulates formation of cyclic AMP by bypassing the occupied b-receptor. Logically an infusion of a phosphordiestrase inhibitor, such as amrinone or milrinone, should help cyclic AMP to accumulate. Alternatively, dobutamine is given in doses high enough to overcome the competitive b-blockade (15 mg/kg/min). In patients without ischemic heart disease, an infusion (up to 0.10 mg/kg/min) of isoproterenol may be used.

Atenolol a cardio selective agent is more potent and has an increased safety profile as compared to other non-selective agents. Its role as a reference drug and first choice in treatment of hypertension has now declined especially after 2 large mega trials LIFE & the ASCOT BPLA study29-30. However, it

Gastroretentive Ethyl Cellulose Floating Microspheres containing Atenolol

Abstract

The aim of this study was to prepare and evaluate ethyl cellulose floating microspheres containing. Atenolol microspheres were prepared by non-aqueous solvent evaporation method using ethanol/ liquid paraffin system. The influence of formulation factors (drug: polymer, stirring speed, concentration of surfactant) on particle size, encapsulation efficiency and in vitro release characteristics of the microspheres were investigated. The yields of preparation and encapsulation efficiencies were high for all formulations obtained. Mean particle size changed by changing the drug: polymer ratio or stirring speed of the system. Although atenolol release rates from ethyl cellulose microspheres were decreased as the concentration of ethyl cellulose increased. By applying one way ANOVA followed by Newman-Keuls Multiple Comparison value obtained ($p < 0.05$) was considered to be statistically significant.

Key words: atenolol; Ethyl cellulose; Floating microspheres; Controlled release

6. Materials and Methods

Atenolol, Alkem laboratories, Mumbai; ethyl cellulose, span 20, liquid paraffin, n-hexane; S.D Fine chemicals, Mumbai. Other chemicals

6.1 Preparation of microspheres

Atenolol floating microspheres were prepared by non-aqueous solvent evaporation technique. Different amounts of polymer (500, 100, 1500 and 2000mg) was dissolved in 25 ml of ethanol by using a magnetic stirrer (Popular India Limited, Mumbai). Powdered atenolol (500mg) was dispersed in polymer solution. The resulting dispersion was then poured into a vessel of 1000 ml containing the mixture of 150 ml liquid paraffin and 30 ml n-hexane while stirring. Span 20 was added drop by drop into vessel during stirr in diameter was used. Stirring was continued for an hour, until ethanol evaporated completely. Drug: polymer ratio (1:1, 1:2, 1:3 and 1:4 w/w), span 20 (0.2, 0.3, 0.4, 0.5 %) and stirring speed (500, 750, 1000 rpm) of the system were changed to obtain spherical particles. After evaporation of ethanol, the microspheres formed were collected by filtration, washed 4-5 times with 50 ml n-hexane for 4 hours.

Table: 3. Optimization of Drug Polymer Ratio

Batch	Drug Polymer Ratio	Average diameter	DEE % (wt/wt)	Buoyancy %
EC 1	**1:1**	212(±2.36)	79 (±1.53)	68.5
EC 2	**1:2**	34(±2.15)	91(±2.24)	72
EC 3	**1:3**	60(±1.56)	80 ±2.16)	69
EC 4	**1:4**	285(±2.47)	78 (±2.96) 95	70

6.2 Optimization of Stirring Speed

Stirring speed plays an important role in the microspheres size distribution and drug loading. Microspheres were prepared by the method described above with optimized ratio of drug and the polymer (1:4), keeping surfactant concentration (0.2%) constant, utilizing three different speeds i.e. 500, 750, and 1000 rpm.

Table: 4. Optimization of stirring speed

Batch	RPM	Average diameter (µm)	DEE (%wt/wt)
EC 4	500	320 (±2.5 □ m)	65.59 (±2.7)
EC 4	750	285 (±1.3 □ m)	75.18 (±1.5)
EC 4	1000	260 (±2.2□ m)	69.23 (±2.8)

6.3 Optimization of emulsifier (span 20)

Concentration of emulsifier is an important parameter which needs to be optimized for optimum particle size and stability of the microspheres. Span 20 was used as an emulsifier and various concentrations of span 20 were taken. Microspheres were prepared according to method described above, with optimized drug polymer ratio i.e. 1:4 and stirring speed 750 rpm with various concentrations i.e. 0.2 %, 0.3 %, 0.4 % and 0.5 % v/v of span 2

Table: 5. Optimization of emulsifier (span20)

Batch	Span 20 (%V/V)	Average diameter(µm)	DEE (%wt/wt)
EC 1	0.2	310 (±2.11 □ m)	70.43 (±2.25)
EC 2	0.3	305 (±2.45 □ m)	72.68 (±1.86)
EC 3	0.4	280 (±3.15 □ m)	76.43 (±2.25)
EC 4	0.5	260 (±2.27 □ m)	69.63 (±1.26)

Microspheres dried at room temperature were then weighed and yield of microsphere preparation was calculated using the formula:

Percent yield= the amount of microspheres obtained (g) ×100/ the theoretical yield (g)

6.4 Scanning electron microscopy

Shapes and surface characteristics of the microspheres were investigated and photographed using scanning electron microscopy.

6.5 Determination of mean particle size

Mean particle size of microspheres was determined by using optical microscopy (Table 3).

6.6 Drug entrapment efficiency

A quantity of microspheres containing 100mg equivalent of atenolol were incubated in 0.1 N HCl for 24 hours to determined drug entrapment efficiency. Atenolol concentration was determined by measuring absorbance at 315 nm against reagent black (Table 3)

6.7 Buoyancy

% buoyancy was carried out using 0.1 N HCl containing 1% span 20 as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37± 0.5 oC. A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collected at a predetermined time point. The collected samples are weighed after drying.

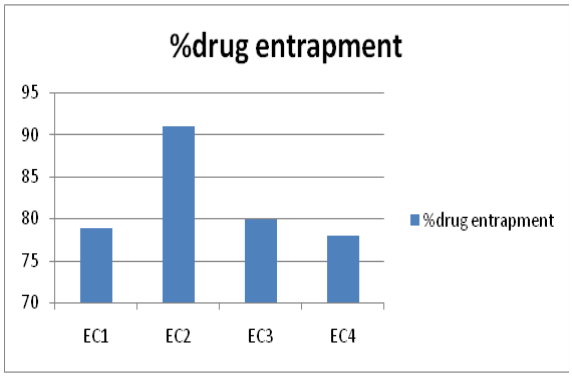


Fig: 7.

% Buoyancy = weight of microspheres floating on the surface/ initial total weight of microspheres

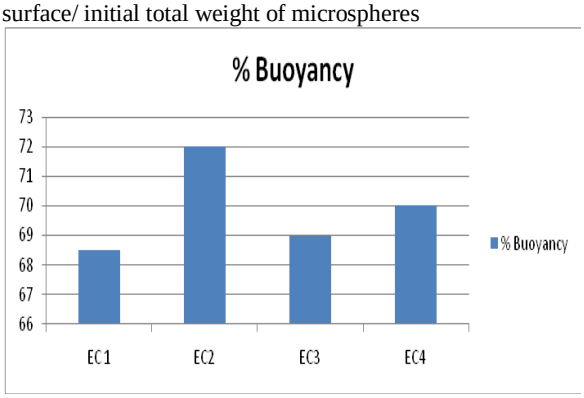


Fig: 8

6.8 In Vitro Release Studies

In vitro drug release study of all the batches wereMcarried out by paddle method using USP type 2 apparatus using 900 ml of 0.1 N HCl as dissolution medium at 750 rpm and 37±0.5oC. A quantity of microspheres containing 100mg equivalent of Atenolol was placed in the dissolution medium. The samples were withdrawn at a predetermined time interval, diluted approximately and weanalyzed on spectrophotomatry at 274 nm against reagent blank.

Table: 6. In- vitro drug release data trial formulation batch 1 (EC1)

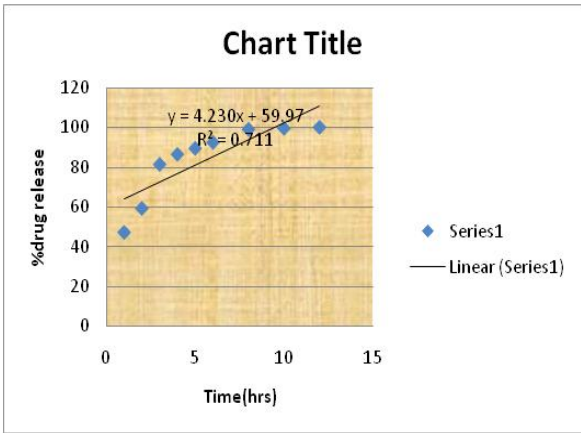


Fig: 9.

Table: 7. In-vitro drug release data of trial formulation Batch 2(EC2)

Sample	Time (hrs)	% Drug release
1	1	10.5
2	2	20.5
3	3	50
4	4	68
5	5	73
6	6	86
7	8	88
8	10	89
9	12	92.5

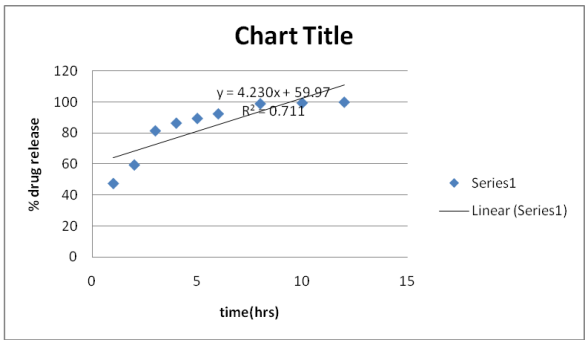


Fig: 10.

Table: 8. In-vitro drug release data of trial formulation batch 3(EC3)

Sample	Time(hrs)	% Drug release
1	1	41
2	2	50
3	3	72
4	4	88.5
5	5	92.5
6	6	92.5
7	8	98
8	10	98.5
9	12	99

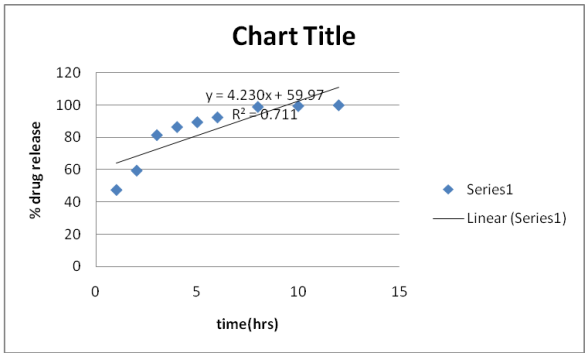


Fig: 11

Table: 9. In-vitro drug release data of trial formulation batch 4(EC4)

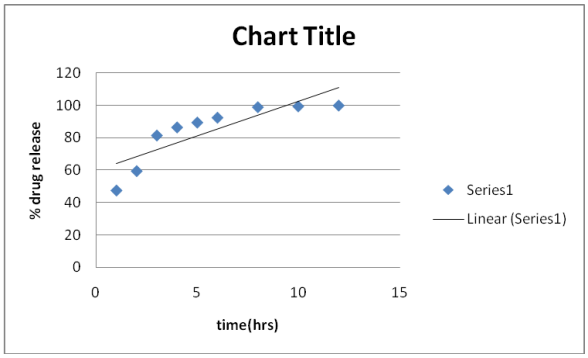


Fig: 12

6.9 Statistical Analysis

The data obtained release rate determination studies of atenolol microspheres were analyzed statistically with one-way ANOVA followed by Newman-Keuls Multiple Comparison value obtained ($p < 0.05$) was considered to be statistically significant

7. Result and Discussion

Viscosity of the inner phase is an important factor for the/preparation of microspheres. Keeping the drug amount and the solvent amount volume constant, spherical particles were obtained as the amount of polymer increased to give a polymer drug ratio (3:1) (stirring speed 750 or 500 rpm) or 4:1(stirring speed 750rpm). However, when polymer : drug ratio was (4:1), the shape of particles were irregular at 500 rpm, because for this high polymer concentration, this stirring speed was not fast enough to disperse inner phase in outer phase. When stirring speed was 750 rpm the best spherical particles with good surface characteristics were obtained with the polymer: drug ratio of 4:1. Two examples of the scanning electron micrographs of the microspheres prepared are shown in figure 3 and4.

On the other hand, drug entrapment efficiency was found to increase with increase in polymer 70.57(±1.96). % buoyancy of optimized formulation (EC 4) found to be 95%. Most of the microspheres obtained were collected in the size range of 200-300 µm drug entrapment efficiency was found to be maximum by all formulation. Increasing the polymer: drug ratio caused the mean particle size to shift towards a higher particle size. Higher concentration of polymer produced a more viscous dispersion which formed larger droplet and consequently larger microspheres. Increasing the stirring speed decreased the particle size of microspheres. The yield of preparation and atenolol entrapment efficiencies were high for all formulations and maximum for optimized formulation (EC 4).The drug release rate from microspheres were studied at pH 1.2 or 2 paddle method. The in vitro drug release profile was biphasic with an initial burst release (34%) in 1 hour attributed to surface associated drug, followed by a slower release phase as the entrapped drug (0.1 N HCl) using the USP types lowly diffuse out into the release medium. 100 % drug release after 12 hours there was a sustain release of drug at a constant rate. The absorbed molecules on surface of particle are rapidly desorbed when in contact with the dissolution medium. The diffusion of drug, the erosion and degradation of polymer are the main mechanism for the drug release. Kinetics model further support the above

statement. Zero order, first order, hixon crowell cube root plot, korsmeyer peppas, were applied on optimized formulation. The n value and r2 value show that the formulation releases the drug by erosion as well as diffusion and optimized batch follow this release kinetic model (Table 9).

Table: 9. Correlation Coefficient of Optimized Batch (EC4)

No	Zero order	First order	Hixon crowell plot	Higuchi plot	korsmeyer peppas
1	0.9671	0.9956	0.918	0.9925	0.8784

Statistical analysis was carried out by applying one way ANOVA followed by Newman Keuls Multiple Comparison, value obtained ($p< 0.05$) was considered to be statistically significant. The studie showed that drug release from all formulations was not found to be statistically significant. But on the basis of required size, shape, drug entrapment efficiency of floating microspheres EC 4, drug: polymer ratio (1:4) was found to be optimum batch4.

8. Conclusion

Atenolol floating microspheres were prepared successfully using non-aqueous solvent evaporation method. Polymer drug ratio and stirring speed of the system were important to obtain spherical particles. The yield of preparation and entrapment efficiency were high for all formulations. Atenolol is water soluble drug which gives a controlled release from ethyl cellulose microspheres. Thus gastroretentive floating microspheres of atenolol supposed to remain in the stomach for longer period of time and give controlled release. These formulations can reduce dosing frequency, decrease side effects and improve patient compliance.

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