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Formulation and Evaluation Of Atenolol Tablets For Gastroretentive drug Delivery System

Saurabh Vijay Nikam [1], Mr. Ravikumar Raosaheb Patil [2]

[1] Email: saurabhnikam58a@gmail.com
Mobile no: 733735490
Department Of Cosmetic Science
Late Narayandas Bhawandas Chhabada Institute of Pharmacy,
Raigaon, Satara. Dist: Satara, Maharashtra. 415020
[2] Guide:
M. Pharm (Pharmaceutics)
Assistant Professor, Department of Pharmacy
Late Narayandas Bhawandas Chhabada Institute of Pharmacy,
Raigaon, Tal: Satara. Dist: Satara, Maharashtra. 415020
Email: saurabhnikam58a@gmail.com
Mobile no: 733735490

ABSTRACT :

Atenolol, a β1-selective adrenergic receptor blocker, is widely used for the treatment of hypertension and cardiovascular diseases. However, its absorption is limited to the upper gastrointestinal (GI) tract, making it an ideal candidate for a gastro-retentive drug delivery system (GRDDS) to enhance its bioavailability and therapeutic efficacy. This study focuses on the formulation and evaluation of a gastro-retentive floating tablet of Atenolol using hydroxypropyl methylcellulose (HPMC), xanthan gum, microcrystalline cellulose (MCC), sodium bicarbonate ($NaHCO_3$), dicalcium phosphate (DCP), magnesium stearate, and talc.The floating tablets were prepared using a direct compression technique, where HPMC and xanthan gum served as hydrophilic polymers to control drug release and enhance buoyancy. MCC was used as a diluent to improve compressibility, while sodium bicarbonate acted as an effervescent agent, generating CO_2 upon contact with gastric fluids to facilitate tablet buoyancy. DCP functioned as a filler to optimize the tablet's mechanical strength, and magnesium stearate and talc were included as lubricants to enhance the flow properties of the formulation.

The prepared tablets were evaluated for various pre-compression and post-compression parameters, including drug-excipient compatibility, hardness, friability, weight variation, swelling index, floating lag time, total floating duration, in-vitro drug release, and stability studies. The results indicated that the optimized formulation exhibited an initial floating lag time of less than 1 minute and remained buoyant for over 12 hours in simulated gastric fluid (pH 1.2). The drug release followed a controlled pattern, governed by diffusion and polymer erosion mechanisms, ensuring prolonged therapeutic action. In conclusion, the developed gastro-retentive floating tablets of Atenolol demonstrated enhanced gastric retention and controlled drug release, making them a promising approach for improving the drug's bioavailability and patient compliance. Further in-vivo studies are recommended to validate the effectiveness of the formulation in clinical settings .

Keywords : Atenolol , Gastro-retentive drug delivery system (GRDDS), Floating tablet, Hydroxypropyl methylcellulose (HPMC), Xanthan gum, Microcrystalline cellulose (MCC), Sodium bicarbonate ($NaHCO_3$), Dicalcium phosphate (DCP), Magnesium stearate, Talc, Buoyancy, Drug release .

Introduction

Atenolol, a widely prescribed β1-selective adrenergic receptor blocker, is commonly used in the management of cardiovascular conditions such as hypertension, angina, and arrhythmias. Despite its efficacy, the clinical benefits of Atenolol are often limited by its poor bioavailability, which results from its incomplete absorption in the upper gastrointestinal (GI) tract. To address this issue and enhance the therapeutic effectiveness of Atenolol, there is a need for novel drug delivery systems that can improve its absorption and provide sustained therapeutic effects.
Gastro-retentive drug delivery systems (GRDDS) have emerged as a promising approach to overcoming the limitations associated with the bioavailability of drugs like Atenolol. These Atenolol, a selective β1-adrenergic blocker, is primarily used to treat hypertension, angina, and cardiovascular diseases.[1]
When formulated as a gastroretentive drug delivery system (GRDDS), it provides several medicinal benefits:

Medicinal Uses of Atenolol in GRDDS:

1. Enhanced Bioavailability:

Atenolol has pH-dependent solubility, with better absorption in the upper gastrointestinal tract (GIT). A gastroretentive system helps in prolonged gastric retention, improving its absorption and bioavailability.

2. Sustained Drug Release:

A floating, mucoadhesive, or expandable gastroretentive system ensures controlled release of atenolol, reducing fluctuations in plasma drug concentration and enhancing therapeutic efficacy.

3. Improved Patient Compliance:

A once-daily formulation reduces dosing frequency, minimizing side effects like bradycardia and hypotension associated with peak plasma concentration.

4. Effective Hypertension Management:

By maintaining steady-state drug levels, GRDDS provides better blood pressure control, preventing sudden spikes or drops.

5. Reduction of First-Pass Metabolism:

Atenolol has minimal hepatic metabolism, but gastric retention ensures prolonged contact with the absorption sites, leading to improved systemic availability.

6. Reduced Gastrointestinal Side Effects:

Controlled drug release in the stomach prevents sudden high drug concentrations, reducing the risk of gastrointestinal irritation.[2]

NEED:

The gastroretentive dosage form will release the drug over an extended period in the stomach and upper G.I, tract thus enhancing the opportunity of absorption. Gastroretentive system is useful for those drugs, which-

1. Are poorly absorbed from gastrointestinal tract have narrow absorption window degrade in colon are poorly soluble in high pH envoirnment.

Atenolol is a drug of choice for the treatment of hypertention. It is a beta -1 cardioselective adrenergic receptor blocker. Atenolol is a good rationale for floating drug delivery system because of the identical physicochemical parameter required to the gastroretentive drug delivery system ,some of them are-

a) The oral bioavailability of Atenolol is 50%.
b) It has short half life(t ½) (6-8 h).
c) It does not undergo first pass metabolism..
d) It has less oil/water partition coefficient.
e) It is poorly absorbed from stomach.[3]

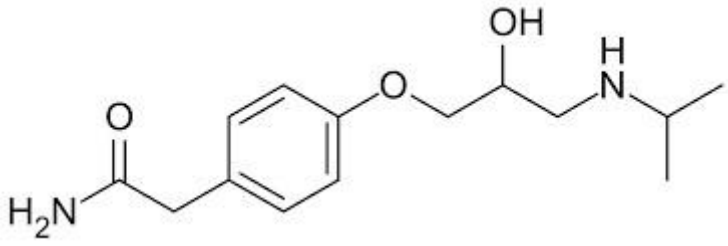
OBJECTIVE:

1. To compare the Marketed preparation of Atenolol and optimized Formulation .
2.To characterize the prepared tablets by physicochemical parameters such as hardness , tablet dimensions, weight variation, uniformity of drug content, floating characteristics (Floating lag time , floating time and matrix integrity),in vitro drug release of marketed preparation and formulation .
3. To use data analysis and mathematical models to explain mechanism and release kinetics of different formulations.[4]

Drug profile:

1. Atenolol

Chemical structure :



Chemical formula : C14H22N2O3

Structure:

- A benzene ring with a carboxamide group attached to it.
- A propanol chain attached to the benzene ring, with an amino group at the end of the chain.
- The propanol chain has an isopropyl group attached to the amino group.

Medicinal uses :

1. Enhanced Bioavailability:

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2. Sustained Drug Release:

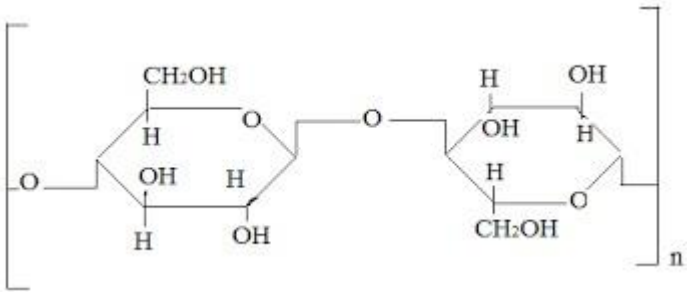
A floating, mucoadhesive, or expandable gastroretentive system ensures controlled release of atenolol, reducing fluctuations in plasma drug concentration and enhancing therapeutic efficacy.

3. Improved Patient Compliance:

A once-daily formulation reduces dosing frequency, minimizing side effects like bradycardia and hypotension associated with peak plasma concentration.[5]

Hydroxypropyl Methylcellulose (HPMC) :

Chemical Structure :



Chemical formula : $C_{56}H_{108}O_{30}$

Structure:

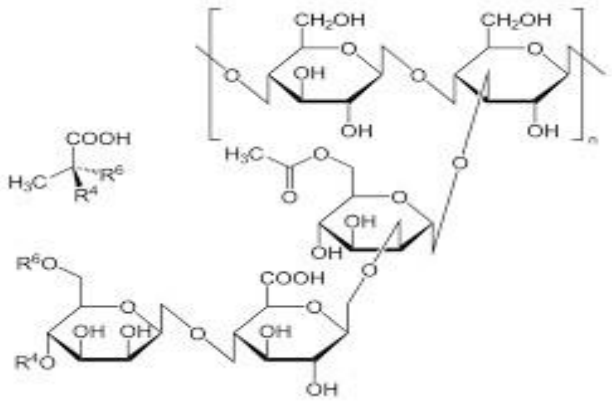
HPMC is a synthetic modification of cellulose, where some of the hydroxyl groups on the cellulose backbone are substituted with methyl (-OCH3) and hydroxypropyl (OCH2CH(OH)CH3) groups.

Medicinal Uses:

1. Controlled and Sustained Drug Release : HPMC is used as a rate-controlling polymer in sustained-release tablets and capsules.
2. Binder in Tablet Formulations : Acts as a tablet binder to enhance tablet strength and prevent breakage.
3. Film-Coating Agent : Used in film-coated tablets to improve stability, taste masking, and controlled drug release.
4. Mucoadhesive Drug Delivery : Improves residence time in the gastrointestinal tract when used in mucoadhesive tablets and films.[6]

Xanthan gum

Chemical structure :



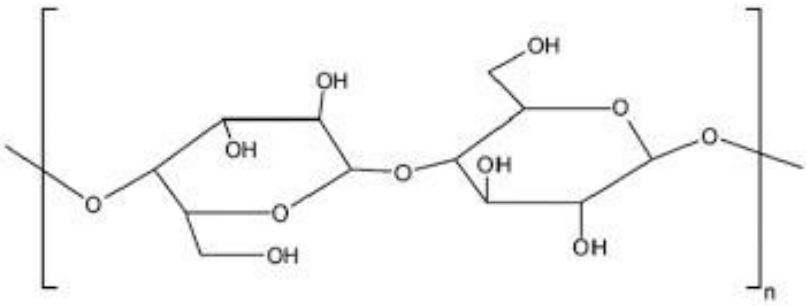
Formula: C35H49O29

Structure :

Xanthan gum is a polysaccharide secreted by the bacterium Xanthomonas campestris. It is composed of pentasaccharide repeat units, comprising glucose, mannose, and glucuronic
acid in the molar ratio 2:2:1. Rheology modifier.
Xanthan gum is produced by the fermentation of glucose and sucrose. The medium is wellaerated and stirred, and the xanthan polymer is produced extracellularly into the medium.

Medicinal uses
Controlled and Sustained Drug Release :
Used as a hydrophilic matrix former in sustained-release tablets to ensure gradual drug release.
Thickening and Suspending Agent :
Used in oral liquid suspensions to prevent settling of drug particles.
Floating Drug Delivery Systems (FDDS) :
Used in floating tablets and gels to increase gastric retention time, beneficial for drugs with narrow absorption windows.[7]
Microcrystalline cellulose (MCC) :

Chemical structure :



Formula : C6H10O5

Medicinal uses :

1. Tablet and Capsule Binder :
Acts as a strong dry binder in tablet compression, ensuring tablet cohesion without requiring excessive binder solution.

2. Diluent/Filler in Solid Dosage Forms:

Used as a diluent in tablets and capsules to provide bulk for low-dose active ingredients.

3. Disintegrant for Fast Drug Release:
Enhances tablet disintegration by absorbing water and swelling, which helps in rapid drug dissolution.

4. Stabilizer in Drug Formulations:

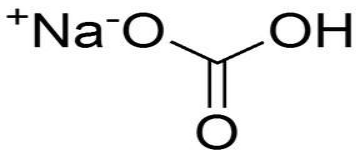
Prevents separation or caking in powders, suspensions, and emulsions.

5. Controlled and Sustained Drug Release:

Used in extended-release drug delivery systems by modifying drug release rates.[8]

Sodium bicarbonate (NaHCO3) :

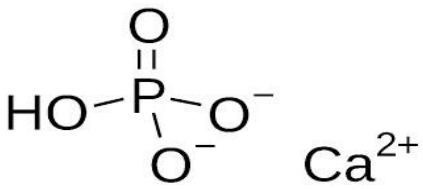
Chemical structure :



Formula : NaHCO3
Structure:
Monoclinic lattice structure
The sodium ion (Na+) and bicarbonate ion (HCO3-) are held together by an ionic bond.
The bicarbonate ion (HCO3-) has a linear structure with the carbon atom at one end and the oxygen atoms at the other end.

Medicinal Uses :
Antacid for Gastric Acidity and GERD :
Neutralizes stomach acid (HCl), providing rapid relief from heartburn, acid reflux, and indigestion.
Systemic Alkalizer in Metabolic Acidosis :
Used to correct metabolic acidosis in conditions like kidney disease, diabetic ketoacidosis (DKA), and lactic acidosis.
Urinary Alkalizer :
Increases urine pH, helping to prevent kidney stones and aid in the excretion of acidic drugs (e.g., aspirin overdose).[9]
Dicalcium phosphate (DCP) :

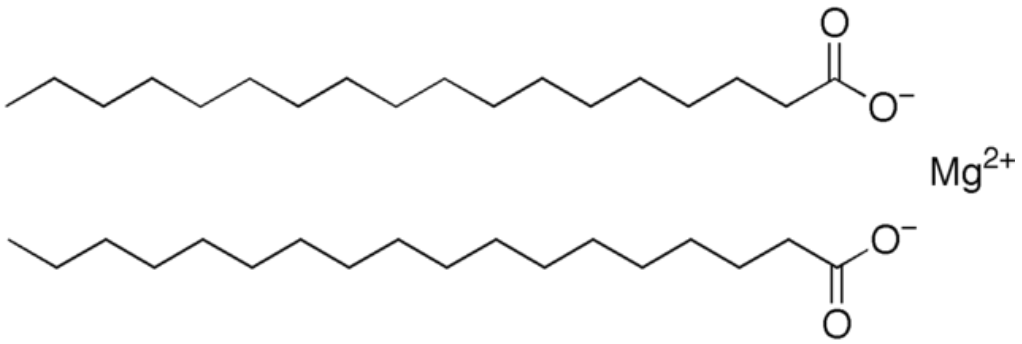
Chemical structure :



Formula : CaHPO4
Its chemical name is Dicalcium phosphate. The CAS Number of Di Calcium Phosphate (DCP) is 7789-77-7 and its chemical formula is CaHPO4. The most common end use is Basic Pharma , Fertilizers .

Medicinal Uses:
1. Filler and Binder in Tablet and Capsule Formulations :
Used as an inert diluent in tablets and capsules to provide bulk for low-dose active ingredients.
2. Source of Calcium in Nutritional Supplements:
Used in calcium supplements to prevent and treat calcium deficiency.
3. Controlled Drug Release in Solid Dosage Forms:
Helps in sustained and extended-release formulations by controlling drug dissolution rates.
4. Acid Regulator and pH Stabilizer:

Used in tablet formulations to help maintain stable pH for better drug stability.[10] **Magnesium Stearate :**
Chemical structure :



Formula : Mg(C18H35O2)2.
Magnesium stearate is a white, soapy powder, a magnesium salt of fatty acids (specifically stearic acid) used as a lubricant and flow agent in pharmaceutical and cosmetic industries, with the chemical formula Mg(C18H35O2)2.
Medicinal uses :

1. **Lubricant in Tablet and Capsule Manufacturing :**

Reduces friction between powder particles and tablet dies, preventing sticking during compression.

2. **Anti-Adherent Agent :**

Prevents powders from sticking to processing equipment, improving flow properties during tablet production.

3. **Enhances Powder Flowability:**

Improves flow characteristics of powder blends, making them easier to handle and compress into solid dosage forms.

4. **Stabilizer in Drug FormulationsL:**

Enhances tablet stability by preventing moisture absorption, reducing drug degradation.[11] **Magnesium silicate (Talc) : Chemical formula :** Mg3Si4O10

Structure:

- **Layers:** Talc's structure consists of layers of magnesium-oxygen/hydroxyl octahedra sandwiched between two layers of tetrahedral silica.
- **Octahedra:** The octahedra contain magnesium atoms, oxygen atoms, and hydroxyl groups.
- **Tetrahedra:** The silica tetrahedra consist of silicon and oxygen atoms.
- **Van der Waals forces:** The binding forces between these layers are weak Van der Waals forces, allowing the layers to slide easily, giving talc its characteristic softness.

Medicinal uses :

1. **Lubricant in Tablet and Capsule Manufacturing :**

Reduces friction between powder particles and tablet punches, ensuring smooth tablet ejection.

2. **Anti-Adherent Agent:**

Prevents powders from sticking to machinery surfaces (e.g., tablet punches, capsule-filling machines).

3. **Glidant for Powder Flow Improvement:**

Enhances flow properties of powders, ensuring uniform drug mixing and accurate dosing.

4. **Moisture and Humidity Protection:**

Acts as a protective barrier to prevent moisture absorption, improving the stability of moisture-sensitive drugs.[12]

Formulation table :

Sr.no	Ingredient	Quantity
1	Atenolol	50mg
2	HPMC	35mg
3	Xanthun gum	35mg

4	MCC	181mg
5	NaHCo3	28mg
6	DCP	175mg
7	Magnesium stearate	1.75mg
8	Talc	1.75mg

Formulation Procedure :

1. **Sifting**

Sift Atenolol, HPMC, Xanthan gum, MCC, $NaHCO_3$, and DCP through a #40 sieve to ensure uniform particle size.

2. **Dry Mixing**

Mix all the sifted powders (except Magnesium stearate and Talc) in a blender (e.g., double cone blender or planetary mixer) for 10–15 minutes to achieve uniform distribution.

3. **Granulation (Optional: Wet Granulation)**

If needed, perform wet granulation using a suitable binder (e.g., PVP K30 in isopropyl alcohol or water).
Pass the wet mass through a #16 or #20 sieve to form granules.
Dry the granules at 40–50°C in a tray dryer or fluid bed dryer until moisture content is <2%.

4. **Lubrication**

After drying, sieve and blend the granules with Magnesium stearate and Talc for 3–5 minutes.

5. **Compression**

Compress the lubricated granules into tablets using a tablet compression machine with appropriate tooling (e.g., 8 mm or 10 mm round flat punches).
Target a tablet hardness of ~5–7 kg/cm².[13]

Evaluation parameter

1. Floating characteristics:

Floating characteristics of the prepared formulation were determined by using paddle apparatus . The dissolution medium was 900 ml of 0.1 N HCl(pH 1.2) at 37+_0.50C throughout the study. Floating lag time and matrix integrity of the prepared formulation was measured

a) Floating lag time:

The time between the introduction of tablet and its buoyancy on the 0.1 N HCl was measured.

b) Floating Time:

The time during which dosage forms remain buoyant was measured.[14]

2. Tablet dimensions (Tablet diameter and Tablet Thickness)

Tablet thickness should be controlled within 5% or less of a standard value . Any variation in tablet thickness should no be apparent to customer. In addition it is important to control thickness to facilitate packaging. Difficulties may be encountered in the use of unit dose and other type of packaging epuipement if the volume of the material being packed is not consistent.
Three sets of factors influence tablet thickness and tablet control. These are :
(1.)The physical properties of the raw material,including crystal form and true and bulk density
(,2.)Control of upper punch and lower punch lengths,which should be appropriately standardized and
(3) The granulation properties including bulk density,particle size and particle size distribution.
The crown thickness of individual tablets is measured with a micrometer.[15]

3. Tablet Hardness :

A tablet requires a certain amount of strength or hardness to withstand mechanical shocks of handling in its manufacture,packaging and shipping.In addition tablet should be able to withstand reasonable abuse when in the hands of consumer.Adequate hardness is necessary requisities for consumer acceptance.
The hardness of the tablet is a function of the die fill and compression force.Hardness increases with increasing die fills and decreases with lower die fills.Lubricants may affect hardness if used in large excess.Changes in partical size distribution,dies having light fill (large particles,low density)will produce hardness problems.
The Hardness of the tablet is determined using Monsanto hardness tester(n=10).The tablet to be tested is placed between the spindle and anvil and pressure is applied by turning the knurled knob just sufficiently to hold the tablet in position The reading of the pointer on scale is then adjusted to zero.The pressure is now increased as uniformly as possible until tablet breaks. The pointer now reads the pressure required to break the tablet.[16]

4. Weight Variation Test:

The weight variation is satisfactory if (1) the tablet contains all drugs or essentially (90-95%) all active ingredient or (2) the uniformity of drug distribution of granulation or powder from which the tablet are made is perfect. Dies may not be uniformly filled ,wide particle size variation, non-uniform density in the granulation, non-uniform length of lower punch;all those problems cause weight variation.

Twenty tablets were accurately weighed and an average weight was calculated. Not more than two of the individual weights deviate from the average weight by the percentage deviation given in the table:

I.P. Standards for Uniformity of weight[17]

Sr .no	Avg. weight of tablet	% of deviation
1	80mg or <	+10
2	>80 to <250mg	+7.5
3	>250 or more	+5

RESULTS AND DISCUSSION :

Here's a sample set of results for a gastroretentive floating tablet of atenolol using the excipients you mentioned: Atenolol, HPMC, Xanthan gum, MCC, $NaHCO_3$, DCP, Magnesium stearate, and Talc. This assumes the tablets were successfully formulated and evaluated in a lab setting.

1. Floating lag time :

The concentration of sodium bicarbonate was optimized to study floating . Tablets were prepared by using various concentrations of sodium bicarbonate (8 % ,10 % ,12%) . It was observed that at higher concentration (12 %) ,there was a fast reaction with hydrochloric acid with the formation of dispersion of tablets . The floating lag time was decreased but the matrix integrity could not be maintained at this concentration . A lower concentration (8 %) led to slow reaction , which prolong the floating lag time . The effect of different concentration of sodium bicarbonate on floating lag time is as shown in Table:

Con. of sod..bicarbonate	Floating lag time (min) 1:1
8	7
Marketed preparation	15.33

Tablet diameter and Tablet thickness :

Diameter of tablets was measured and found in the range of 9.98 to 10 mm and thickness of the tablets was found in the range of 2.99 to 3 mm.

Tablet Diameter	9.98 to 10 mm
Tablet Thickness	2.99 to 3 mm

3.Tablet Hardness :

Tablet hardness has influence on the tablet density and porosity result in different release pattern of the drug . It affects the rate of penetration of dissolution fluid in the tablet . But many researchers have reported that the tablet hardness has a little or no effect on the release profile . The hardness of tablet in the range of 4 to 4.1 kg / cm 2 was found to be optimum to impart the compactness to the system.

Tablet Hardness	4 to 4.1 kg/cm

4. Weight variation test :

Tablets of all the formulations passed the weight variation test . This ensures the uniform die fill , the uniform length of lower punches , uniform particle size , and uniform distribution of drug.

formulation	**Weight variation**
F1	348.90mg
Marketed preparation	349.9mg

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