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FORMULATION AND EVALUATION OF GASTRO RETENTIVE MATRIX TABLETS OF ATENOLOL USING MELT GRANULATION TECHNIQUE

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Keywords:

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ABSTRACT: The main objective of this present work was to develop and evaluate matrix tablets of Atenolol by melt granulation technique and compare the drug release between bess wax and glyceryl monostearate (GMS). Polymers like HPMC K 4 M, HPMC K 100 M, bees wax, glyceryl monostearate and ethyl cellulose were incorporated in the formulation. Formulations were prepared by keeping the HPMC and ethyl cellulose at constant ratio. Bees wax and glyceryl monostearate (GMS) were used in different ratios. FTIR studies indicate that there is no interaction between drug and excipients. Developed tablets were evaluated for weight variation, friability, hardness, thickness, drug content, swelling index and drug release profiles. The dissolution studies showed that drug release was better in the formulations where glyceryl monostearate (GMS) is higher than the bees wax. Thus, it was concluded that HPMC K 4 M, HPMC K 100 M along with Bees wax and Glyceryl monostearate can be successfully used in the formulation of Atenolol sustained release gastro retentive floating drug delivery system.

INTRODUCTION: Oral drug delivery system is the most preferable drug delivery route due to the ease of administration, flexibility in formulation and patient compliance[1]. The numerous oral drug delivery systems (ODDS) have been implemented to act as drug reservoirs from which the pharmaceutically active substance can be released over a defined period of time at a predetermined and controlled rate [2].

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The conventional dosage forms stay in the stomach for 0.5-2 hours, then passes to small intestine and absorbed within 3-6 hours. So, difficult to regulate release retardation and stomach retention of drug for longer period of time. The gastro retentive drug delivery system came from the need to localize the drug at a site specific in the body. When the site of drug absorption is mainly in stomach or upper part of the small intestine, then it is necessary to retain the dosage form at the site of absorption, but the gastro intestinal transit is the limitation for such type of dosage forms.

The gastro retentive dosage forms are formulated to increase the gastric residence time. The majority of drugs are preferentially absorbed from the upper part of the small intestine hence drug release at the

site of absorption can enhance the therapeutic efficacy of drug. Drugs having pH dependent solubility i.e., highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH) are the suitable drug for the floating drug delivery. In the treatment of angina, hypertension, cardiac arrhythmias, myocardial infarction a loading as well as maintenance dose is required. Drugs having short biological half life, poor bioavailability and pH dependent solubility are appropriate for the development of floating sustained drug delivery system [3, 4].

Atenolol is chemically (*RS*)-2-{4-[2-Hydroxy-3-(propan-2-ylamino) propoxy phenyl acetamide belonging to the β – blockers group. These class of drugs were used in the treatment of cardiovascular diseases. It induces its effect by slowing down the heart rate and decrease the workload of heart. It is poorly absorbed from the lower gastro intestinal tract and the oral bioavailability of Atenolol has been reported to be ~50%. Atenolol has a short biological half-life (6–7 hours). Development of sustained release formulation of Atenolol can be advantageous, that can provide prolong gastric retention and increase efficacy of the dosage form. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Being weak acid, pKa – 0.23, the Atenolol well absorbed from the upper portion of the GIT. Moreover, less solubility in alkaline pH of Atenolol is partly responsible for the poor bioavailability from the colon. These properties of Atenolol do not favor the traditional approach to sustained release delivery.

Hence, clinically acceptable sustained release dosage forms of Atenolol prepared with conventional technology may not be successful[5]. The purpose of development of sustained drug delivery system is to decreases the dosing frequency or to increase drug effectiveness by localization at the site of action, reducing the dose required, or providing uniform drug delivery. The multiple dosing of conventional dosage form for prolonged therapy, leads to adverse effects or toxicities and poor patient compliance, so it can be minimized by controlled-release drug delivery systems [6-12].

The main aim of this present work was to develop and evaluate matrix tablets of Atenolol by melt granulation technique and compare the drug release between bess wax and glyceryl monostearate (GMS). Polymers like HPMC K 4 M, HPMC K 100 M, bees wax, glyceryl monostearate and ethyl cellulose were incorporated in the formulation. Formulations were prepared by keeping the HPMC and ethyl cellulose at constant ratio. Bees wax and glyceryl monostearate (GMS) were used in different ratios.

MATERIALS AND METHODS:

Materials:

Atenolol was procured as gift sample from Aurobindo laboratories, Hyderabad, India. Glyceryl monostearate (GMS), HPMC K 4 M and HPMC K 100 M were obtained as gift sample from Yarrowchem, Mumbai, India. Lactose, beeswax and sodium bicarbonate were obtained as gift samples from Finar chemicals, Mumbai, India. Magnesium stearate was purchased from Otto chemicals, Mumbai, India. All solvents and reagents used were of analytical grade.

Methods:

Preparation of standard calibration curve of Atenolol:

100mg of Atenolol was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N Hcl to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1N Hcl to get 10 to 50µg/ml of Atenolol. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve. The results were shown in **Fig. 1** and **Fig. 2.** The absorption maxima found to be at 275 nm.

Preparation of Gastro retentive floating tablets:

Floating tablets containing Atenolol were prepared by melt granulation technique. Weighed amount of bees wax was taken in a china dish and melted under the steam, after melting weighed amount of glyceryl monostearate was added and melted again. To the melted mass, the drug was added and mixed well. To this remaining excipients were mixed. The mass is then passed through 22 mesh sieve. The granules were dried at room temperature, size

reduced and lubricated before compression to tablets. The tablets were prepared by using different concentrations of bees wax, glyceryl monostearate, HPMC K 4 M, HPMC K 100 M and sodium bicarbonate. The composition of gastro retentive matrix tablets shown in **Table 1.**

TABLE 1: COMPOSITION OF GASTRO RETENTIVE MATRIX TABLETS

Formulation Code	HPMC K 100 M	HPMC K 4 M	Bess wax	GMS	$NaHCO_3$
F1	20	-	10	-	8
F2	20	-	-	10	8
F3	20	-	15	-	10
F4	20	-	-	15	10
F5	24	-	15	-	12
F6	24	-	-	15	12
F7	24	-	20	-	12
F8	24	-	-	20	12
F9	28	-	25	-	12
F10	28	-	-	25	12
F11	30	-	25	-	12
F12	30	-	-	25	12
F13	-	30	25	-	12
F14	-	30	-	25	12
F15	-	34	25	-	12
F16	-	34	-	25	12

Tablet weight fixed to 200 mg. All formulations contain 50 mg drug, 1% w/w of magnesium stearate and 1% w/w of aerosil. Lactose was added as diluent.

Pre formulation studies:

It is one of the important prerequisite in development of any drug delivery system. Pre formulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Determination of Melting Point:

Melting point of Atenolol was determined by capillary method. Fine powder of Atenolol was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermo meter and the thermometer was placed in fire. The powder at what temperature it will melt was noticed.

Solubility studies:

Solubility of Atenolol was determined in ethanol (95%), chloroform, acetone, ether, water and 0.1 N Hcl. Solubility studies were performed by taking excess amount of Atenolol in different beakers containing the solvents. The mixtures were shaken for 24 hours at regular intervals. The solutions were filtered by using filter paper grade no. 41. The filtered solutions are analyzed spectrophotometrically.

Compatibility Studies:

Compatibility studies drug with excipients was confirmed by carried out by IR studies. The pure drug and its formulations along with their excipients were subjected to IR studies. IR spectroscopy was conducted using a PerkinElmer FTIR spectrophotometer and potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The FTIR spectrums were shown in **Fig. 5**, **Fig. 6**, **Fig. 7**, **Fig. 8** and **Fig. 9**.

Identification of Atenolol:

A solution of Atenolol containing the concentration 10 µg/ ml was prepared in 0.1 N Hcl and UV spectrum was taken using Agilent UV/ Vis double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Evaluation of Powder Blend:

Angle of repose: The angle of repose of powder blend was determined by the fixed funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$, Where, h and r are the height and radius of the powder cone.

Bulk density:
Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index:
The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Total Porosity:
Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V).

Porosity (%) =V_{bulk}-V/V_{bulk} x 10

Evaluation of tablets:
Weight variation test:
To study weight variation twenty tablets of the formulation were weighed using a Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content:
Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N Hcl, the drug content was determined measuring the absorbance at 275nm after suitable dilution using Agilent UV- Visible double beam spectrophotometer.

Hardness:
Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness:
The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Friability Test:
The friability of tablets was determined using Elico Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by:

% F = 100 (1-W_0/W); where % Friability of tablets less than 1% are considered acceptable.

Tablet Density:
Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of 0.1N Hcl (1.004). The density was determined using following formula:

$V = \pi r^2 h$; d = m/v;

where v = volume of tablet (cc), r = radius of tablet (cm), h = crown thickness of tablet (cm), m = mass of tablet.

***In vitro* buoyancy studies:**
The The *in vitro* buoyancy by floating lag time method described by Dave B.S.67. The tablets were placed in 250 ml beaker containing 0.1 N Hcl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form, its buoyancy in 0.1 N Hcl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or

buoyancy lag time (BLT) and the total duration of time by which dosage form remain buoyant is called total floating time (TFT).

Swelling index:

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

% Swelling index = $(W_t - W_0)/ W_0 \times 100$

Where, W_t = Weight of tablet at time t, W_0 = Initial weight of tablet

Effect of hardness on Buoyancy Lag Time:

Formulation F12 and F 16 was selected to study the effect of hardness on buoyancy lag time. The tablets of batches were compressed at different compression pressures to get the hardness of 5kg/cm^2, 6kg/cm^2, 7kg/cm^2, 8kg/cm^2 and 9kg/cm^2. The tablets were evaluated for buoyancy lag time.

***In Vitro* dissolution studies:**

Dissolution rate study of the tablets were performed by using the U.S. Pharmacopoeia (USP) model digital dissolution test apparatus type-2 (Lab India, Mumbai) at the paddle rotation speed of 50 rpm using 900 ml of 0.1 N Hcl as dissolution media at 37±0.5^{o}C. At particular time points (1, 2,3,4,6,8,10 and 12h), 10 ml samples were withdrawn by using syringe filter (0.45µm) (Sepyrane, Mumbai) and then assayed for the drug content by measuring the absorbance at 275 nm using the UV-Visible spectrophotometer (Agilent) and the volume is adjusted with a fresh medium maintained at 37 ^{o}C after each sampling to maintain its constant volume throughout the test. Dissolution experiments were conducted in triplicate (n=3). The results were shown in **Fig. 3** and **Fig.4**.

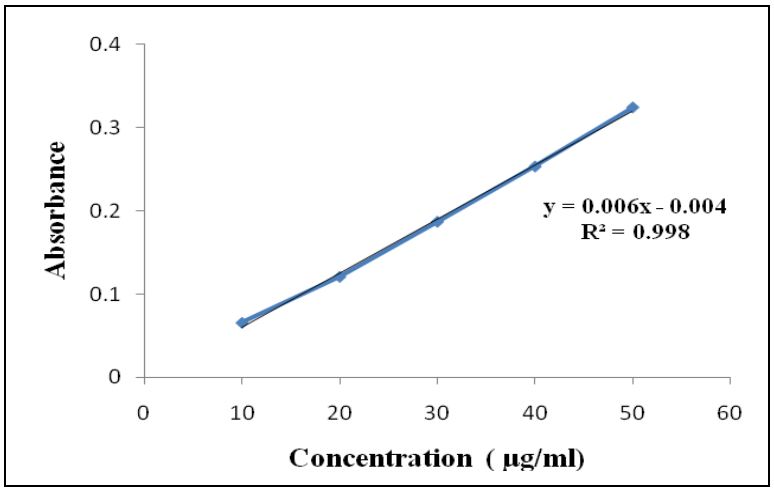

FIG. 1: STANDARD CURVE OF ATENOLOL

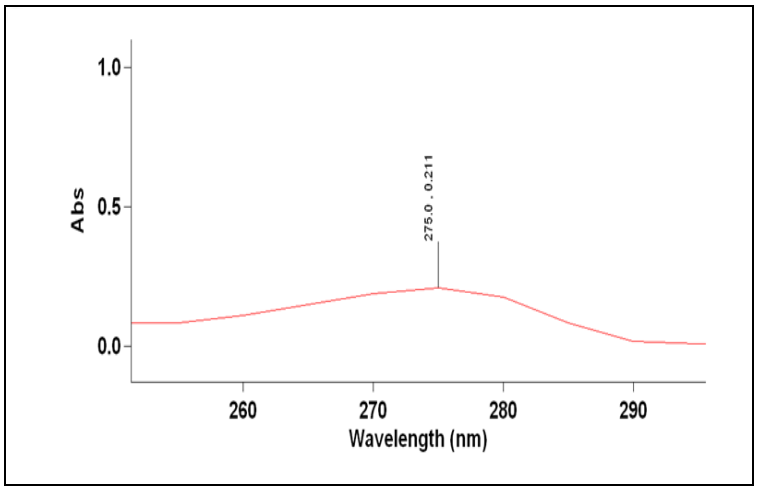

FIG. 2: MAXIMUM WAVELENGTH OF ATENOLOL

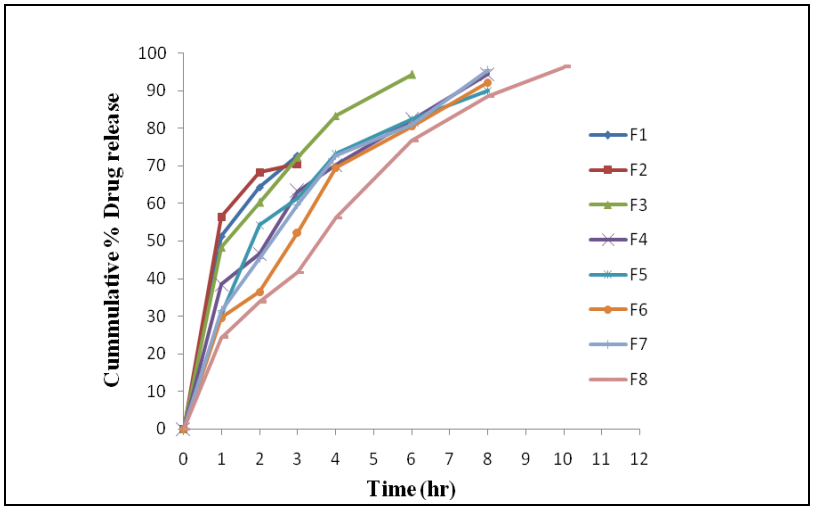

FIG. 3: DRUG RELEASE FROM FORMULATION BATCHES (F1-F8)

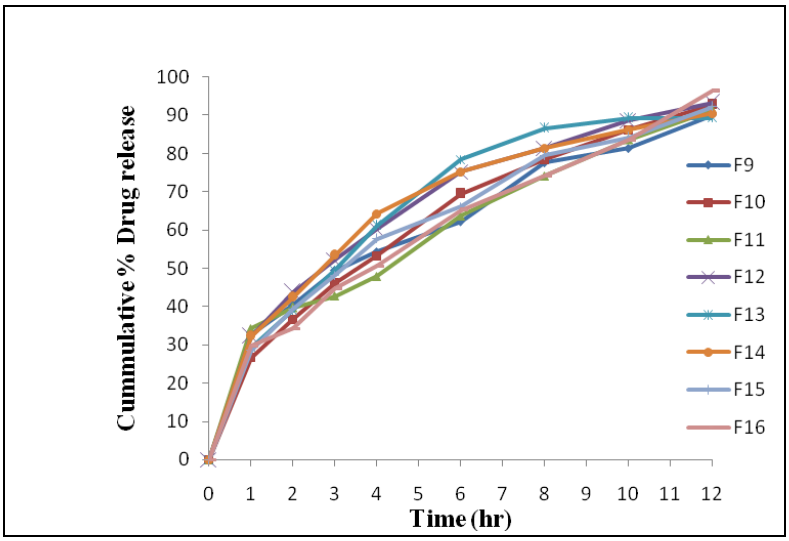

FIG. 4: DRUG RELEASE FROM FORMULATION BATCHES (F9-F16)

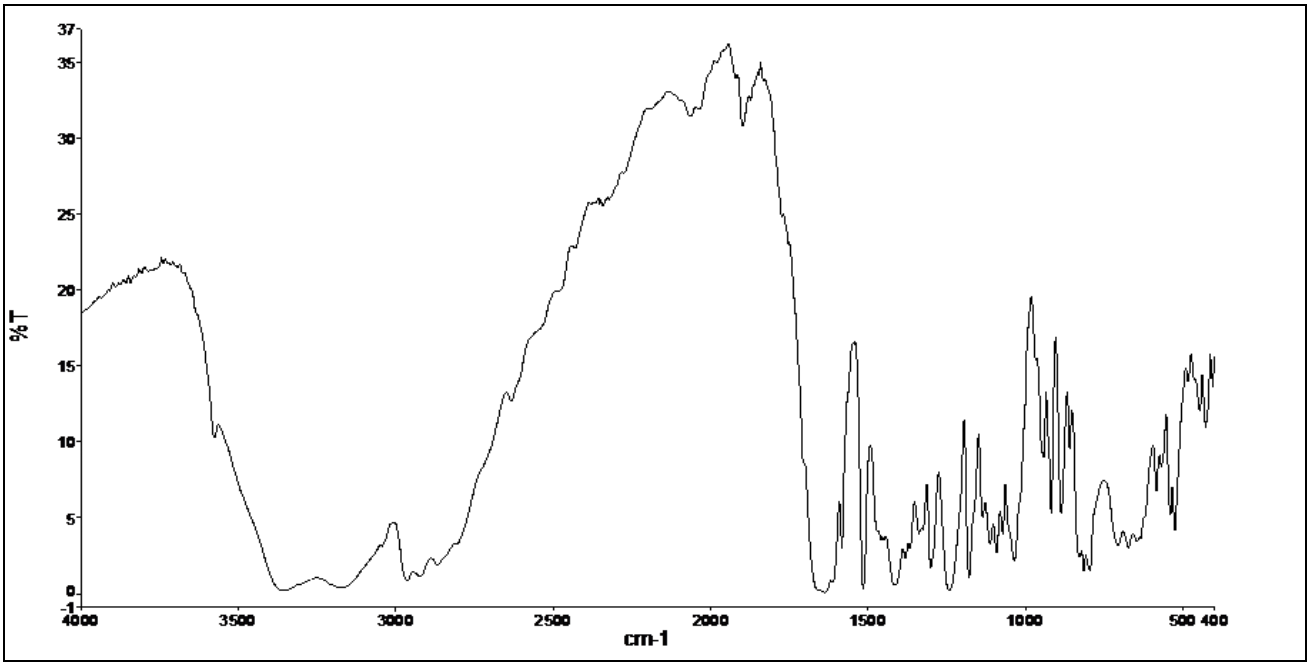

FIG. 5: IR SPECTRUM OF PURE DRUG

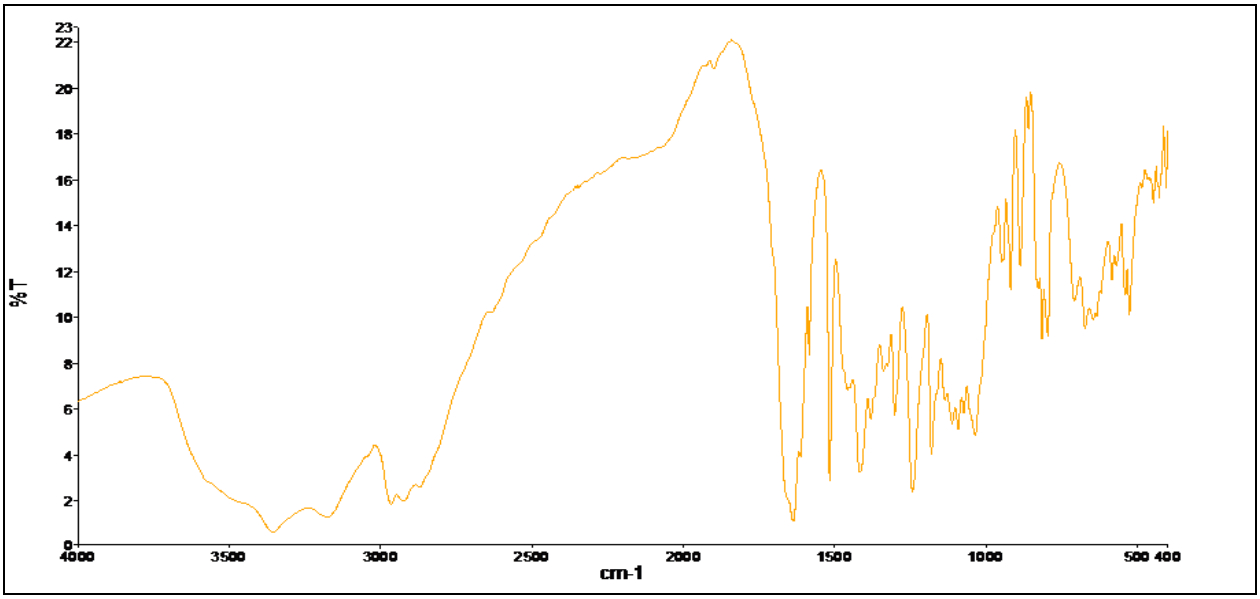

FIG. 6: IR SPECTRUM OF PHYSICAL MIXTURE OF DRUG, HPMC K 4 M, BEESWAX AND ETHYL CELLULOSE

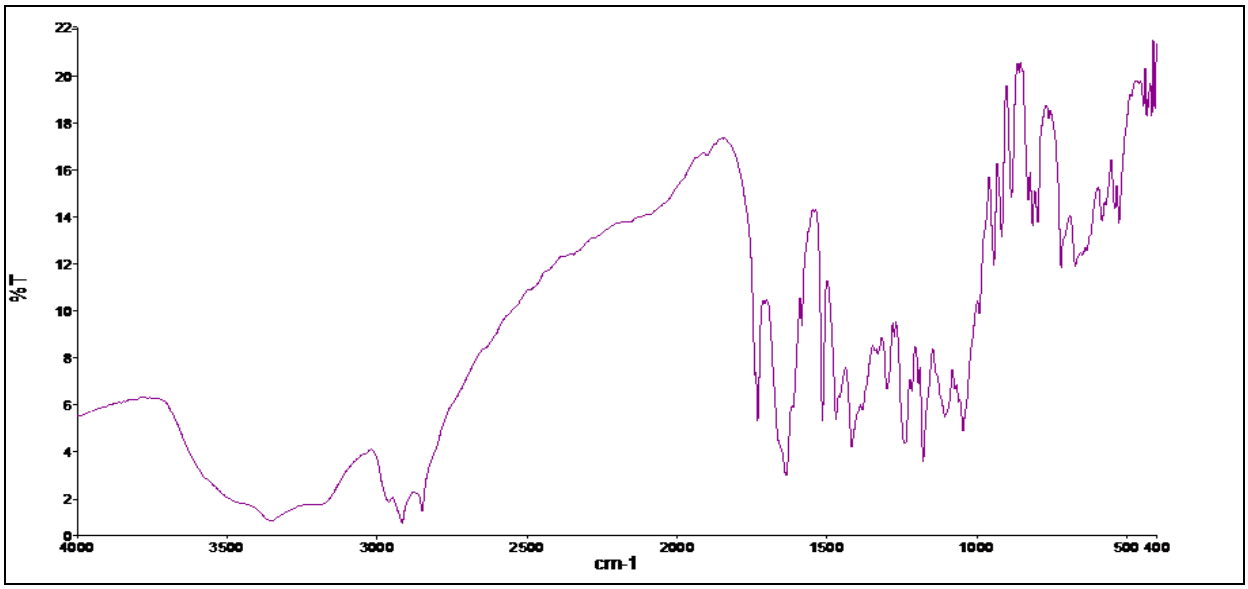

FIG. 7: IR SPECTRUM OF PHYSICAL MIXTURE OF DRUG, HPMC K 4 M , GMS AND ETHYL CELLULOSE

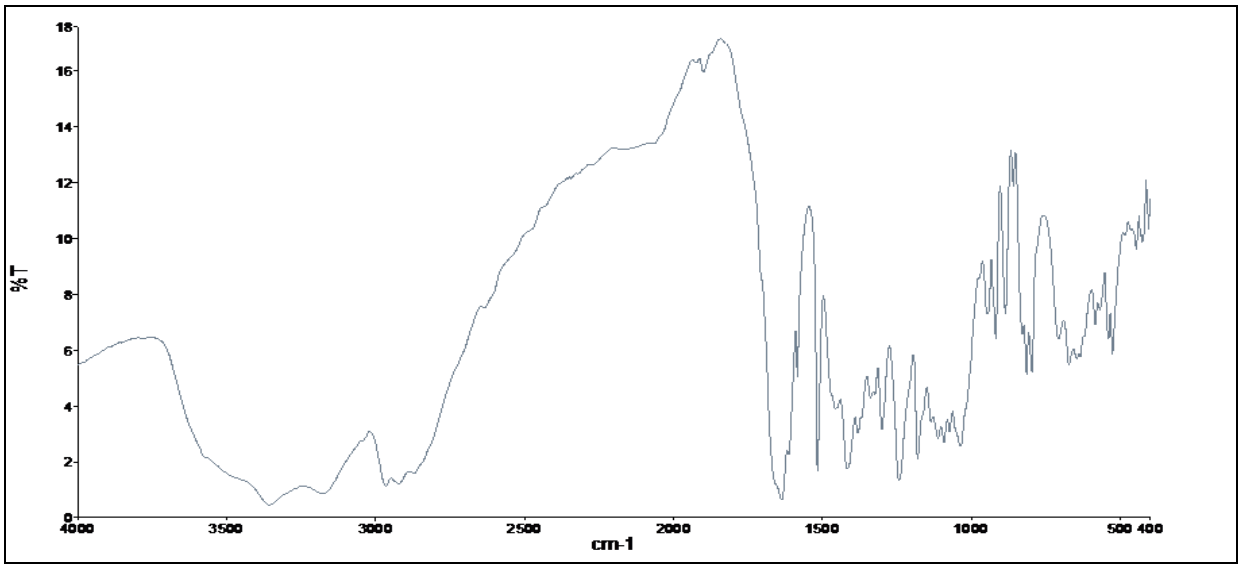

FIG. 8: IR SPECTRUM OF PHYSICAL MIXTURE OF DRUG, HPMC K 100 M , BESSWAX AND ETHYL CELLULOSE

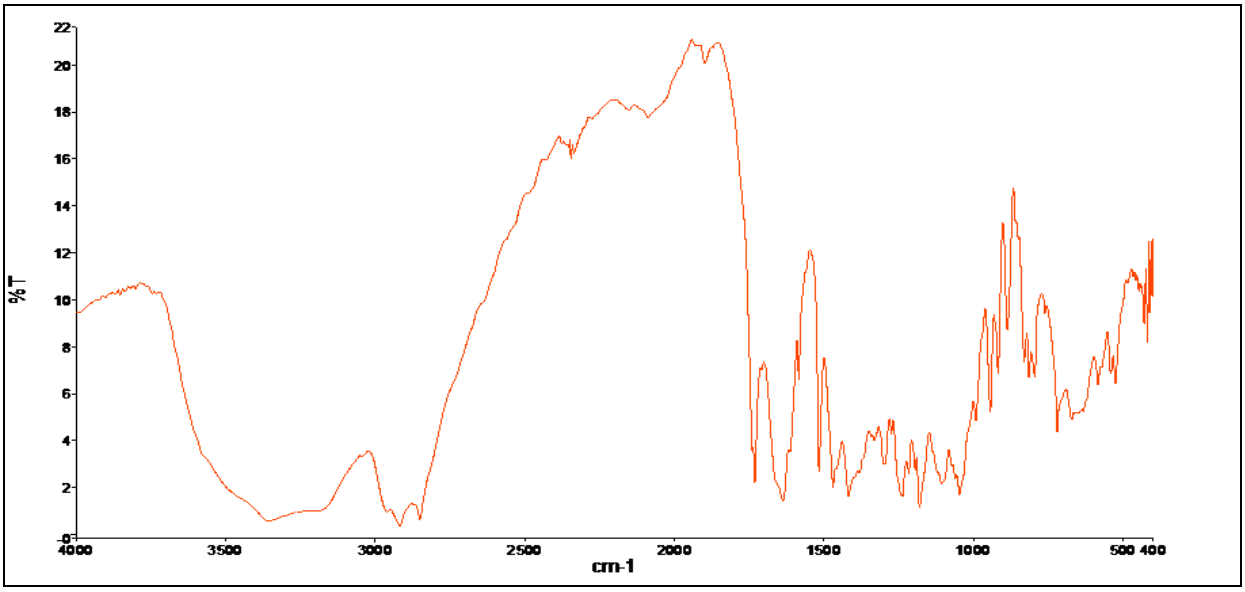

FIG. 9: IR SPECTRUM OF PHYSICAL MIXTURE OF DRUG, HPMC K 100 M , GMS AND ETHYL CELLULOSE

RESULTS AND DISCUSSION:

The hydrodynamic balanced system (HBS) is also called floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. Hydro dynamically balanced tablets Atenolol (gastro retentive drug delivery systems) were prepared and evaluated to increase its local action and bioavailability. In the present study 16 formulations with different concentration of polymer were prepared and evaluated for physico-chemical parameters, *in-vitro* buoyancy studies, *in-vitro* release studies and stability studies.

Pre-formulation studies:

Melting Point Determination:

Melting point of Atenolol was determined by capillary method. The melting point of Atenolol was found to be in the range 158-160 ^{o}C, which complied with IP standards, it indicating that the purity of the drug sample.

Solubility studies:

Atenolol was found to be freely soluble in ethanol (95%), in chloroform, ether, and practically insoluble in water. Adjusting the pH to a higher value can solubilize Atenolol, as solubility increase at pH values above its pKa.

Compatibility studies:

FT-IR results show that the crystals prepared from liquid assisted grinding method has change in their peak intensity when compared to pure drug and others. But only a slight change in peak wavelength was identified for pure drug, and crystals prepared from liquid assisted grinding method and the bonds observed are stretching bonds. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymers were studied. The characteristic absorption peaks of Atenolol were obtained at 3842.52, 3576.87, 3356.21, 3173.13, 2964.53, 2922.6, 2867.37, 2633.75, 2343.53, 2063.86, 1898.7, 1637.5 cm^{-1}. Drug- excipients interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been studied.

Here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between Atenolol and the polymers used. From the **Fig. 5, Fig. 6, Fig.7, Fig.8** and **Fig.9** were observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The

peaks obtained in the spectra's of each polymer correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

Angle of Repose (θ):
The angle of repose for the formulated blend was carried out. It concludes all the formulations blend was found to be in the range 24^0.32' to 29^0.50'. The results were shown in **Table**.**2**.

Compressibility Index:
Compressibility index was carried out, it found between 12.35% and 16.66% indicating the powder blend has the required flow property for compression. The results were shown in **Table**.**2**.

Hausner Ratio:
The Hausner ration was found between1.14 and 1.42. The results were shown in **Table**.**2**

TABLE 2: MICROMETRIC PROPERTIES OF POWDER BLEND

Powder Blend	Angle of Repose (o)	Loose Bulk Density (g/ml	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Hansner Ratio
F1	24°.50'	0.131	0.156	16.02	1.19
F2	26°.40'	0.112	0.128	15.62	1.14
F3	25°.35'	0.092	0.108	14.81	1.20
F4	28°.60'	0.110	0.132	16.66	1.20
F5	29°.50'	0.123	0.145	15.17	1.17
F6	25°.40'	0.113	0.132	14.39	1.16
F7	26°.50'	0.133	0.152	12.50	1.14
F8	24°.32'	0.135	0.154	13.47	1.14
F9	26°.68'	0.140	0.160	12.35	1.42
F10	28°.82'	0.110	0.130	15.38	1.18
F11	26°.40'	0.128	0.157	14.36	1.36
F12	28°.60'	0.133	0.125	15.45	1.28
F13	26°.50'	0.107	0.138	12.96	1.20
F14	24°.50'	0.121	0.122	14.66	1.18
F15	25°.40'	0.110	0.160	13.28	1.24
F16	28°.82'	0.116	0.158	15.15	1.40

Evaluation of tablets:
Shape of the tablet:
Microscopic examinations of tablets from F1 to F16 were found to be circular shape with no cracks.

Hardness test:
The measured hardness of tablets of each batch ranged between 4.2 to 6.2 kg/cm^2. This ensures good handling characteristics of all batches.

Friability Test:
The values of friability test were tabulated in **Table 3**. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation Test:
The percentage weight variations for all formulations were tabulated in **Table 3**. All the formulated (F1 to F16) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5 % of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content Uniformity:
The percentage of drug content for F1 to F16 was found to 98.24% to 101.52% of Atenolol, it complies with official specifications. The results were shown in **Table 3.**

Tablet density: When tablet contacts the test medium, tablet expanded (because of swell able polymers) and there was liberation of CO_2 gas (because of effervescent agent, $NaHCO_3$). The density decreased due to this expansion and upward force of CO_2 gas generation. This plays an important role in ensuring the floating capability of the dosage form. To provide good floating behavior in the stomach, the density of the tablets should be less than that of the gastric contents the density below (1.004g/cm3) than of gastric fluid. For formulation F1-F16 density were found to be less than that of the gastric content. The results were shown in **Table**.**3**.

TABLE 3: EVALUATION OF PHYSICAL PARAMETERS OF FLOATING TABLETS

Tablets Batch	Weight variation test (%)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
F1	± 1.75	0.37	5.9 ±0.47	4.04 ± 0.2	98.50
F2	±3.52	0.76	4.6 ±0.72	4.12 ±0.015	99.05
F3	±2.15	0.56	4.8 ±1.29	4.19 ±0.017	98.47
F4	±1.56	0.76	5.4 ±0.28	4.13 ±0.06	101.20
F5	±3.54	0.59	6.2 ±0.45	4.14 ±0.11	99.75
F6	±1.42	0.70	4.5±0.29	4.15 ±0.012	99.37
F7	±2.11.	0.56	4.2 ±0.64	4.12 ±0.014	100.59
F8	±1.89	0.79	5.2 ±0.24	4.13 ±0.016	101.52
F9	±2. 56	0.93	5.7 ±0.28	4.06 ±0.012	98.24
F10	±2.04	0.67	5.4 ±0.86	4.08±0.011	98.36
F11	±1.56	0.70	6.2 ±0.45	4.19 ±0.017	99.57
F12	±1.89	0.37	5.7 ±0.28	4.15 ±0.012	99.36
F13	±1.42	0.27	5.9 ±0.47	4.06 ±0.012	101.45
F14	± 1.75	0.33	5.4 ±0.86	4.08±0.011	99.17
F15	±1.89	0.29	5.4 ±0.28	4.19 ±0.017	99.37
F16	±1.42	0.57	5.7 ±0.28	4.14 ±0.11	99.45

***In vitro* Buoyancy Study:**

On immersion in 0.1N Hcl solution pH (1.2) at 37^{o}C, the tablets floated and remained buoyant without disintegration. From the results it can be concluded that the batches containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation containing HPMC K 4 M, HPMC K 100 M and Ethyl cellulose showed good BLT of 52 sec. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Swelling study: Swelling study was performed on all the batches (F1 to F16) for 5 hr. The results of swelling index were shown in **Table 4**. From the results it was concluded that swelling increases as the time increases, because the polymer gradually absorb water due to hydrophilicity. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batches F12 and F16 Containing HPMC K 4 M, HPMC K 100 M and Ethyl cellulose. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence it can be concluded that linear relationship exists between swelling process and viscosity of polymer. The results were shown in **Table**.**4**.

TABLE 4: SWELLING INDEX OF TABLETS OF BATCH F1 TO F16

Formulation	1 h	2 h	3 h	4 h	5 h
F1	32	39	41	-	-
F2	33	38	43	-	-
F3	31	38	44	52	68
F4	40	51	62	13	90
F5	35	42	49	57	68
F6	29	36	48	59	62
F7	36	46	56	64	77
F8	48	59	65	78	82
F9	30	41	46	54	60
F10	42	51	67	76	91
F11	36	48	65	79	86
F12	40	61	72	82	91
F13	31	48	56	69	75
F14	33	49	55	65	72
F15	35	47	59	67	81
F16	36	49	68	78	90

***In vitro* Dissolution Study and Kinetic modeling of drug release:**

All the sixteen formulation of prepared floating tablets of Atenolol were subjected to *in-vitro* release studies these studies were carried out using dissolution apparatus, 0.1N Hcl (pH 1.2). The kinetic values obtained for formulation F12 and F16 were shown in **Table 5**. The values of *in vitro* release were attempted to fit into various mathematical models. The regression coefficients values for formulation F12 of zero order and first order plots were found to be 0.858 and 0.993 respectively. The regression coefficients values for the formulation F 16 of zero and first order plots were found to be 0.933 and 0.894 respectively. This Higuchi plot was almost linear with regression coefficient values of 0.99 and 0.993 for formulations F12 and F16 respectively.

The linearity suggests that the release of Atenolol from glyceryl monostearate and HPMC was diffusion controlled. Peppas – korsmeyer model is widely used when the release mechanism is not well known or when more than one type of release phenomenon was involved. The 'n' value for F12 and F 16 were found to be 0.438 and 0.492 respectively, which indicates that the release was approximates fickian diffusion. The *in-vitro* drug release profile of tablet from each batch (F1 to F16) was carried out and results shown in **Fig.3** and **Fig.4**. From the *in-vitro* dissolution data it was found that formulations F1 and F2 shown the drug release for 3 hours. This is because the tablets were not intact in nature and floating time was decreased due to lesser amount of sodium bicarbonate and HPMC.

Formulations F1 to F8 showed their drug release less than 10 hours indicating that the polymer amount is not sufficient to control the drug release F7 released more than 90% of drug before 10 hr of the study. While F9 to F16 shows good drug release, it concludes F9 to F16 had better controlled release than the other formulations. Formulation F12 and F16 were optimized by the following data: 1) The formulations showed better floating lag time.2)The tablets remained intact for 12 hrs and buoyancy floating time upto 12hrs. 3) The formulations showed better drug release.4) F12 showed first order kinetic drug release where as F16 showed zero order kinetic release.

TABLE 5: KINETIC VALUES OBTAINED FROM *IN VITRO* RELEASED DATA OF FORMULATIONS F12 AND F16

		Zero	First	Krossmayer peppas	Higuchi	Hixon	N peppas
F12	K	6.717	-0.2118	32.5	27.17	-0.194	0.438
	r^2	0.858	0.993	0.995	0.99	0.995	
F16	K	6.954	0.227	26.73	27.02	-0.212	0.492
	r^2	0.933	0.894	0.979	0.993	0.954	

CONCLUSION: The aim of the study was to develop and physico- chemically characterized gastro retentive matrix tablets of Atenolol based on a low density polymer. Different types of matrix forming polymers were studied: HPMC K 4 M, HPMC K 100 M, glyceryl monostearate and Bees wax, for the study. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. The release rate could effectively be modified by varying the ''wax/polymer'' ratio. The floating behavior of the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns. The batch optimization was done using HPMC K 4 M, HPMC K 100 M , glyceryl monostearate and Bees wax, as they gave optimum FLT as well as long acting affect and no / least eroding effect. It was also found that the tablet formulations released more than 90 % drug in 12 hours as desired.

Gastro retentive (low density) tablets of Atenolol were prepared using polymer which not only imparted buoyancy to the formulations but also reduced floating lag times to a great extend. The use of HPMC K 4 M, HPMC K 100 M polymer in matrix tablets as density reducing agent has given a different look while Waxes used as release retardants. During the study with the polymer various characteristics of the material were observed; like highly porous spherical structure, good compressibility, good flow property with drug

and other polymers, no significant effect on drug release and compatibility with drug and other polymers as seen through IR spectra. Thus it is summarized and concluded that HPMC K 4 M, HPMC K 100 M, Bees wax and glyceryl monostearate can be successfully used in the formulation of Atenolol sustained release gastro retentive floating drug delivery system. From the compatibility studies, it was concluded that HPMC K4M, HPMC K100M, Bees wax and Glyceryl monostearate were compatible with Atenolol and thus suitable for the formulation of Atenolol floating tablets.

In vitro buoyancy studies were performed for all the formulations, F1 to F16 by using 0.1 N HCL solution at 37 ºC. All the formulations were floated except F1, F2, F3 and F4. The formulation F12 and F16 containing HPMC K 100 M and HPMC K 4 M respectively showed optimum drug release than the other formulations. *In vitro* dissolution studies were also performed for all formulations. The formulation F16 showed the controlled release for 12 hours with HPMC K 4 M and glyceryl monostearate. F12 showed optimized release of drug with HPMC K 100 M, glyceryl monostearate. Thus F12 and F16 were identified as ideal batches based on their results. Finally, it was concluded that HPMC K 4 M, HPMC K 100 M along with Bees wax and Glyceryl monostearate can be successfully used in the formulation of Atenolol sustained release gastro retentive floating drug delivery system.

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