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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ATENOLOL BY USING NATURAL GUM

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Keywords:

Chronopharmaceutical drug delivery system, Pulsatile drug delivery system, Controlled Release Drug Delivery System and Sustained Released Drug Delivery System.

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ABSTRACT: The recent work is based on the extraction and purification of natural gum from the bark of plant *Terminalia elliptica* (local name - Saaj) and the use of this gum to prepare pulsatile Drug Delivery System of Atenolol for the chronotherapy of cardiovascular diseases. Three formulations CF1, CF2, CF3 of core tablets were prepared by direct compression technique by varying concentrations of crospovidone and evaluated. Formulation CF3 showed the highest 98.71% of drug release after 30 min was selected for press coating. Press coated tablets of Formulation F1 to F5 were prepared by direct compression technique using varying combinations of Saaj gum and Ethylcellulose in the ratio of 1:0, 3:1, 1:1, 1:3 and 0:1 respectively by taking CF3 as core in all. The extracted gum, powder blends, core tablets, and press coated tablets all were evaluated for their physicochemical properties. From the dissolution study of formulation F1 To F5 it was found that F2 having 3:1 combination of Saaj gum and EC shows a significant lag time of around 7 h by releasing only 4.09% of drug which followed by a bulk release of 97.61% of drug in between 7 to 8 h. The drug release kinetic studies of F2 shows the highest R^2 value *i.e.* 0.463 for the Korsmeyer Peppas model. The evaluation parameters like weight variation, hardness, friability, the thickness of F2 was found to be 555 ± 5, 6.6 ± 1.1 kg/cm^2, 0.43 ± 0.1%, 5.7 ± 0.7 mm respectively, which meets with the official limits given in IP, BP, and USP.

INTRODUCTION: Today's world's hypertension and heart diseases are global health challenges. These diseases follow the circadian rhythm. Most of the heart-related problems take place in the early morning due to fluctuation in blood pressure at a weak up period. For a long time, CRDDS or SRDDS are commonly adopted to manage such problems.

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These dosage forms release the drug for 24 h, hence confirms the presence of the drug in the body for the whole treatment period. A long term exposure of our body to certain drugs especially during the treatment of chronic heart diseases may lead to drug tolerance by the body. This situation demands such dosage forms which unlike CRDDS & SRDDS release the drug in a time-specific manner based on the circadian cycle of the diseases.

During chronic therapy, this kind of dosage forms not only reduces the unnecessary side effect exerted by the drugs to the body but also reduces the drug tolerance as well as the amount of drug required during the whole treatment period.

Some recently designed pulsatile drug delivery systems are as follows. N. A. Paul, *et al.,* in 2017 prepared press coated pulsatile release tablets of Cilnidipine using an admixture of hydrophilic polymer *i.e.* hydroxypropyl methylcellulose and pH-sensitive polymers like ethylcellulose, eudragit S-100 in order to achieve a predetermined lag time for chronopharmacotherapy of hypertension [1].

V. V. Bilaskar, *et al.,* in 2018 designed the pulsincap of Irbesartan used for the treatment of high blood pressure and diabetic nephropathy to control heart attack [2]. S. Saraf, *et al.,* in 2018 successfully designed pulsatile release capsule of Ramipril for controlling morning spate of blood pressure using xanthan gum and guar gum *etc.* [3]

C. Adhikari *et al.,* in 2018 designed a time-controlled single unit oral pulsatile drug delivery system containing salbutamol sulphate for the prevention of nocturnal asthma attacks using different compositions of hydrophobic and hydrophilic polymers ethylcellulose-20, hydroxy-propyl methylcellulose K4M and low substituted hydroxypropyl cellulose [4]. A.Y. Kanugo, *et al.,* in 2018 prepared a pres coated tablet for pulse release of candesartan cilexetil using a hydrophilic polymer as HPMC and hydrophobic polymer as ethyl cellulose in various combinations [5].

Nikunja B. Pati *et al.,* in 2018 fabricated pulsatile Press-coated tablets of tapentadol HCl by using various combinations of HPMC K100, HPC, EC as the rate-controlling membrane [6]. Recently A. Shrivastava in 2018 made a review on the requirement of pulsatile drug delivery systems for beta-blockers [7].

The rationale of this study is to design and evaluate a novel cost-effective oral pulsatile chrono-modulated drug delivery system of Atenolol by press coated technique using blends of Saaj gums and Ethyl Cellulose as coating materials in such a way that, taking a tablet at night at a specific time before sleeping release the drug at early morning before weak up of the patient.

The drug is contained within the core tablet separated from the polymer. The entire core tablet is coated by polymers blends to achieve the desired lag time in drug release.

EXPERIMENTAL:

Materials and Methods:

TABLE 1: SOURCES OF INGREDIENTS

Ingredients	Source
Atenolol	Yarrow chem. products, Mumbai-400037, (India)
Micro |Crystalline cellulose	Yarrow chem. products, Mumbai-400037, (India)
Cross Povidone	Yarrow chem. products, Mumbai-400037, (India)
Talc	LOBA CHEMIE PVT. LTD. P. BOX NO. 6139, MUMBAI-400005 (India)
Magnesium stearate	Central drug house (P) LTD. P Box No-1495, Delhi-6
Ethyl cellulose	Himedia Laboratories PVT. LTD. 23, Vadhani Ind Est, LBS Marg, Mumbai-400086, India
Saaj gum	Nrusinghanath of Bargarh District, Odisha

TABLE 2: INSTRUMENT USED

Analytical Digital Balance	Precisa 205Ascs.Rolex.India
Standard Sieve	Rolex. Ambala
Tablet punch machine	Single Punch Hand Operated Rolex. India
Friability Tester	Thermonik, FT-20, Cambell electronics
Monsanto hardness tester	Rolex. Ambala
pH meter	Unilab India
Disintegration apparatus	ELECTROLAB.
Dissolution Apparatus	ELECTROLAB. Model-TDT-08L USP
Double beam UV	SHIMAZDU. model-UV-1800

Identification and Standardization of Natural Gum Extract: The Gummy exudates were collected from the bark of the plant *Terminalia elliptica* (Saaj gum) in the forest of Nrusinghanath of District Bargarh, Odisha and dried under the sunlight at room temperature. Then the obtained solid mass was triturated and passed through mess no. 100. 10 gm of powders were dissolved in 250 ml of distilled water under stirring and precipitated with two times its volume of acetone. Then the precipitate was dried in the oven till complete drying. Powdered obtained passed through sieve number 80 and stored in desiccators for use in sub-sequent tests. The yield was found to be 6.4 gm [8, 9].

Molisch's Test: 100 mg of dried gum powder were mixed with Molisch's reagent and concentrated H_2SO_4 on the side of a test tube. The result is given in **Table 3**.

Organoleptic Properties: The isolated gums were evaluated for color, odor, shape, taste and special features like touch and texture. The majority of information on the identification, purity, and quality of the material can be drawn from these observations. The results are given in **Table 3**.

Solubility Test: The separated gums were evaluated for solubility in water, acetone, chloroform, methanol, ether, and ethanol in accordance with the Indian Pharmacopoeial specifications. The results are given in **Table 3**.

Loss on Drying (LOD): LOD is used to determine high levels of moisture or solvents present in the sample. 1.0 g of the powder gum were weighed and transferred into petridish and then dried in an oven at 105 ºC for 2 h constant weights were obtained. The sample was cooled in the dry atmosphere of desiccators and then reweighed. The percentage loss of moisture on drying was calculated using the formula and expressed as a percentage. The result is given in **Table 3**.

LOD (%) = (Weight of water in sample / Weight of dry sample) × 100

Swelling Index: Accurately weighed 1 g of gum powder was transferred into a 25 ml glass Stoppard measuring cylinder. The initial bulk volume was noted. Then 25 ml of water was added and the mixture was shaken thoroughly every 10 min for 1 h. It was then allowed to stand for 3 h at room temperature. Then the volume occupied by mucilage was measured. The same procedure was repeated thrice and the mean value was calculated. The results are given in **Table 3**.

$$\text{Swelling index (SI)} = V_2\text{-}V_1/V_1\times 100$$

Where: V_1 is an initial volume of gum powder before hydration. V_2 is a volume of swollen gum powder after (3 h) hydration.

pH Determination: 1% w/v solution of gum with water was prepared and shaken for 5 min. The pH of the solution was determined using a digital pH meter. The result is given in **Table 3**.

Ash Values:

Total Ash: Procedure based on Indian Pharma-copoeia. Accurately 3 g of sample was taken in a silica crucible, which was previously ignited and weighed. The powder was spread as a fine, even layer on the bottom of the crucible. The crucible was incinerated gradually by increasing temperature to make it dull red hot until free from carbon. The crucible was cooled and weighed. The procedure was repeated to get constant weight. The percentages of total ash were calculated with reference to air-dried sample. The result is given in **Table 3**.

TABLE 3: IDENTIFICATION TESTS OF THE GUM

S. no.	Parameters	Observed	Results
Terminalia elliptica gum	Molisch's test	Violet-green color present at the junction of two layers	Carbohydrate present

Parameters	Observed
Organoleptic properties	Light green color, amorphous nature, odorless.
Solubility of *Terminalia elliptica* gum	Gums is well soluble in water and swell to form gel and practically insoluble in acetone, ethanol, chloroform and other organic solvents.
Loss on drying (%)	7.3%
Swelling index in distilled water	62.2%
Bulk density	0.384 g/ml
Tapped density	0.5 g/ml
Compressibility index	23.2%
Hausner's ratio	1.412
Angle of repose (º)	18.52°
pH (1% w/v)	6.5
Total Ash (%)	19%

FTIR Study of Atenolol and its Mixture with Excipients: The pure drug and its formulations along with their excipients were subjected to FTIR spectroscopy, results were shown in **Fig. 1**, **2**, **3** and **4** & **Table 4** and **5** [10].

TABLE 4: FTIR STUDIES OF ATENOLOL

Group	Range (cm^{-1})	No. of peaks
C-H Stretching (alkane)	2960-2850	1
C-H bending (aromatics)	700-850	2
C=C Stretching (alkene)	1680-1620	1
C=C Stretching (aromatics)	1450-1600	7
O-H bending (alcohol)	1050-1150	1
C-O Stretching (alcohol)	1250-1350	2
C-O Stretching (phenol)	1310-1410	2
N-H Bending	1500-1650	5
C-N Vibration	1000-1400	7
C=N Stretching	1630-1690	1
N=N Stretching	1575-1630	1
C=S Stretching	1050-1200	2
S=O Stretching	1050-1400	6

Spectrophotometric Analysis of Atenolol: A 10 µg/ ml solution of Atenolol was prepared in 6.8 phosphate buffer and absorbance maximum (λ max) was determined by scanning in the range of 200 – 400 nm using the double beam, Shimadzu UV/Visible 1700 spectrophotometer. The λ_{max} was found to be 271 nm.

Preparation of Calibration Curve of Atenolol: 1 mg/ml (1000 µg/ ml) stock solution of drug with 6.8 phosphate buffer was prepared. From this stock solution, 5 ml of solution was withdrawn to 50 ml of volumetric flask and made of the volume with 6.8 pH phosphate buffers to produce 100 µg/ml concentrations. From the above solutions 2, 4, 6, 8, 10, 12 ml of the samples were pipette out into 10 ml volumetric flask. The volume was made up to mark with 6.8 pH buffer solutions to produce concentration as 20, 40, 60, 80, 100 and 120 µg/ml of Atenolol respectively. The absorbance of the prepared solution of Atenolol was measured at 271 nm against the blank. The standard graph was plotted by taking concentration on X-axis and absorbance on Y-axis. The graph yields a straight line, which shows that the drug obeys Beer's law in the concentration range of 20-120 mcg/ml. The results are shown in **Fig. 5** & **Table 6** [11].

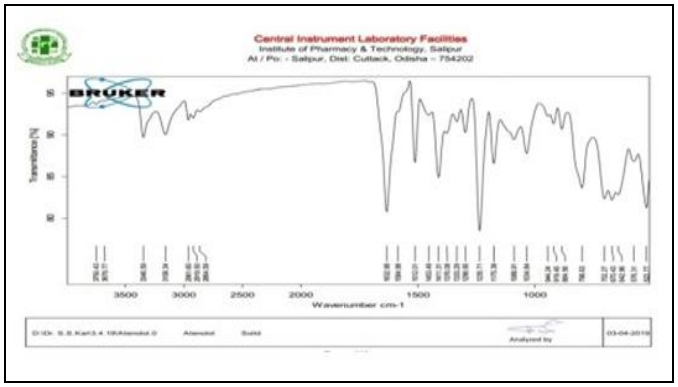

FIG. 1: FTIR SPECTRUM OF PURE DRUG (ATENOLOL)

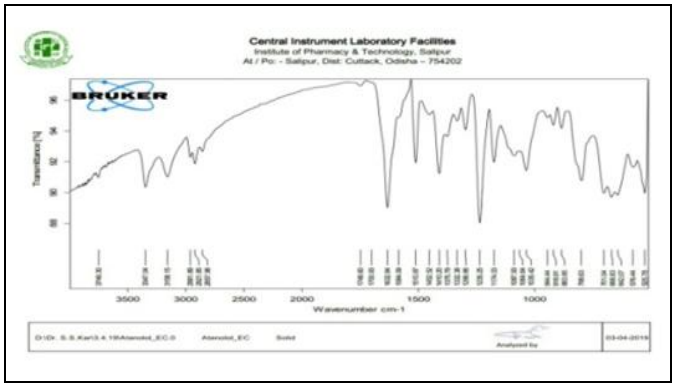

FIG. 2: FTIR SPECTRUM OF ATENOLOL WITH ETHYL CELLULOSE

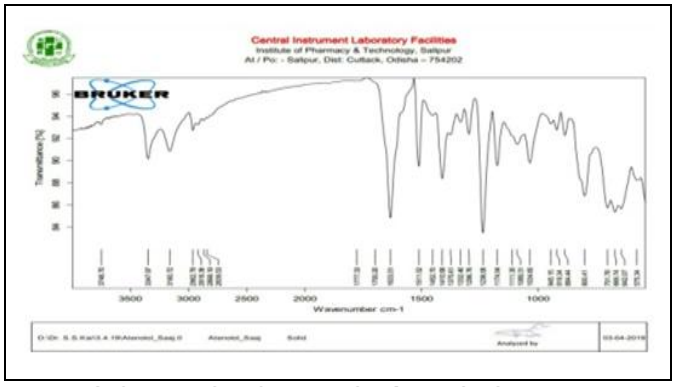

FIG. 3: FTIR SPECTRUM OF ATENOLOL WITH SAAJ GUM

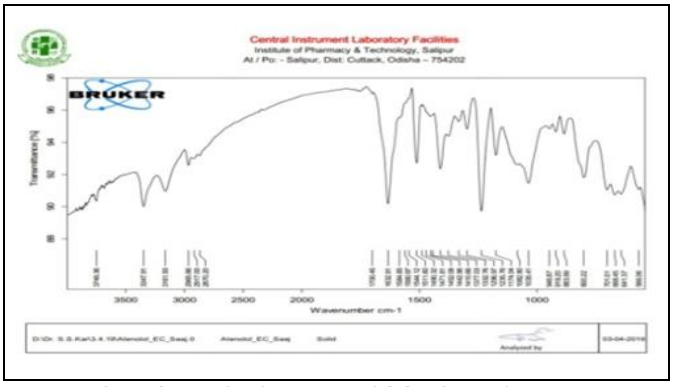

FIG. 4: ATENOLOL WITH SAAJ GUM & ETHYL CELLULOSE

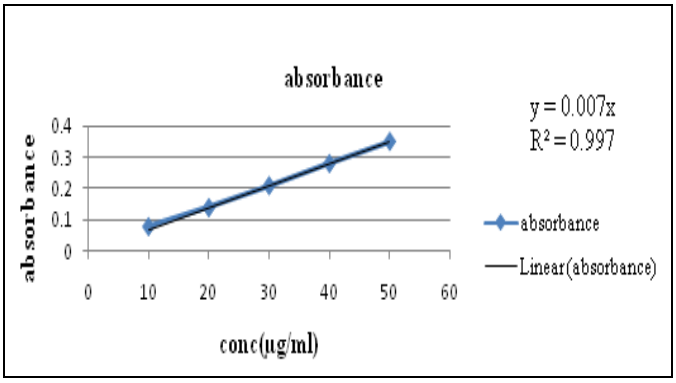

FIG. 5: CALIBRATION CURVE OF ATENOLOL

TABLE 5: FTIR STUDY OF ATELOLOL WITH ETHYL CELLULOSE AND SAAJ GUM

Group	Range (cm^{-1})	No. of peaks in atenolol
C-H Stretching (alkane)	2960-2850	2
C-H Bending (aromatic)	700-850	2
C=C Stretching (alkane)	1680-1620	1
C=C Stretching (aromatic)	1450-1600	3
O-H Bending (alcohols)	1050-1150	1
C-O Stretching (alcohols)	1250-1350	2
C-O Stretching (phenols)	1310-1410	2
N-H Bending	1500-1650	3
C-N Vibration	1000-1400	7
N=N Stretching	1575-1630	2
C=S Stretching	1050-1200	2
S=O Stretching	1050-1400	7

TABLE 6: ABSORBANCE OF ATENOLOL IN pH 6.8 PHSPHATE BUFFER

Concentration (µg/ml)	Absorbance
10	0.08
20	0.14
30	0.21
40	0.28

Formulation of Powder Blends for Core Tablets: Based on the given **Table 7** an accurately weighed amounts of atenolol, microcrystalline cellulose (Avicel), crospovidone and talc were dry blended for about 15 min followed by addition of magnesium stearate. The mixture was then further blended for 10 min.

TABLE 7: CORE FORMULATION OF ATENOLOL

Ingredients	CF1	CF2	CF3
Atenolol	25	25	25
Micro Crystalline Cellulose	118	116.5	115
Crospovidone	3	4.5	6
Talc	2	2	2
Mg. stearate	2	2	2
Total wt.	150	150	150

Bulk Characterization of Powders Blends:

Bulk Density: A quantity of 2 g of powder blend from each formula, previously shaken 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 [12].

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

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

Results are given in **Table 8.**

Tapped Density (D_t): It is the ratio of the total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%.

If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$D_t = M / V_t$$

Where M and V_t are mass of powder and tapped volume of the powder respectively. The results are given in **Table 8**.

Hausner Ratio: Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\text{Hausner ratio} = D_t / D_b$$

Where D_t and D_b are tapped density and bulk density respectively. The results were shown in **Table 8**.

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:

$$\text{Carr's Index (\%)} = [(TBD-LBD) \times 100] / TBD$$

The results are given in **Table 8.**

Angle of Repose: The angle of repose of the 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 θ = h/r, Where, h and r are the height and radius of the powder cone. The results are given in **Table 8**.

TABLE 8: BULK CHARACTERIZATION OF THE POWDER BLENDS FOR CORE TABLETS

Batch	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's index	Hausner's ratio	Angle of repose
CF1	0.2396	0.281	14.90	1.17	27.84
CF2	0.2393	0.276	13.38	1.15	27.39
CF3	0.2383	0.275	13.43	1.15	26.90

Preparation of Core Tablet: Base on **Table 7** the inner core tablets were prepared by using the direct compression method. 150 mg of the resultant powder blend was manually placed in the die and compressed using Single Punch Hand Operated tablet punching machine [13].

Evaluation of Core Tablets:

The Percentage Weight Variations Test: The weight of the core tablet being made was routinely determined to ensure that a tablet contains the proper amount of drugs. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. Results are given in **Table 9** [13].

Hardness Test: The resistance of core tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester according to IP. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded. The results are given in **Table 9**.

Disintegration Test: Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in the Electro lab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top and held against a 10 mesh screen, at the bottom end of the basket rack assembly.

To test the disintegration time of core tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing 6.8 phosphate buffer solution at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted in **Table 9**.

Friability Test: 20 core tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded in **Table 9**.

Thickness Test: Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation, recorded in **Table 9**.

TABLE 9: EVALUATION PARAMETERS OF ATENOLOL CORE TABLETS

Formulation	Wt. variation	Hardness (Kg)	Friability (%)	Thickness (mm)	Content uniformity test (%)	Disintegration time (min)
CF1	150 ± 5	4 ± 0.4	0.7 ± 0.3	3.2 ± 0.3	93.09	4 min 23 sec
CF2	149 ± 3.5	4.5 ± 1.5	0.4 ± 0.2	2.9 ± 0.4	91.22%	3min 22 sec
CF3	148 ± 2	5.3 ± 1.4	0.6 ± 0.3	3 ± 0.9	98.82	3 min 54 sec

Content Uniformity: The core tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 200 mg was weighed accurately and dissolved in 100 ml of the buffer used. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman's filter paper no. 41. The results are given in **Table 9**.

Dissolution Test of Core Tablets: The *in-vitro* release of Atenolol core tablets was performed using IP dissolution apparatus type 1 (Paddle). The test was carried out in 900 ml of 7.4 pH phosphate buffer solution. The test was performed at a temperature of 37 ± 0.5 ºC and 50 rpm for 60 minutes. Tablets were in dissolution jar and 5 ml samples were taken at 10 min interval for 60 minutes. The samples were withdrawn and filtered. The solution was replaced with the same dissolution medium. The samples were analyzed for Atenolol at 275 nm by using a UV spectrophotometer using ph 7.4 phosphate buffer solutions as blank. Results are given in **Table 10** & **Fig. 6**.

TABLE 10: % DRUG RELEASE OF CORE TABLETS

Time (Min)	CF1 (3%)	CF2 (4%)	CF3 (5%)
5	31.32	36.00	4232
10	43.45	44.09	51.81
15	59.60	66.32	69.76
20	79.33	81.42	80.01
25	86.01	89.00	93.35
30	92.21	96.59	98.71

TABLE 11: FORMULA OF ATENOLOL PRESS COATED TABLET

S. no.	Ingredients	F1	F2	F3	F4	F5
1	Saaj gum	400	300	200	100	0
2	EC	0	100	200	300	400
3	Total Wt	400	400	400	400	400

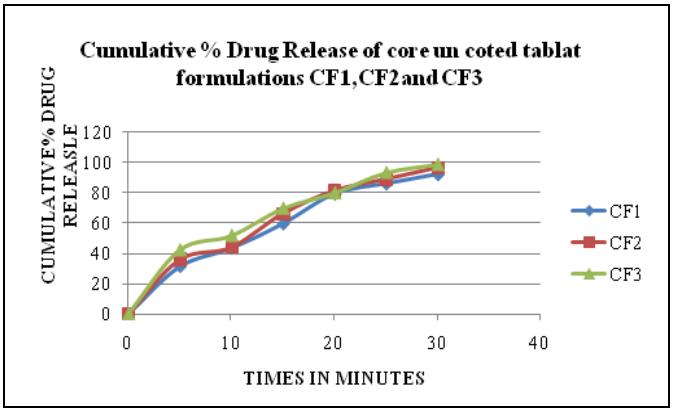

FIG. 6: PERCENTAGE DRUG RELEASE OF CORE TABLETS

Formulation of Press Coated Tablet: The different concentrations of mixtures of Saaj gum and EC as given in **Table 11** were accurately weighed and dry blended for 10 min. The pulsatile press-coated tablets were prepared by half of the barrier layer mixture into die, then the core tablet was placed manually at the center of the die. The remaining half mg of the barrier layer mixture was added into the die and directly compressed. Thus, formed Atenolol press coated tablets are ready for further tests and *in-vitro* drug release [13, 14].

Evaluation of Press Coated Tablets:

Weight Variation Test: The percentage of weight variations for all formulations were given. All the formulated (F to F5) tablets passed weight variation test and compared with the specified limit according to USP. Results are given in **Table 12** [13, 14].

Hardness Test: The hardness of each batch of press coated tablet was checked by using Monsanto hardness tester according to IP. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded. The results are given in **Table 12**.

Thickness: Thickness was measured using Vernier Calipers in millimetre. Results are given in **Table 12**.

TABLE 12: EVALUATION PARAMETERS OF ATENOLOL PRESS COATED TABLETS

Formulation	Wt. variation	Hardness (Kg)	Friability (%)	Thickness (mm)	Swelling index (%)
F1	557 ± 4	5.9 ± 1.2	0.62 ± 0.5	5.9 ± 0.2	278%
F2	555 ± 4	6.6 ± 1.1	0.43 ± 0.1	5.7 ± 0.7	153%
F3	554 ± 5	6.9 ± 0.3	0.49 ± 0.3	6.1 ± 0.4	145%
F4	549 ± 4	7.5 ± 0.3	0.67 ± 0.7	5.8 ± 0.7	141%
F5	550 ± 5	6.3 ± 1.3	0.48 ± 0.2	6 ± 0.8	99%

Friability Test: 20 press coated tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded in **Table 12**.

Swelling Index: Accurately weighed press coated tablet was transferred into a watch glass. A very few ml of water was added. It was then allowed to stand for 3 h at room temperature. Then the final weight was measured. And the swelling index was calculated by the formula given above. The same procedure was repeated thrice and the mean value was calculated. The results are given in **Table 12**.

TABLE 13: PERCENTAGE DRUG RELEASE FOR PRESS COATED TABLETS

Time (h)	F1	F2	F3	F4	F5
1	1.31	0	0	0	0
2	3.67	0	0	0	0
3	19.44	0	0.9	1.27	89
4	32.34	1.93	1.22	3.54	95.08
5	44.89	2.16	2.89	78.67	96.59
6	67.67	2.93	74.42	89.77	96.45
7	79.55	4.09	87.60	91.23	95.10
8	95.70	97.61	96.95	99.24	95.06

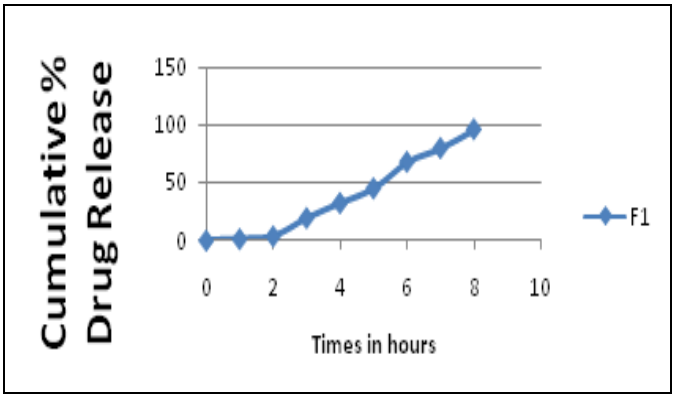

FIG. 7: CUMULATIVE % DRUG RELEASE OF F1

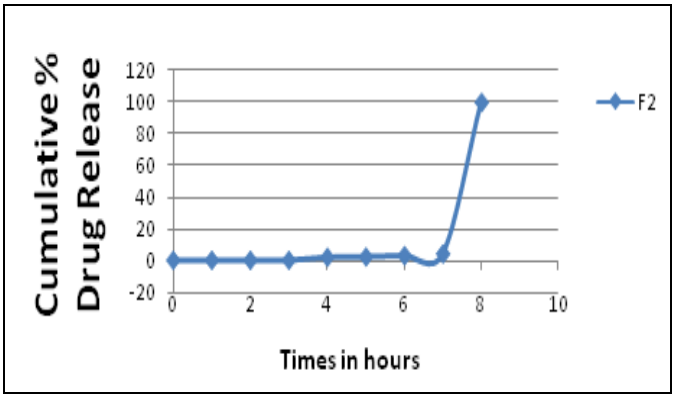

FIG. 8: CUMULATIVE % DRUG RELEASE OF F2

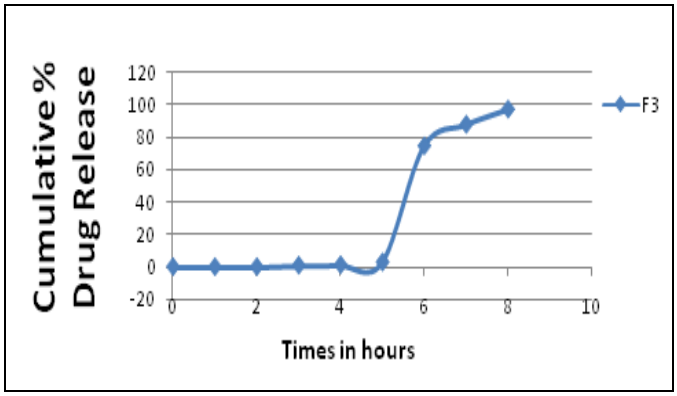

FIG. 9: CUMULATIVE % DRUG RELEASE OF F3

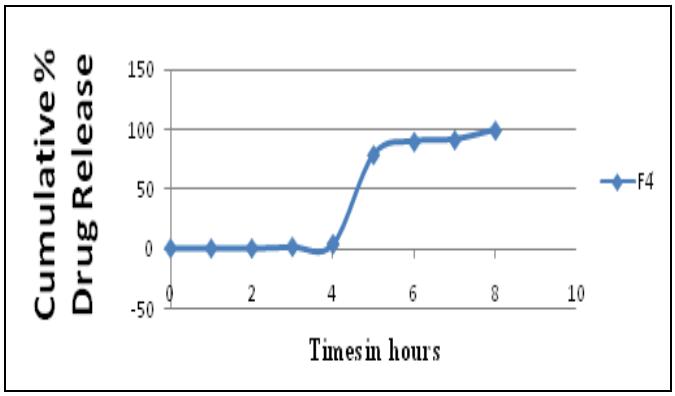

FIG. 10: CUMULATIVE % DRUG RELEASE OF F4

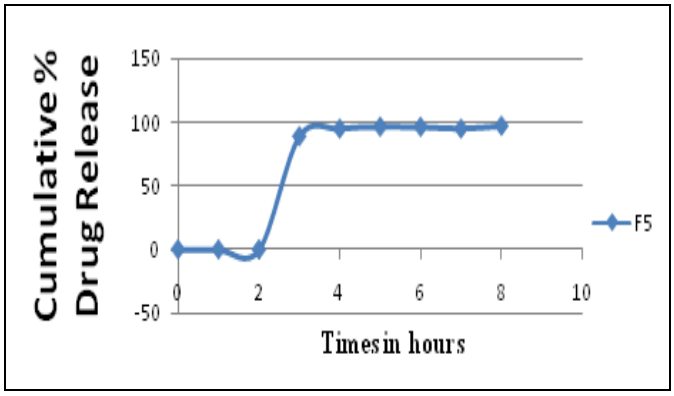

FIG. 11: CUMULATIVE % DRUG RELEASE OF F5

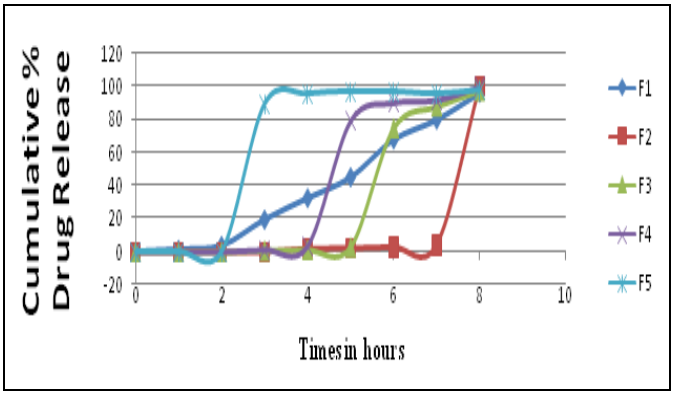

FIG. 12: DISSOLUTION PROFILE OF PRESS COATED TABLET OF FORMULATION OF F1 TO F5

***In-vitro* Release Study of Press Coated Tablets:** The *in-vitro* release of Atenolol tablets was performed using IP dissolution apparatus type 1 (Paddle). The test was carried out in 900 ml of 0.1 N HCl for 2 h and 7.4 pH phosphate buffer solution for subsequent hours. The test was performed at a temperature of 37 ± 0.5 ºC and 50 rpm for 8 h. Tablets were in dissolution jar and samples were taken at one hour intervals. The samples were withdrawn and filtered. The solution was replaced with the same dissolution medium. The samples were analyzed for Atenolol at 275 nm by using UV. Results are given in **Table 13** and **Fig. 7**, **8**, **9**, **10**, **11** and **12**.

Release Kinetics: As a model-dependent approach, the dissolution data of best formulation was fitted to four popular release models such as zero-order, first-order, Higuchi and Korsmeyer Peppa's equations. The order of drug release from matrix systems was described by using zero-order kinetics or first-order kinetics. The mechanism of drug release from the matrix systems was studied by using the Higuchi equation and Koresmeyer Peppa's equation. The results are given in **Table 1**4 and **Fig. 13**, **14**, **15**, **16** [14, 15, 16].

Q = kot (zero order release kinetics)

In (1-Q) = - K1t (First order release kinetics)

Q = K2t½ (Higuchi equation)

M_t/M_0 = K.tn Koresmeyer Peppa's equation (Power Law)

Where Q is the amount of drug released at time t, K_0 = zero-order rate constant, K_1 = first-order rate constant, K_2 = Higuchi rate constant, Mt is the amount of drug released at time t and M_0 is the amount released at time 0, Thus, the M_t/M_0 is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent.

TABLE 14: R^2 VALUES OF FORMULATION F2 (OPTIMIZED FORMULATION)

Formulation F2	Zero order	FIrst order	Higuchi model	K. Pappas
R^2	0.374	0.344	0.294	0.463

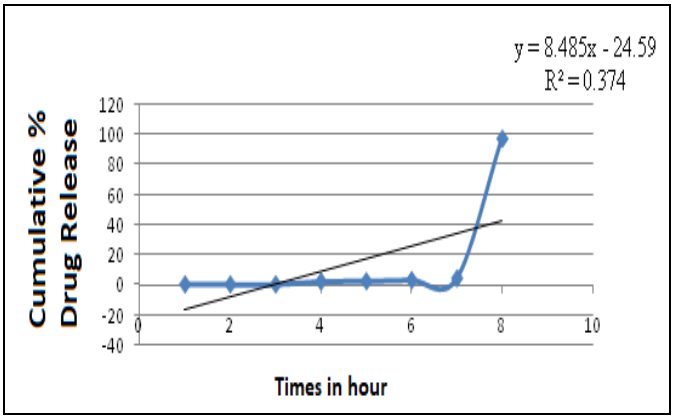

FIG. 13: ZERO ORDER RELELASE KINETICS (F2)

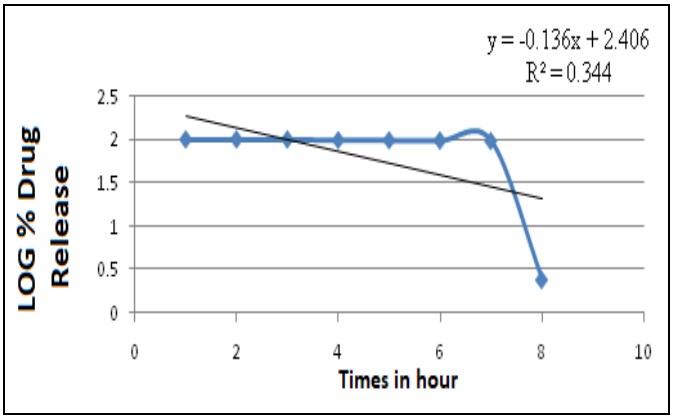

FIG. 14: FIRST ORDER RELEASE KINETICS (F2)

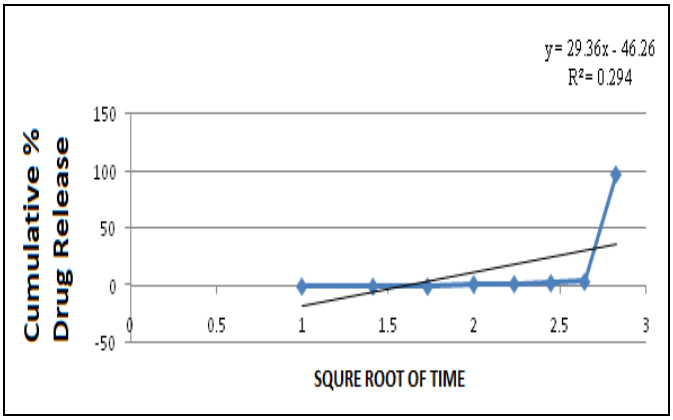

FIG. 15: HIGUCHI MODEL OF DRUG RELEASE OF FORMULATION OF F2

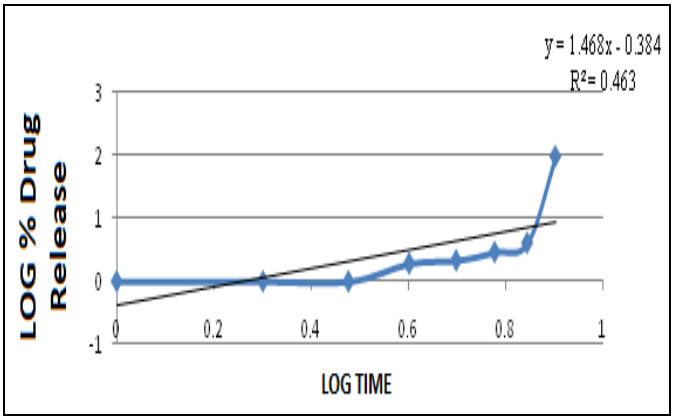

FIG. 16: K. PAPASS MODEL DRUG RELEASE OF FORMULATION F2

RESULTS AND DISCUSSION:

Identification and Standardization of Gum Extract: From the result given in table 3 for Molisch's test, it was observed violet-green color at the junction of two layers of gum which suggests the presence of carbohydrate in the gum. Results obtained for solubility analysis show that the collected and purified extract is easily soluble in water, which indicates as an important property of gum. The loss on drying & the percentage ash content of the natural gum was found to be 7.6 & 25% respectively, which is under the standard limit. The swelling index of the gum is found to be 62.2% which indicates a good release controlling capacity of gum extract. From **Table 3** the pH of the gum was found to be 6.5 which is very nearer to neutral pH, that ensure less chances of irritation to GIT when taken orally.

Determination of Melting Point of Drug: The melting point of Atenolol was determined by capillary method. The melting point of Atenolol was found to be in the range 159-161 ºC is complied with IP standards which is indicating towards the purity of the drug sample.

Solubility Studies of Drug: 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

FTIR Studies for Identification of the Drug and its Compatibility with Excipients: The pure drug and its formulations along with their excipients were subjected to FTIR studies The FTIR spectrums were shown in **Fig. 1**, **2**, **3**, **4** & **Table 4**, **5**. The characteristic absorption peaks of pure drug of Atenolol were obtained at 3750.43, 3679.77, 3346.59, 3158.34, 2961.60, 2919.50, 2864.59, 1632.98, 1584.98, 1512.01, 1453.49, 1411.31, 1376.08, 1333.29, 1296.95, 1235.71, 1175.39, 1088.91, 1034.84, 944.24, 919.45, 884.56, 798.63, 702.27, 670.43, 642.96, 576.31, 522.77 cm^{-1}.

Drug- excipient interactions play a vital role with respect to the release of drug from the formulation amongst others. FTIR techniques have been studied. From the FTIR results of a mixture of drugs and polymers, it could be observed that there were no significant changes in these main peaks of the pure drug in presence of other excipients, which show there were no physical interactions because of some bond formation between drug and polymers.

Determination of Λ_{max} of Atenolol in 0.1 N HCL by UV Visible Spectrophotometer: A solution of Atenolol containing the concentration 10 µg/ml was prepared in 0.1 N HCl and UV spectrum was taken using vis double beam spectrophotometer. The solution was scanned in the double beam UV visible spectrophotometer range of 200 - 400 nm. The lambda max was found to be 271 which is very much nearer to the official value.

Preparation of Calibration Curve of Atenolol: From **Table 6** and **Fig. 5** the standard calibration curve yields a straight line with coefficient correlation $R^2 = 0.996$, which shows that the drug obeys Beer's law in the concentration range of 20-120 mcg/ml.

Bulk Characterization of the Powder Blends for Core Tablets: From results given in **Table 8** shows that the compressibility index values vary from 13.38 to 14.90 which are less than 21, Hausner's ratio from 1.15 to 1.17 and angle of repose from 26.90 to 27.84 which is less than 300. All these results indicate towards passable and good flow properties of the powder blends for core tablets.

Post Compression Parameters of Core and Press Coated Tablets:

Weight Variation Test: The standard weight variation limit for tablets weighing 120 mg-300 mg is ± 7.5% and for tablets weighing more than 300 mg is ± 5%. From **Table 9** and **12** for core tablets, the variation in weights was found to be from ± 2% to ± 5% which are under the prescribed limits and passes the weight variation test. From **Table 14** for press coated tablet the values vary between ± 4 to ± 5% which passes the weight variation test.

Hardness: The acceptable limits of hardness ranges from 4-8 kg/cm^2. The measured hardness of press coated tablets of all the formulations ranged between 5.08 - 5.28 kg/cm^2. This ensures good handling characteristics of all batches. The formulated Atenolol core and press coated tablets were found to be within the prescribed limits and are shown in **Table 9** and **12**.

Thickness: The thickness variation limits allowed are ± 5% of the size of the tablet. The measured thickness of core and press coated tablets of all the formulations ranged between 3 to 3.2 & 5.8 to 6.1 mm respectively were found to be in the prescribed limits and passes thickness test and are shown in **Table 9** and **12**.

Friability: The formulated core and press coated tablets was shown in **Table 9** and 12 respectively. The % friability in all the formulations was less than 1% acceptance limit of IP. Where ensures mechanical stability of tablets from wear and tears.

The Percentage of Drug Content: The percentage of drug content for all the formulations of core tablets were found to be above 90% *i.e.* between 91.22% - 98.82%.

Disintegration Time for Core Tablets: Generally the disintegration time for uncoated tablets is 15 minutes. The formulated Atenolol core tablets were found to be in the prescribed limits and are shown in **Table 9**.

Swelling Index of Press Coated Tablets: From **Table 9** swelling index ranges from higher 278% to lower 99%. It was concluded that swelling increases as time passes because the polymer gradually absorbed water due to hydrophilic nature and swells. The higher swelling index was found in F1. It may be because F1 composed of swellable Saaj gum alone which is hydrophilic in nature and can absorb more amount of water which leads to produce high swelling index without significant lag time When we move from F2 to F5 the swelling index found to be decrease, this is probably because decrease in concentration of Saaj gum and increase in concentration of Ethyl Cellulose. The ethylcellulose is a hydrophobic polymer having the less water-absorbing capacity as compared to Saaj gum which leads to a decrease in swelling index and an increase in release lag time with the increase of the ethylcellulose concentration. However, it was found that Saaj Gum: EC having a ratio of 3:1 shows a considerable swelling index with significant lag time.

***In-vitro* Dissolution Profile of Core Tablets:** *In-vitro* release profile of core tablets are shown in **Table 10** and **Fig. 6**. The results shows increase in dissolution rate with the increase of Crospovidone concentration. Formulation CF3 showed the highest 98.71% of drug release after 30 min is selected for press coating.

***In-vitro* Dissolution Profile Press Coated Tablets:** From the results of **Table 13** and **Fig. 7**, **8**, **9**, **10**, **11** & **12**. It was found that the weight ratio (Saaj gum and Ethyl Cellulose = 1:0) showed the lag time of around 2 h and release was rapid which showed the complete release within 6 h of study The weight ratio (Saaj gum and Ethyl Cellulose = 3:1) showed the lag time of around 7 hours and release was rapid after lag time and showed the complete drug release within 1 h after lag time. The weight ratio (Saaj gum and Ethyl Cellulose 1:1) showed the lag time of 6 hours and complete release was within 8 h. The weight ratio (Saaj gum and Ethyl Cellulose 1:3) showed the lag time of around 5 h and complete release was within 5 h The weight ratio (Saaj gum and Ethyl Cellulose 0:1) showed the lag time of 2 h and complete release was within 3 h due to cracking. In time-controlled press coated tablets, drug-containing core compressed with the outer barrier layer which prevents the rapid drug release from core tablets. The drug will not be released unless the coat is broken. The dissolution medium only can reach the core after eroding or rupturing of the outer barrier layer which leads to significant lag time and a rapid drug release after it.

It is concluded that different lag time was observed for different formulations of Press coated tablets. Formulation F1 showed the lag time of around 2 h is probably due to the creation of a barrier layer of swelling hydrophilic gel surrounding the core tablet due to the absorption of an aqueous medium by Saaj gum. But when Saaj gum was used alone, it formed a mechanically weak swellable layer, which could rupture easily upon exposure to the dissolution medium which produces the development of internal pressure within tablet core which leads to rapid diffusion of the dissolved drug through the hydrophilic gel layer. The formulation containing ethylcellulose alone (F5), showed the lowest lag time of only two hours. This is probably because no swelling, hydrophobic and porous nature of EC. Although, it is naturally insoluble in water, but due to semipermeable nature it controls the passage of water inside the core, core swells and ruptures the EC coat.

After hydration of core, the drug was released. When Saaj gum was used with a combination of Ethyl Cellulose (F2, F3 & F4), it causes synchronization between swelling and erosion of the polymer in maintaining a constant gel formation for a longer period of time. Upon contact with dissolution medium Saaj gum hydrated and formed compact with ethyl cellulose. The hydrophobicity of ethylcellulose retards the hydration of Saaj gum.

Therefore, the dissolution medium did not penetrate the outer coating layer, but the coating eroded slowly. In this way combination of Saaj gum and Ethyl Cellulose produce a synergistic effect on the increase of lag time. The finding indicates that the lag time of press coated tablet can be modulated from 2 h to 7 h by combining different weight ratio of Saaj gum and Ethyl Cellulose. Maximum 7 h of lag time was achieved by the formulation F2 having 3:1 ratio of Saaj gum & EC. Thus the dosage form can be taken at bedtime, so that the content will be released in the morning hours, *i.e.* at the time when the symptom is more progressive. The release was rapid after the completion of lag time. Lag time can be controlled by adjusting the mixture containing different weight ratios of Saaj gum and EC.

Drug Release Kinetics Study of Best Formulation F2: The best formulation F2 were subjected to various kinetic studies like zero-order (Cumulative percentage drug released vs. Time), first-order (Log cumulative percentage of drug unreleased *vs.* Time), Higuchi equation (Cumulative percentage of drug unreleased *vs.* Square root of time) and Koresmeyer (Log cumulative percentage released vs. Log time) and are reported in **Table 14** & **Fig. 13**, **14**, **15**, **16** respectively. From R2 values it is observed that formulation F4 follows zero-order release kinetics.

CONCLUSION: A pulsatile drug delivery system of Atenolol in the form of press coated tablet was successfully prepared and evaluated. The blend of naturally extracted Saaj gum and ethylcellulose was successfully used for achieving the desired lag time in the release of the drug from the dosage form. The formulation F2 having the coating ratio of (3:1) Saaj gum: EC has been proved as the most efficient combination in this work. The release kinetics of the best formulation follows the Koresmeyer Pappas model. Thus in this approach of pulsatile release where a tablet of Atenolol is taken at specific time before sleeping at night, could release the drug in the morning hours before the rise of the patient can prove to be a revolution to control not only the early morning deaths rate of the patients due to fluctuation in blood pressure but also overcome the problems like drug tolerance associated with the SRDDS and CRDDS therapy of chronic CVD diseases.

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CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

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