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FORMULATION DEVELOPMENT AND EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLET OF ATENOLOL

Ayesha Sultana[1*], D. Varun[2]

[1] Research Scholar, Faculty of Pharmacy, Pacific Academy of Higher Education and Research, Udaipur, Rajasthan-313003, India.

[2] Professor & Principal, Department of Pharmaceutics , Sri Indu Institute of Pharmacy, Sheriguda, Ibrahimpatnam-501510 , Hyderabad, Telangana, India.

[*]**Corresponding author E-Mail:** ayeshafaith@yahoo.com

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Key Words

Atenolol, Hypertension, Osmosis, Osmogens, Pore former, Semi Permeable Membrane.

ABSTRACT

In the present study Controlled Porosity Osmotic Pump tablet of Atenolol was prepared and evaluated. The osmotic systems utilizes the principle of osmosis and osmotic pressure for delivery of drugs. Controlled drug delivery system is used in the long term therapy for treatment of chronic conditions like hypertension. In this research ten formulations were prepared by wet granulation technique and evaluated. The micromeritics properties of powder blend have very good flow property. The core tablets were coated with two coating solutions C1 & C2 with varying concentrations of pore formers. All the post compression parameters were as per pharmacopeial limits. The optimised formulation F5 C2 showed drug release of 97.6% upto 28 hours. The optimised formulation follows zero order kinetics, R^2 0.999 of zero order kinetics represents goodness of fit. The omogens used are mannitol and citric acid, the pore formers are sodium chloride and sorbitol. Osmogens, coating thickness, osmotic pressure and pore formers have significant effect on drug release of optimised formulation. The other formulation variables like pH and agitational intensity are independent of external variables. The concentration of pore former also had significant effect on burst strength. Eudragit RLPO is used in coating of core tablets which acts as semi permeable membrane.

INTRODUCTION:

This work aims towards the design and development of Controlled Porosity Osmotic Pump (CPOP) of Atenolol which is an advance drug delivery system, for treating Hypertension considered to be “Silent Killer”. Beta blockers are used as the first choice of drug by JNC VI & WHO-ISH. The objective of the work is to provide controlled release for longer duration of time. This delivery system is aimed to release the drug by zero order kinetics. It’s designed to study the effects of formulation variables like effect of pH, effect of agitation, influence of amount of pore former on drug release, to know the effect of osmotic pressure, to also evaluate the effect of coating thickness and burst strength. The term ‘Controlled release’

implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another. Activation controlled drug delivery system depends on osmotic pressure to activate the release of the drug. Innovative methods were developed for controlled drug release and the best approach for development of controlled drug delivery is Controlled porosity osmotic pump (CPOP). CPOP was developed by **Zentner et al.** CPOP contains water soluble additives in coating membrane which after coming in contact with water, dissolve resulting in in-situ formation of microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems is primarily osmotic, with simple diffusion a minor role. Antihypertensive action of most beta blockers is maintained over 24 hours with single daily dose. There are several reasons to prefer a beta 1 selective hydrophilic drug like Atenolol over others, because of absence of postural hypotension, bowel alteration, salt and water retention, a low incidence of side effects, low cost, once a day regimen and cardio protective potential . The beta blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the CNS and inhibit the release of rennin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone, agents such as Atenolol are selective for beta 1 receptors. Atenolol decreases the heart beat, which slows down with less force, reducing the amount of blood pumped through arteries which slows down the BP. It blocks the effects of adrenaline. According to first comprehensive high BP guidelines of US in **2017** stated high BP should be treated earlier when it reaches 130/80 mm Hg rather than 140/90. This was as per the new guidelines issued this year. High blood pressure is now defined as readings of 130 mm Hg and higher for the systolic BP measurements or readings of 80 and higher for diastolic measurement. This new guidelines stress the importance of using proper technique to measure BP. High BP accounts for the second largest number of diseases and stroke deaths. This was published by the American Heart Association and the American College of Cardiology for Detection, Prevention, Management and Treatment of high BP. Many patents were filed in osmotic drug delivery system, US patent [3845770A] published in the year 1974 by Higuchi T & Theeuwes on 'osmotic dispensing device for releasing beneficial agent' in which the objective of invention was to develop a wall surrounding & forming a compartment for drug and having a passage for dispensing. US patent [4326525 A] in the year 1982 invented by David Swanson & David Edgren invented the 'osmotic device that improves delivery properties of agents in situ. Patent EP [0169105A2] in 1986 invented by Gaylen M. Zentner, Gerald S. Rork and J. Himmelstein invented on 'Controlled Porosity Osmotic Pump delivering one active ingredient surrounded by water insoluble wall'. US patent [4755180A] published in 1988 invented by Atul D. Ayer & Patrick S.L. Wong invented that the 'solubility of drugs can be enhanced by using solubility regulating agents'. One more patent US [4880631A] in 1989 was invented by John L Haslam & Gerald S.Rork on 'Controlled Porosity Osmotic Pump of Diltiazem L-Maleate.'

Materials and Methods:

Atenolol (API) and Mannitol was procured from SD Fine Chemicals Mumbai. Citric acid, Starch, Magnesium stearate, Colloidal silicon dioxide, Tartrazine yellow were purchased from Yarrow Chem Products, Mumbai. Eudragit, Sodium Chloride, Sorbitol,

Ethanol, Acetone and PEG 400 were obtained from Dr. Reddy's Laboratories, Hyderabad. All the chemicals and solvents were of Analytical grade.

METHODS:

Preparation of CPOP core tablets:

All the formulations were prepared by wet granulation method. The ingredients are weighed and sifted through 40 mesh. The drug (Atenolol) was mixed with the osmogens (mannitol and citric acid) in V-shaped mixer for 15 minutes. The above mixer was again passed through sieve no 30. This blend was granulated by using starch paste as a binder. The wet mass formed was granulated by passing through 20 mesh and dried at 50 -55ºC and again screened. Colloidal silicon di oxide was added as glidant and the granules were lubricated with magnesium stearate and compressed in tablet punching machine with 8mm standard round concave punches. The weight of each tablet was maintained constantly in the range of 150 ± *5* mg. The formulation is provided in Table 1.

Procedure for coating of core tablets:

The core tablets were coated in conventional pan coating apparatus. The coating solution was prepared and the ingredients used for the preparation of coating solution was mixed with the solvents. The pore formers (sodium chloride and sorbitol) were dissolved in the solvent system completely, then semi permeable membrane (Eudragit RL PO) was added and mixed by magnetic stirrer to get homogenous solution. All the ingredients were be dissolved before adding the next ingredient. The plasticizer (PEG 400) was added to solvent system of ethanol and acetone in the ratio of (1:8), finally the colorant (Tartrazine Yellow) in very less quantity is added to obtain the desired color. Coating of tablets at pan speed of 25 revolutions per minute (rpm) and temperature of hot air inside the pan is maintained at 40ºC. Coating thickness and weight of the tablets were maintained by the volume of coating solution utilized in coating procedure. After coating, the tablets are removed and dried in oven at 50ºC for 2 hours followed by maintaining it at room temperature for 12 hours. The coated tablets are stored in a desiccator for further evaluations. The coating composition is provided in Table 2.

I. Characterisation of the API (Atenolol):

1. Melting point: It is one of the important physical properties which helps in identification or characterisation of the drug. It helps to determine the purity of the drug. Melting point was determined by using capillary tube method. The Melting point of the drug (Atenolol) was found to be 153ºC.

2. Standard Calibration: The standard calibration of the drug was determined in ethanol. The straight line obtained helps to know the nature, and also proves the drug is in pure form. The samples were analysed in UV Spectroscopy at lamba max 225 nm. Calibration curves absorbance vs cocentration is provided in Table 3 & Figure 1.

3. Solubility: The drug (Atenolol) solubility was found out in the solvents: water, ethanol and phosphate buffer pH 6.8 and 0.1 N Hcl by analysing in UV Spectrophotometer. Results of solubility of Atenolol in solvents is tabulated in Table 4.

4. Loss on Drying: The weight loss measured is 0.3%.

II. Pre Formulation Studies: The micromeritics properties of the powder blend was evaluated to determine its flow property which is an important parameter before manufacturing of tablets. The following parameters are evaluated: Bulk density, Tapped density, Hausner's ratio,

Carr's Compressibility index, Angle of Repose.

Bulk density: It is determined by using the formula: Bulk density (**ρ**) = Mass of the powder (w) / Bulk volume (V_b)

Tapped density: The tapped density can be performed manually by tapping onto a wooden surface or by using a Bulk density apparatus. Tapped density = Weight of the powder (W) (g/cc) / Volume after tappings (V)

Hausner's Ratio: It is defined mathematically as: Hausner's ratio = Tapped density/Bulk density

Carr's Compressibility Index: It is a measure of the potential strength that a powder could build up in its arch in a hopper and also the ease with such an arch could be broken.

% Compressibility= (Tapped density – Bulk density) / (Tapped density) X 100

Angle of repose: It is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane, the flow of powder and the angle of repose is: Tan θ = h/r,

(θ) = $\tan^{-1}$ h/r, h = height of pile, r = radius of the base of the pile, θ = Angle of repose.

The results of densities, hausner's ratio, carr's compressibility index and angle of repose indicated that the powder blend has very good flow property and the powders can be further processed into granules by wet granulation method. The results were tabulated in Table 5.

III. IPQC tests for uncoated core tablets:

In process testing of tablets helps in identifying the problems which can be corrected, it helps to control the procedures involved in manufacturing from the start. It ensures to detect the errors caused. The results of IPQC physical observations and other parameters were tested and tabulated in Tables 6 and 7 respectively.

IV. Post Compression evaluation of tablets: The following parameters are evaluated after coating: Thickness and Diameter, Hardness, Friability, Weight variation, Disintegration, Dissolution, Drug content uniformity.

Thickness and Diameter: The physical dimensions of the tablet is determined by Screw gauge micrometer.

Least count= Pitch/ No of division on circular scale. Formula to measure the dimensions: Reading = Main Scale Reading + Thimble Scale Reading X Least Count.

The thickness and diameters of all the tablets from the 10 formulations were determined and shown in the Table 8. The tablet thickness should be controlled within a ±5% variation of standard value.

Hardness: In this work it is determined by using Pfizer tester. It works on the mechanical principle as pair of pilers. The limits for conventional tablets is 2.5 to 5 kg/cm^2, for control release tablets it is 5 to 7.5 kg/cm^2. The hardness of all tablets from 10 formulations were determined and provided in the Table 8.

Friability: The friability of the tablets is determined by using Roche friabilator. The results are provided in the Table 8. The formula to calculate friability is:

% Friability = W1 – W2/W1 X 100

W1 = Initial weight of tablets before testing, W2 = Final weight after testing.

Weight variation: As per USP, 20 tablets are weighed individually, calculate the average and by comparing the individual tablet weights to average weights. The tablet passes the test if no more than 2 tablets are outside the percentage limit and

if no tablet differs by more than 2 times the percentage limit. It is an official test for tablets. The weight variation is determined and the results are shown in the Table 8. Digital balance is used to note the weights.

Disintegration: In this work the apparatus used is USP/NF Disintegration apparatus. This test helps in the preparation of the optimum tablet formula and control test to ensure lot-to-lot uniformity. The results are provided in the Table 9.

Drug Content Uniformity: The 20 tablets are weighed randomly from all the 10 formulations and dissolved in 500 ml of distilled water. The samples were mixed thoroughly and filtered through 0.45 µm nylon membrane filter. The samples are diluted and analyzed at 225nm using UV Spectrophotometer**.** The results are provided in the Table 10.

In - Vitro **Dissolution test:** The dissolution media used is 0.1 M Hcl and simulated intestinal fluid (pH 6.8, 900 ml) maintained at 37º C ± 0.5ºC. The samples were withdrawn and replenished. The samples are analyzed by UV Spectrophotometer at 225nm. The percentage drug release versus time was plotted. The samples were withdrawn at the time intervals of 1, 2, 4, 8, 12, 16, 20, 24 and 28 hours respectively. The results of Post compression parameters, Disintegration, Drug content uniformity and Dissolution are provided in Tables 8, 9, 10, 11 & 12 and the plots for Dissolution is seen in Figures 2, 3 & 4 respectively.

V. Discussions on effect of formulation variables:

Effect of pH: The drug release studies of optimized formulation i.e (F5 C2) was performed in different media at pH 1.2, 6.8 and 7.4 which is mimicked by 0.1 M Hydrochloric acid, Phosphate buffer 6.8 and 7.4 respectively. The dissolution apparatus used is USP basket type – I maintained at 50 rpm speed and temperature of 37 ± 0.5ºC. The 5 ml samples were withdrawn and analysed in the UV Spectrophotometer at λ max 225nm. It is independent of the external variables and there is no change in drug release in different pH media. It is shown in Figure 5.

Effect of Agitation Intensity: The release studies of optimised formulation i.e(F5 C2) was carried out in USP type I apparatus at different rotational speeds of 25, 50, 75 and 100 rpm. The media used is phosphate buffer pH 6.8 and the temperature maintained is 37 ± 0.5ºC, the 5 ml sample were withdrawn at regular time intervals and it is analysed in UV Spectrophotometer at λ max 225nm. It was found that there was no significant difference in the drug release with the change in agitation intensity. It is provided in Figure 6.

Effect of osmotic pressure: The effect of osmotic pressure is performed on the optimized formulation (F5 C2) and the rate of drug release was carried out in USP Type I Dissolution apparatus, 50 rpm speed maintained at 37 ± 0.5ºC and the samples were analysed by UV Spectrophotometer. In the dissolution media the Lactose (osmogen) is added in the concentration of 0.5%, 1% and 1.5% respectively as the concentration increases in the media the drug release is decreased. To compare and obtain the drug release by adding same amount of different osmogens in dissolution media it was observed that osmogens with high osmotic pressure increases the lag time but decreases the drug release. The three different types of osmogens added to dissolution media is Fructose, Potassium chloride and Sodium phosphate having osmotic pressures of 355, 245 and 28 atm respectively. This shows that mechanism of drug release is by osmotic pressure. The plots are provided in Figures 7 and 8.

Table 1: Composition of CPOP core tablet formulations:

Formulation (mg/tablet)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Atenolol	100	100	100	100	100	100	100	100	100	100
Mannitol	3	5	7	10	40	38	36	33	-	43
Citric acid	40	38	36	33	3	5	7	10	43	-
Starch	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colloidal silicon di oxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150	150	150	150	150

Table 2: Composition of coating solutions:

Ingredients	C 1	C 2	C3	C4
Eudragit RLPO (g)	5	2.5	1.5	0.5
Sodium chloride (mg)	2	5	7	-
Sorbitol (mg)	-	1	2	3
PEG 400 (g)	2	2	2	2
Ethanol (ml)	10	10	10	10
Acetone (ml)	80	80	80	80
Tartrazine Yellow	q.s	q.s	q.s	q.s

Table 3: Standard calibration for ethanolic solution of Atenolol

S.no	Concentration Microgram/ml	Absorbance at (225nm)
1.	0	0
2.	2	0.07
3.	4	0.14
4.	8	0.286
5.	12	0.418
6.	20	0.694
7.	24	0.84

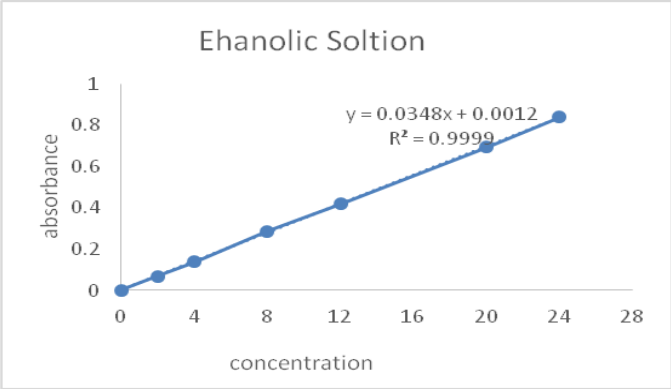

Figure 1: Standard calibration curve of ethanolic solution of Atenolol

Table 4 : Solubility of Atenolol in solvents

S.No	Solvent	Wave length(nm)
1.	Water	236
2.	Ethanol	225
3.	0.1N Hcl	240
4.	Phosphate buffer pH 6.8	228

Table 5: Results of micromeritic properties:

Formulation	Bulk density(g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's Index (%)	Angle of repose (θ)
F 1	0.270 ± 0.032	0.322 ± 0.021	1.22 ± 0.021	16.14 ± 1.31	28 ± 0.23
F 2	0.264 ± 0.015	0.319 ± 0.003	1.20 ± 0.011	17.24 ± 1.24	32 ± 0.34
F 3	0.261 ± 0.012	0.302 ± 0.029	1.15 ± 0.016	13.57 ± 1.32	29.14 ± 0.21
F 4	0.294 ± 0.224	0.331 ± 0.015	1.13 ± 0.022	11.17 ± 1.36	31.17 ± 0.41
F 5	0.289 ± 0.036	0.326 ± 0.022	1.12 ± 0.012	11.34 ± 1.21	28.14 ± 0.26
F 6	0.290 ± 0.032	0.327 ± 0.034	1.12 ± 0.027	11.31 ± 1.28	27 .19± 0.24
F 7	0.257 ± 0.026	0.294 ± 0.002	1.14 ± 0.016	12.58 ± 1.11	34 .11± 0.21
F 8	0.282 ± 0.038	0.317 ± 0.024	1.12 ± 0.025	11.04 ± 1.32	32.11 ± 0.22
F 9	0.287 ± 0.017	0.326 ± 0.031	1.13 ± 0.011	11.96 ± 1.21	34.19 ± 0.51
F 10	0.282 ± 0.010	0.320 ± 0.008	1.13 ± 0.018	11.87 ± 1.28	31.17 ± 0.43

Table 6: IPQC Physical observations

S. no	IPQC	Observation
1	Shape	Round
2	Color	White
3	Surface texture	Roughly smooth
4	Mottling	Not observed.

Table 7: IPQC results

Formulations	Thickness(mm)	Weight variation(mg)	Hardness(kg/cm^2)	Friability(%)
F 1	2.21 ± 0.25	150.3 ± 0.01	4 ± 0.14	0.44
F 2	2.22 ± 0.32	152.1 ± 0.07	4 ± 0.47	0.52
F 3	2.23 ± 0.34	152.1 ± 0.01	3 ± 0.28	0.26
F 4	2.22 ± 0.32	152.1 ± 0.03	4 ± 0.19	0.12
F 5	2.21 ± 0.32	150.4 ± 0.04	4 ± 0.11	0.44
F 6	2.22 ± 0.34	150.4 ± 0.04	3 ± 0.28	0.43
F 7	2.18 ± 0.27	152.1 ± 0.07	4 ± 0.47	0.44
F 8	2.14 ± 0.28	152.1 ± 0.03	4 ± 0.49	0.52
F 9	2.22 ± 0.32	150.4 ± 0.04	4 ± 0.45	0.51
F 10	2.21 ± 0.34	152.1 ± 0.01	4 ± 0.48	0.44

Table 8: Post compression parameter results:

Formulation		Thickness (mm)	Diameter (mm)	Weight Variation(mg)	Hardness (kg/cm^2)	Friability (%)
F1	C1	3.42 ± 0.31	6.35 ± 0.01	154.2 ± 0.05	6.5 ± 0.01	0.1
	C2	3.41 ± 0.01	6.33 ± 0.03	155.5 ± 0.01	6.4 ± 0.06	0.2
F2	C1	3.52 ± 0.21	6.40 ± 0.01	155.1 ± 0.04	6.9 ± 0.32	0.2
	C2	3.50 ± 0.56	6.38 ± 0.05	155.6 ± 0.02	6.7 ± 0.05	0.1
F3	C1	3.56 ± 0.21	6.51 ± 0.01	155.1 ± 0.04	6.8 ± 0.44	0.1
	C2	3.55 ± 0.23	6.50 ± 0.05	155.2 ± 0.03	6.5 ± 0.11	0.2
F4	C1	3.58 ± 0.22	6.48 ± 0.02	155.2 ± 0.04	7.5 ± 0.32	0.1
	C2	3.48 ± 0.25	6.49 ± 0.02	155.4 ± 0.01	6.6 ± 0.33	0.1
F5	C1	3.52 ± 0.11	6.50 ± 0.02	154.1 ± 0.05	6.5 ± 0.02	0.1
	C2	3.53 ± 0.11	6.45 ± 0.01	154.1 ± 0.01	6.5 ± 0.01	0.1
F6	C1	3.58 ± 0.32	6.44 ± 0.01	154.2 ± 0.04	7.8 ± 0.44	0.2
	C2	3.64 ± 0.21	6.45 ± 0.02	154.3 ± 0.04	7.2 ± 0.21	0.2
F7	C1	3.55 ± 0.32	6.48 ± 0.02	155.4 ± 0.04	6.9 ± 0.65	0.1
	C2	3.55 ± 0.25	6.48 ± 0.04	155.3 ± 0.02	6.9 ± 0.42	0.2
F8	C1	3.52 ± 0.31	6.50 ± 0.01	154.2 ± 0.02	6.5 ± 0.29	0.1
	C2	3.54 ± 0.27	6.52 ± 0.01	154.2 ± 0.05	6.5 ± 0.01	0.1
F9	C1	3.56 ± 0.24	6.51 ± 0.03	154.1 ± 0.01	7.7 ± 0.23	0.2
	C2	3.54 ± 0.22	6.50 ± 0.01	155.3 ± 0.02	7.5 ± 0.11	0.1
F10	C1	3.46 ± 0.31	6.48 ± 0.02	155.1 ± 0.04	6.9 ± 0.36	0.1
	C2	3.47 ± 0.29	6.50 ± 0.01	155.1 ± 0.01	6.5 ± 0.022	0.2

Table 9: Disintegration results:

Formulations	Media	Time in Minutes
F1, F2, F3, F4, F5	0.1 M Hcl Mixed	No Disintegration is observed.
F6, F7, F8, F9, F10.		
F1, F2, F3, F4, F5	Phosphate Buffer (pH- 6.8)	Disintegration started in 62 to 65 minutes in all formulations.
F6, F7, F8, F9, F10.		

Table 10: Drug content results:

Formulations	% Drug Content
F1	98.03 ± 0.55
F2	99.68 ± 1.07
F3	99.38 ± 1.11
F4	99.01± 1.58
F5	98.65 ± 0.22
F6	99.39 ± 0.89
F7	99.98 ± 0.22
F8	98.41 ± 0.90
F9	99.65 ± 0.16
F10	99.29 ± 0.01

Table 11: Results of Dissolution: Cumulative % Drug Release Profile of all Formulations (F1- F5) :

Time (Hours)	F1		F2		F3		F4		F5	
	C1	C2	C1	C2	C1	C2	C1	C2	C1	C2
0	0	0	0	0	0	0	0	0	0	0
1	0.5	1.2	0.5	1.2	0.9	1.5	1.2	2.0	3.1	3.5
2	1.5	3.2	2.0	3.5	3.2	4.0	3.5	5.1	8.1	7.1
4	8	10	10	12	12.2	14.5	12.0	16.3	17.6	14.7
8	17	19	21	24	20.6	26.1	23.8	28.9	28.2	28.2
12	24	28	29	33	32.2	38.8	32.0	41.6	39.0	42.5
16	32	35	38	46	40.9	46.2	40.6	53.2	47.7	56.2
20	40	51	44	51	46.1	52.4	47.1	60.7	59.7	70.7
24	45	56	49	60	50.1	58.2	52.3	65.5	72.1	84.1
28	53%	61%	57%	64%	56.5%	63.2%	60.5%	71.2%	81.1%	97.6%

Table 12: Results of Dissolution: Cumulative % Drug Release Profile of all Formulations (F6- F10) :

Time (Hours)	**F6**		**F7**		**F8**		**F9**		**F10**	
	C1	**C2**	**C1**	**C2**	**C1**	**C2**	**C1**	**C2**	**C1**	**C2**
0	0	0	0	0	0	0	0	0	0	0
1	3.3	3.9	3.2	3.6	4.0	4.6	0.2	0.5	3.3	3.5
2	11.2	12.8	13.5	15.3	14.2	15.5	1.5	2.4	14.0	15.6
4	19.5	26.3	23.1	28.6	22.8	27.2	7.3	9.8	25.8	29.9
8	28.9	39.6	38.8	40.5	35.2	39.8	15.0	18.5	39.2	40.4
12	46.0	58.2	49.5	54.3	48.6	50.2	24.4	29.9	57.3	60.7
16	59.2	69.9	57.2	68.5	60.3	62.4	32.8	39.2	67.9	72.3
20	72.3	85.1	69.1	76.6	74.1	70.3	41.2	45.5	77.4	86.5
24	76.1	89.2	74.4	82.3	79.7	76.5	45.3	50.2	81.2	89.2
28	81.0%	92.8%	80.4%	90.1%	82.3%	86.5%	50.2%	54.2%	89.2%	94.4%

F - Formulation Code C - Coating Code

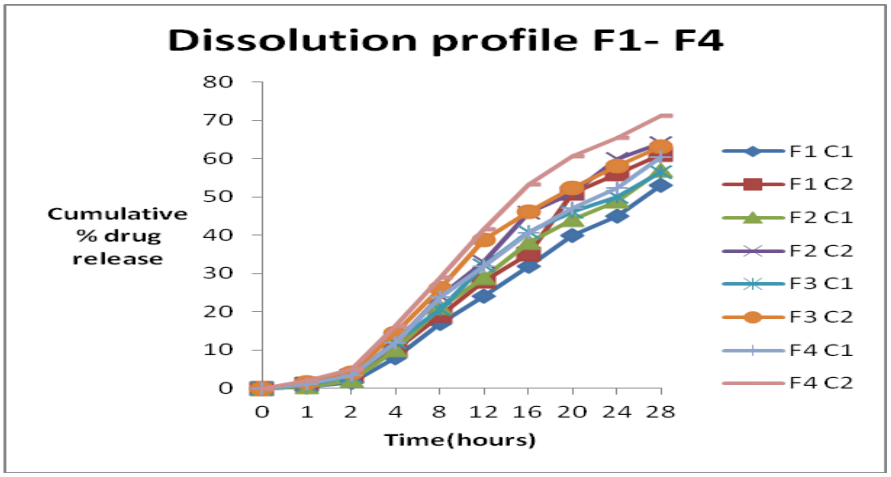

Figure 2: Dissolution profile of F1 to F4 formulations:

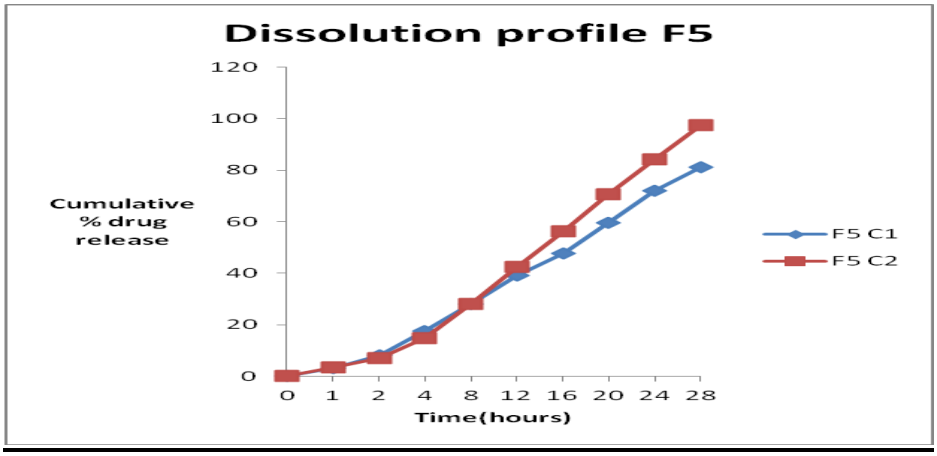

Figure 3: Dissolution profile of optimised formulation F5 C2.

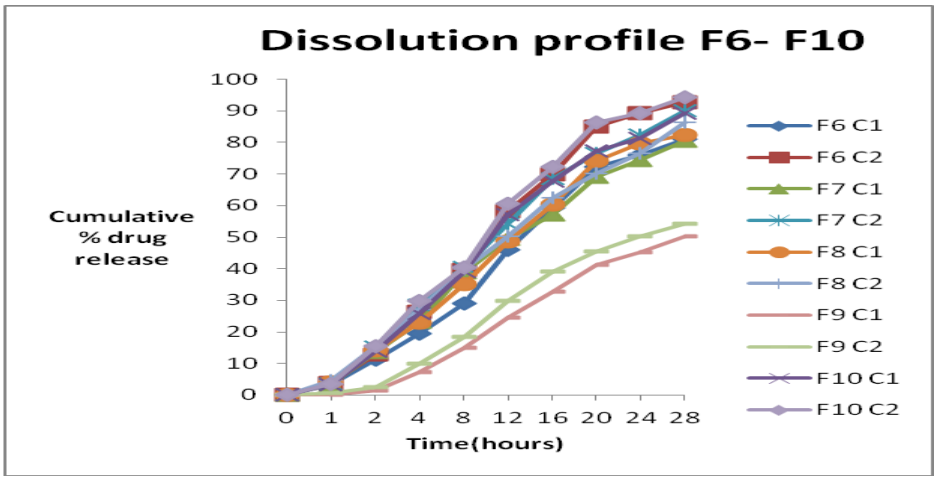

Figure 4: Dissolution profile of formulations F6 to F10

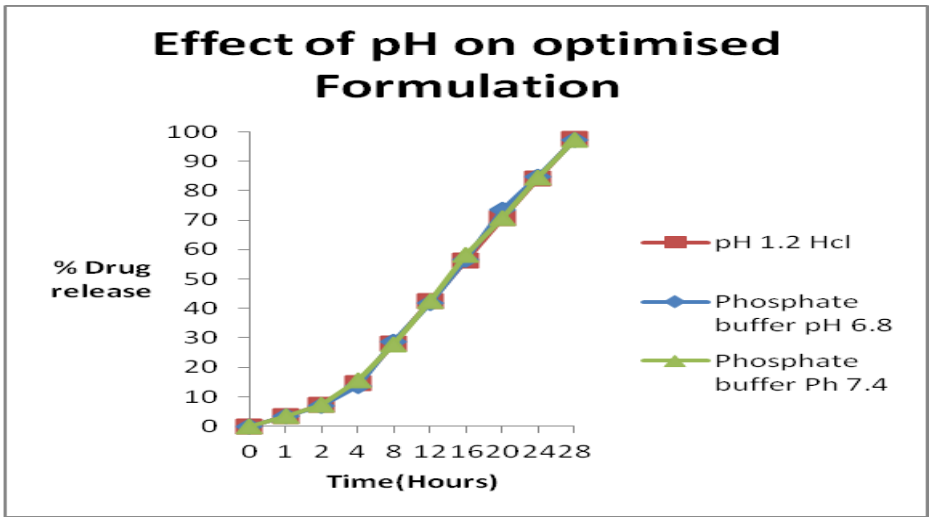

Figure 5: Effect of pH on optimised formulation (F5 C2)

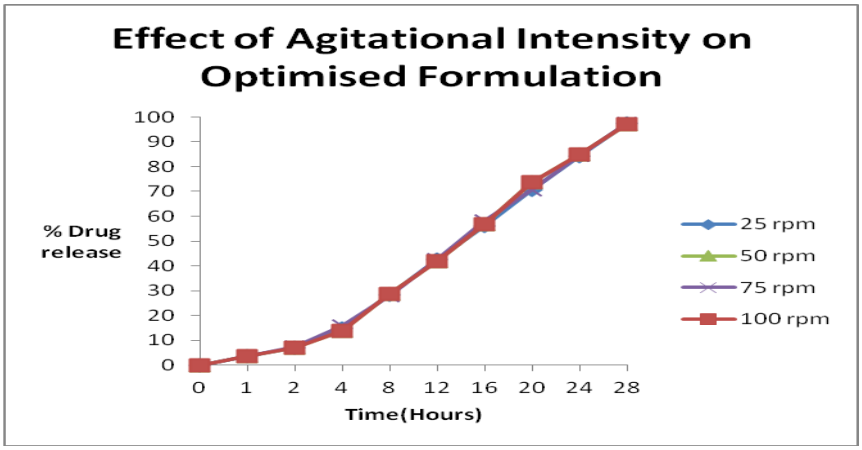

Figure 6: Effect of agitational intensity on optimised formulation (F5 C2)

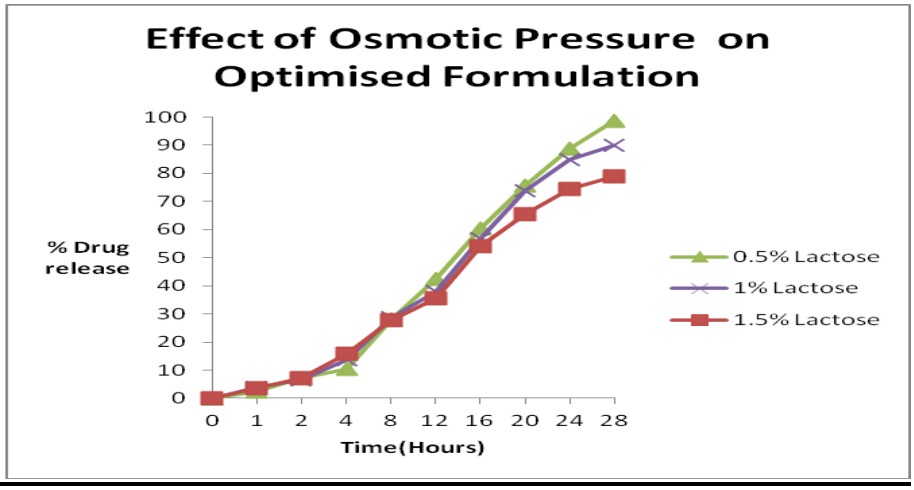

Figure 7: Effect of osmotic pressure on optimised formulation(F5 C2)

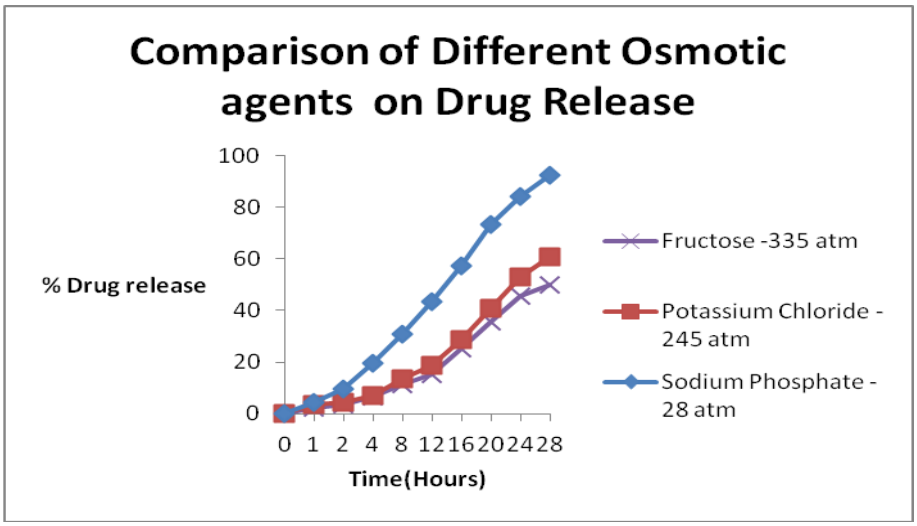

Figure 8: Comparison of different osmotic agents on drug release

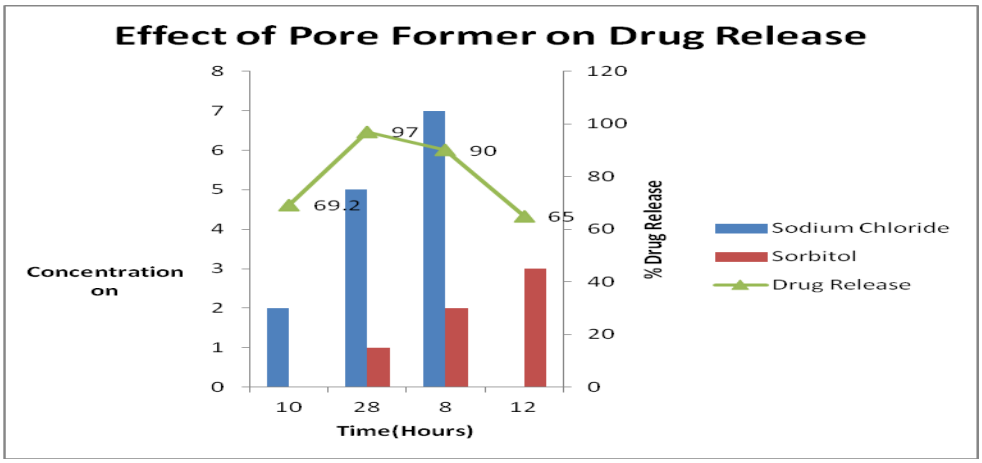

Figure 9: Bar diagram showing effect of pore formers on drug release

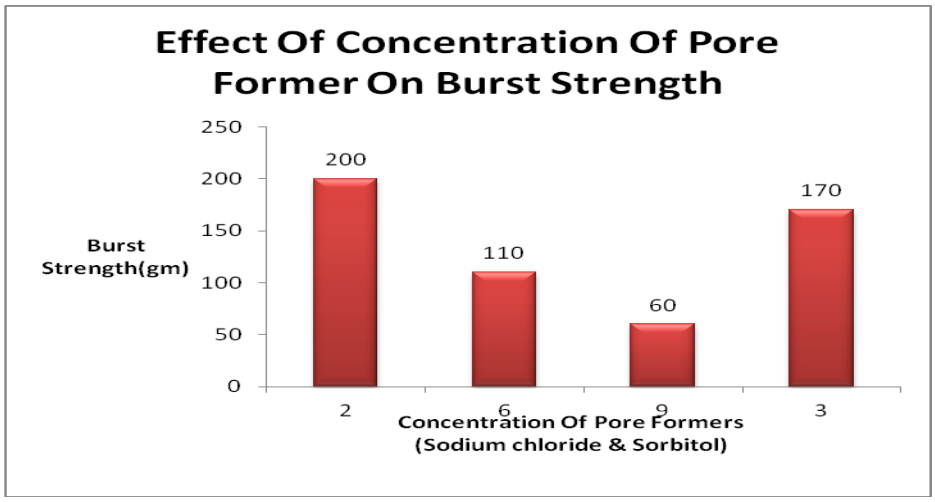

Figure 10: Bar diagram showing effect of concentration of pore former on burst strength

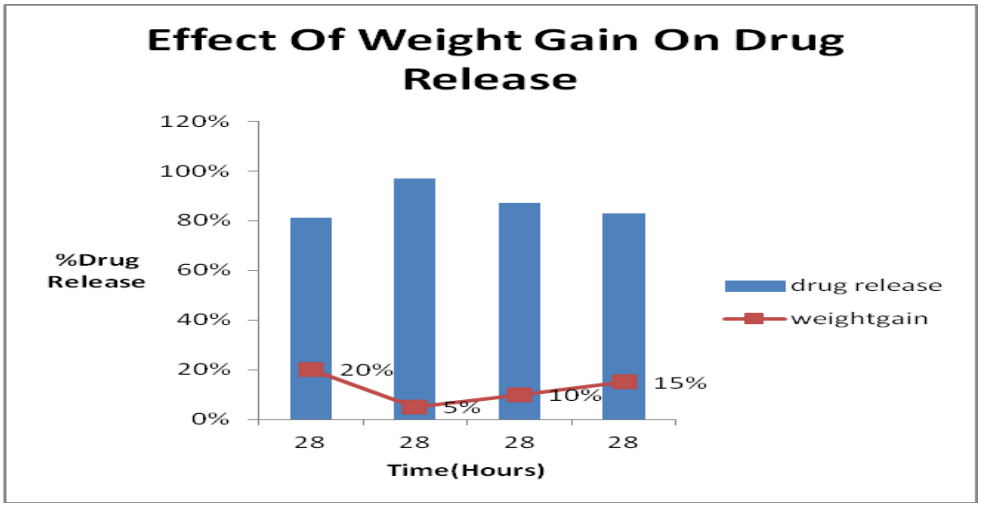

Figure 11: Bar diagram showing effect of weight gain on drug release

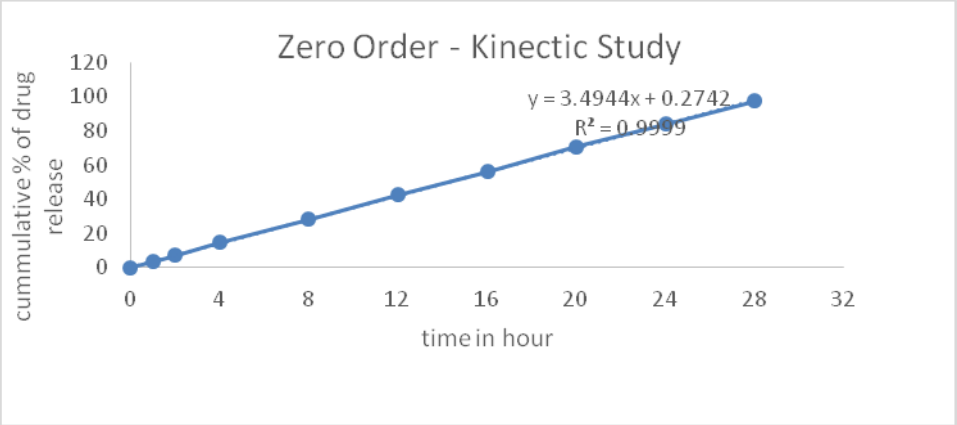

Figure 12 : Zero order kinetics of optimised formulation (F5 C2)

Effect of amount of pore former on drug release: The effect of pore formers (sodium chloride and sorbitol) used in coating solution to coat core of the tablets is studied. The optimised formulation was coated with (C1 & C2) coating solutions and also with two other coating solutions (C3 & C4). It was found that as the level of pore former increases the membrane becomes more porous after coming into contact with the fluids which helps in faster release of the drug. The concentration of pore formers sodium chloride and sorbitol were in the ratios of 2:0, 5:1, 7:2, 0:3 in C1, C2, C3 & C4 respectively. The release was significant when the concentration was in the range of (5:1). The concentration ratio of 7:2 releases the drug very rapidly as it became highly porous when coming in contact with the internal aqueous medium so the concentration of 5:1 was considered as optimum. So it is concluded that as the concentration of pore former increases the rate of drug release also increases. The Bar diagram is provided in Figure 9.

Burst Strength: The burst strength of the optimized formulation was carried out after dissolution for 12 hours and it was evaluated to check the integrity of the tablets in GIT to avoid dose dumping. The level of pore former effects the burst strength. The dissolution was carried out in USP type I apparatus, temperature maintained is 37 ± 0.5 ^{o}C at 50 rpm speed. The burst strength is defined as the force required to rupture the shells after dissolution. The Texture Analyser with 5 kg load cell and 25 mm aluminium cylindrical probe was used in this work. Test speed of 5 mm/s with a distance of 2.5 mm was selected. As the level of pore former increases the membrane becomes porous when it comes in contact with water but the burst strength is decreased. Burst strength is inversely proportional to initial level of pore former. The Bar diagram is provided in Figure 10.

Effect of coating thickness: The Core tablets were coated with polymer (Eudragit RLPO) with varied concentration and dissolution was carried out in USP type I apparatus, the effect of coating thickness of SPM on drug release was studied, the optimized formulation was coated with coating solutions of C1, C2, C3 and C4 (The Weight gain maintained for F5C1 is 20%, F5C2 is 5%, F5C3 is 10% and for F5C4 is 15%), the drug release decreased with increase in coat thickness of SPM. The increase in concentration of SPM showed increased resistance of SPM to fluid imbibitions which leads to decrease imbibitions and reducing the drug release.

The rate of drug release was inversely proportional to coating thickness of the tablet. The thickness of the coating slowed the release of the drug due to polymer loading increasing the weight of the tablet but the lag time was increased. The F5 coated with C2 coating solution showed good release as it has optimum concentration of polymer. The Bar diagram showing effect of weight gain on drug release is provided in Figure 11.

CONCLUSION:

Controlled porosity osmotic pump of Atenolol was developed and the effect of its variables were studied. The drug release was significant when the concentration of pore formers (sodium chloride and sorbitol) was in the range of 5:1. The osmogens with high osmotic pressure increases the lag time but decreases the drug release, as the level of pore former increases the membrane becomes porous when it comes in contact with water but the burst strength is decreased. Burst strength is inversely proportional to initial level of pore former. The F5 coated with C2 coating solution showed good release as it has optimum concentration of polymer and the weight gain maintained for F5 C2 is 5% . This technique has good industry adaptability as the production scale up is easy. Bioavaliality enhancement of drugs by using Controlled Porosity Osmotic Pumps is the need of the hour in R&D, and can be boon to the pharmaceutical sector. As per Clincalc.com the statistics of Atenolol by 2014 showed 30,837,680 total prescriptions and its usage has increased over the years. This research was aimed to provide treatment in controlled manner by reducing the multiple dosing of drug. There is a great scope of developing this technology on larger scale as kinetics of drug by zero order have lot of potential yet to be tapped by the pharmaceutical sector worldwide.

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