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A REVIEW ON OSMOTIC DRUG DELIVERY SYSTEM IN TREATING HYPERTENSION BY ATENOLOL

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Abstract:

Hypertension results from increased peripheral vascular smooth muscle tone which leads to increased arteriolar resistance and reduced capacitance of the venous system. Elevated BP is an extremely common disorder and many of the individuals have no symptoms. Chronic hypertension either systolic or diastolic can lead to congestive heart failure, myocardial infarction, renal damage and cerebro vascular accidents. The beta blockers are used individually or in a combination therapy to treat hypertension. The development of oral osmotic systems has a strong and good market potential. Atenolol is a cardio selective beta-1 blocking agent which is used to reduce systolic and diastolic B.P and it is widely used to treat hypertension, introduced in the year 1976. It reduces heart rate and cardiac output when resting and during exercise. The osmotic drug delivery system utilises the principle of osmosis and drug release is aimed to release by zero order kinetics, to prolong the release of the drug for longer duration of time, providing the treatment in controlled manner by reducing the multiple dosing of drug.

Keywords: *Atenolol, Beta -1 blocking agent, Diastolic, Hypertension, Systolic, Osmotic, Zero order.*

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INTRODUCTION:

Hypertension is one of the disease which causes high mortality, its treatment is very pivotal in reducing the risk of cardiovascular diseases as it is directly related to BP. The incidents of hypertension has doubled in the last 5 years, if we can treat and manage we can easily prevent 10-15 million deaths globally. In India the cases of BP have rapidly escalated both in urban and rural population as there is less awareness, treatment and control in India [1,2]. There is urgent need for preventing its onset in long term management using proper approaches.

By using Atenolol and osmotic technology as once a day medication, it helps to enhance the efficacy of the product and reduces the risk factors of mortality and also prevents the drug toxicity. Atenolol is one of the top 20 drugs used globally as per the statistics of 2016. The Atenolol is widely used beta blocker clinically and globally, because the side effects showed are minimal and manageable. As per clincalc.com the statistics of Atenolol by 2014 showed 30,837,680 total prescriptions and its usage has increased over the years [3-5].

Osmotic drug delivery system is used in the long term therapy for treatment of chronic conditions like hypertension and heart diseases. Control release osmotic formulations are preferred to maintain uniform dosing, reduce dose and increase safety margins for high potency drugs. Osmotic pressure activated drug delivery system consists of drug reservoir which can be either a solution or a solid formulation, contained within a semi permeable housing with controlled water permeability. A osmotic system releases a drug at a pre determined zero order delivery rate based on osmosis. The osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. The beta blocker Atenolol formulated as osmotic drug delivery system is good potential drug in treating hypertension effectively [6-10].

HYPERTENSION STATISTICS IN 2018:

The study by researchers at **Harvard T.H. Chan school of public health** found high rates of hypertension among young adults. The study appears online on Jan 29, 2018 in JAMA internal medicine. They used health data collected from 1,320,555 adults across India between 2012 & 2014 with high BP measurements. It was observed that hypertension was 20% among women and 24.5% in men. The global average was recorded 29.2% in men and 24.8% in women [11-15].

Hypertension was high among adults under 45, than previously estimated. It was higher than in Central and Eastern Europe. In India urban areas are greater in cases of hypertension (33- 40%) as compared to rural population (12-17%).

CARDIAC OUTPUT:

Hypertension is a chronic disease in which the blood pressure in the arteries is increased. It is expressed by two measurements i.e. systolic and diastolic pressures which are maximum and minimum pressures respectively [16-20]. The terms systolic and diastolic are derived from Greek words meaning “a drawing together or a contraction” and “a drawing apart”. BP can be determined by three factors:

1. Cardiac output
2. Blood viscosity
3. Total peripheral resistance (TPR): The resistance the blood encounters on its voyage within the blood vessels.

Cardiac output is made up of heart rate and stroke volume. These factors contribute to rise in BP. Changes in the volume of blood within the cardiovascular system also effects BP.

Q = HR x SV

Q = Cardiac output

HR = Heart rate

SV = Stroke volume

Units: ml of blood / minute = ml of blood / beat x beat / minute

Cardiac output is the measure of amount of blood that is pumped out of the heart in one minute. Heart rate refers to number of times the heart beats every minute and stroke volume is the quantity of blood pumped out of the left ventricle with every heart beat.

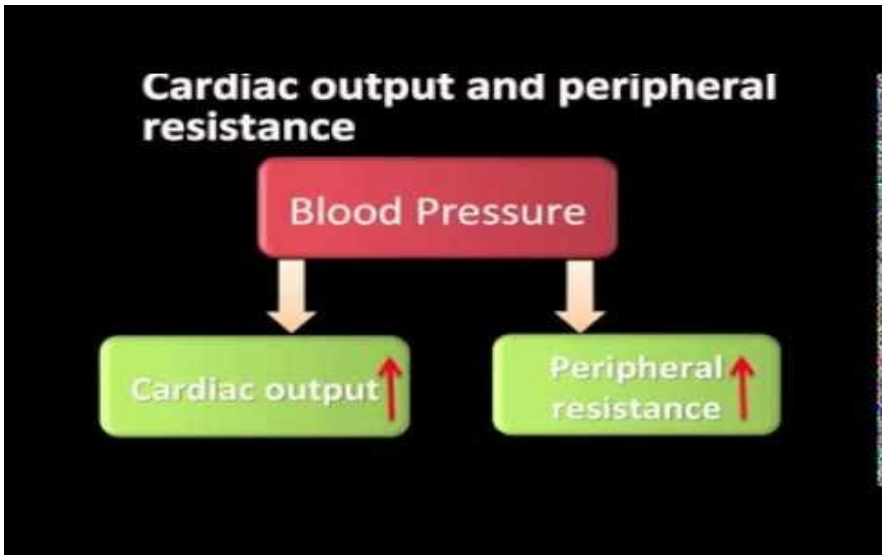

Fig. 1: Cardiac output

The pathophysiology of hypertension depends on these factors:

1. Genetics
2. Autonomic nervous system-excess activity of sympathetic nervous system increases BP
3. Renin- Angiotensin - Aldosterone system- peripheral resistance, extracellular fluid volume if disturbed causes BP.
4. Endothelial dysfunction- local nitric oxide and endothelin are main factors for maintaining vascularity and BP.
5. Sodium & potassium ratio hypothesis is also a reason for essential hypertension.

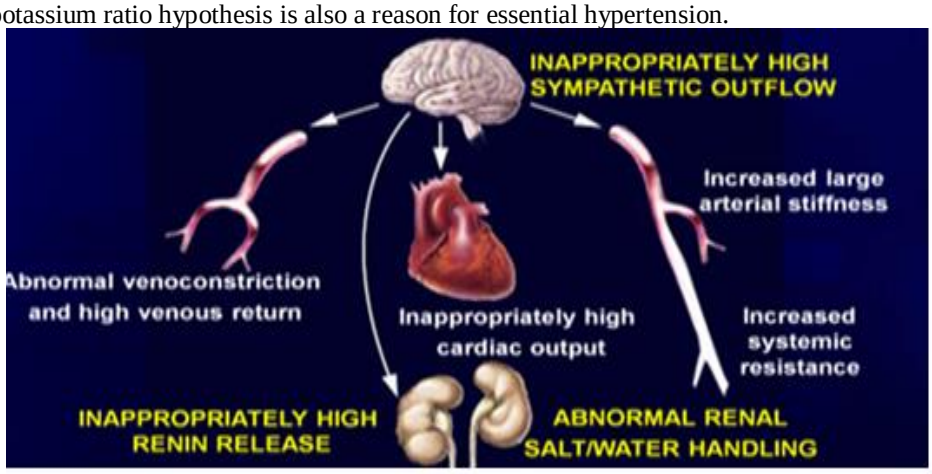

Fig. 2: Pathophysiology of hypertension

ATENOLOL DRUG PROFILE:

IUPAC NAME: Chemically it is Benzene acetamide, 4-[2^1 - hydroxy - 3^1 - [(1- Methyl ethyl) Amino] propoxy].

CAS number - 29122-68-7

Drug class - Beta adrenergic receptor antagonists.

Molecular formula - $C_{14}H_{22}N_2O_3$

Molecular mass - 266.34 g/mol

Melting point -It's in between 152° & 156.5°C

Dissociation constant - 9.6 at 25° C.

Partition coefficient - This drug have low partition coefficient for octanol- phosphate buffer (0.16M) and log partition coefficient for (octanol/water) is 0.23.

Solubility:

It is freely soluble in methanol & alcohol. Soluble in acetic acid & DMSO. Spraringly soluble in 96% ethanol, lightly soluble in isopropanol.Very slightly soluble in acetone and dioxane. Insoluble in acetonitrile, ethyl acetate, ether and chloroform.

Pharmacokinetics & Metabolism:

Oral absorption - 50-60%
Extent of absorption - 90%
Biological half-life - 6-7 hours
Protein binding - 6-16%.
Excretion - Renal i.e excreted by kidneys
Lipid solubility - Low
Metabolism - Hepatic < 10%

The peak plasma levels are 2 to 4 hours. It is excreted through kidneys. Atenolol inhibits the release of renin, inhibits lipolysis & causes elevated levels of plasma triglycerides and fall in HDL levels.

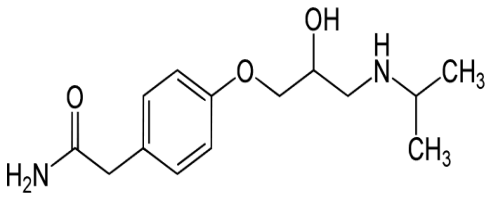

Fig. 3: Structure of Atenolol

Pharmacodynamics:

It reduces heart rate & cardiac output when resting and during exercise. The systolic and diastolic BP is also reduced at rest with the intake of Atenolol. Maximum effect of this drug is from 2 to 4 hours and persists till 24 hours. By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing BP, atenolol reduces the oxygen requirement of heart making it useful in long term management of hypertension and angina pectoris.

Action of Atenolol in treating hypertension:

Atenolol blocks myocardial beta 1 receptors. It can be used alone or in combination. It works by slowing down the heart and reducing its workload. It doesn't pass through blood brain barrier (BBB) to large extent thus decreasing the incidence of various central nervous system side effects. It does not have (Intrinsic sympathomimetic) partial agonist and membrane stabilizing activities.

Uses: It is used in the treatment of:

1. Hypertension
2. Acute myocardial infarction
3. Angina pectoris and chest pain.

LITERATURE REVIEW

S.NO	TITLE	NAME OF THE JOURNAL	VOLUME NO	ISSUE NO	MONTH/YEAR	PAGE NO'S
1.	Formulation aspects in development of controlled porosity osmotic pump tablet (CPOP Review).	Pharmaceutical & biological evaluations.	3	1	Feb-2016	1-18
2.	Formulation and evaluation of cpop tablets of **Pregabalin.**	International journal of Pharmaceutical research and bio science.	4	2	April-2015	305-319
3.	Controlled porosity osmotic pump-(CPOP) An advanced delivery system for Cardio selective beta-1 blockers (Review).	International journal of Pharmaceutical & chemical science.	4	3	July-Sept 2015	336-350
4.	Development of cpop of **Metoprolol succinate:** Design, optimization & characterization.	Journal of pharmaceutical science & research.	7	11	2015	1021-1031
5.	Studies on formulation & evaluation of osmotically controlled drug delivery system of **Carbamazepine**.	International journal of pharmacy & pharmaceutical sciences.	6	2	Jan-2014	239-250
6.	Formulation & in-vitro evaluation of SR tablets of **Venlafaxine HCL** by porous osmotic technology.	International journal of scientific & research publications.	4	2	Feb-2014	1-8
7.	Formulation & evaluation of controlled microporous osmotic tablets tablets of **Rivastigmine hydrogen tartrate**	World Journal of pharmaceutical research.	3	2	Feb-2014	2493-2503
8.	Controlled drug delivery systems: Past forward & future back.	Journal of controlled release (ELSEVIER).	190	2014	April-2013	3-8

9.	Microporous surfaces in controlled drug delivery system: Design and evaluation of **Diltiazem HCL** CPOP using non ionic surfactants as pore formers.	Pharmaceutical development & technology.	19	4	June-2014	507-512
10.	Controlled porosity osmotic pump (Review).	International journal of pharmaceutical research & development.	5	12	Feb-2014	71-80
11.	Recent work on controlled drug delivery systems (Review).	Advance research in pharmaceuticals & biological.	4	3	July-2014	702-709
12.	Formulation & evaluation of CPOP of **Propranolol HCL.**	International journal of biological & Pharmaceutical research.	5	5	2014	403-407
13.	Monolithic osmotic tablets for controlled & enhanced delivery of **Cefixime.**	SCHOLARS research library (Der pharmacia letter).	6	1	2014	16-29
14.	Development & optimization of **Buspirone** oral osmotic pump tablet.	Research in pharmaceutical sciences.	9	4	Aug-2014	233-241
15.	Controlled porosity solubility modulated osmotic pump tablets of **Gliclazide.**	AAPS pharm sci tech.	16	3	Nov-2014	554-568
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17.	Fabrication and in –vitro evaluation of osmotic pump tablets for controlled delivery of **Diltiazem HCL**.	International journal of pharmacy & sciences.	5	12	Dec-2014	4091-4095
18.	Osmotic drug delivery system: An overview.	International journal of pharmacy and pharmaceutical research.	2	1	Dec-2014	29-44
19.	Formulation & evaluation of CPOP for oral delivery of **Ketorolac.**	Journal of basic & clinical pharmacy.	4	1	Feb-2013	2-9
20.	Formulation & evaluation of oral CPOP tablet of **Methyl phenidate HCL.**	Pharma science monitor-An International journal of pharmaceutical science.	4	3(20)	April-2013	1-12
21.	Osmotic drug delivery systems: Basics & design approaches.	Recent patents on drug delivery & formulations.	7	2	Dec-2013	
22.	Development & in-vitro evaluation of **Metoprolol succinate** cpop tablets.	International research journal of pharmacy.	4	4	April-2013	1-9
23.	Development & evaluation of swellable elementary osmotic pump tablets of **Metoprolol succinate & Ramipril**	Global journal of Pharmacology.	7	2	2013	179-186
24.	Design & evaluation of PH triggered osmotically controlled oral drug	Asian journal of pharmaceutical research.	3	2	2013	66-74

	delivery system of **Carvedilol.**					
25.	Osmotic pump drug delivery system: A novel approach (Review).	Journal of drug delivery & therapeutics.	3	5	2013	156-162
26.	Evaluation & development of osmotic drug delivery of **Venlafaxine HCL.**	Asian journal of pharm research.	3	2	April-June-2013	89-97
27.	Design & development of controlled porosity osmotic tablets of **Captopril.**	Journal of pharmaceutical science& bio scientific research.	3	4	Aug-Sept-2013	145-150
28.	Osmotic drug delivery system: A promising drug delivery technology.	Asian journal of research in chemistry & pharmaceutical sciences.	1	1	July-Sept -2013	7-22
29.	Formulation & evaluation of oral controlled release osmotic tablets of **Glimepiride.**	IOSR JOURNAL of pharmacy & biological science.	7	4	Sept-Oct-2013	1-7
30.	Osmotic micro pumps for drug delivery.	Advanced drug delivery reviews (ELSEVIER).	64	2012	Feb-2012	1617-1627
31.	Formulation & evaluation of cpop tablets of **Lornoxicam.**	International journal of Pharmaceutical sciences & research.	3	6	March-2012	1625-1631
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33.	Formulation & evaluation of oral cpop tablet of **Zaltoprofen.**	International journal of pharmaceutical research scholars	1	2	May-2012	254-267
34.	A review on osmotic drug delivery system.	International research journal of pharmacy.	3	4	March-April-2012	88-94
35.	Design & development of cpop tablet of **Diltiazem HCL.**	Journal of advanced pharmaceutical technology & research	3	4	Oct-Dec-2012	229-236
36.	Fabrication and in vitro evaluation of porous osmotic pump based controlled drug delivery of **Metoprolol succinate.**	International journal of pharmacy & pharmaceutical science.	4	3	May-2012	697-704
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43.	Development of an osmotic pump system for controlled delivery of **Diclofenac sodium.**	Drug discoveries & therapeutics.	6	5	2012	269-277
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46.	Osmotic pump drug delivery-A novel approach. (Review)	International journal of research in pharmacy & chemistry.	2	2	2012	1-10
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49.	Osmotic drug delivery systems: A review.	International journal of drug formulation & research.	2	3	May-June-2011	14-28
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51.	Formulation & evaluation of CPOP of **Valsartan.**	International journal of pharmaceutical & biological archives. .	2	3	June-2011	967-972
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62.	Osmotically controlled oral drug delivery system: A Review.	International J Ph. Sci	1	2	Sep-Dec-2009	269-275
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2.	Osmotic device that improves delivery properties of agent in situ.	David Swanson , David Edgren	US Patent 4326525A	-	-	1982	
3.	Oral osmotic controlled drug delivery system.	D.N.Bhalachand, M.A Prabakar	US Patent 2003219485	-	-	2003	
4.	Controlled porosity osmotic pump tablet of high permeable drugs and the preparation method thereof.	Haisong Jiang , Jingang Wang	EP Patent 20070816581,	-	-	2010	
5.	Osmotic drug delivery system.	Argaw Kidane, Padmanabh P Bhatt	US Patent 8747897B2	-	-	2014	
6.	Controlled porosity osmotic pump.	G.M Zentner, G.S Rork, K.J. Himmelstein	US Patent 4,968,507	-	-	1990	
7.	Controlled porosity osmotic pump based drug delivery system.	Chodankar Nand Kumar, Kashinath, Pat Vardhan, Pramod Dattatrya.	Indian Patent 226882	-	-	2009	
8.	Controlled porosity osmotic Enalapril pump.	Gerald S. Rork , John L. Haslam	WO Patent 1994001093A1	-	-	1994	
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CONCLUSION:

Hypertension kills 8 millions every year and its incidence is expected to increase by 60% by 2025. It is leading to other ailments, so it's important to prevent it by using beta blockers which are safest and most effective antihypertensive drug. Atenolol which is beta- adrenergic blocking agent reduces both systolic and diastolic blood pressures. Atenolol as osmotic drug delivery system significantly is used in the treatment of hypertension for longer duration of time in controlled manner by zero order kinetics.

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