INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.6 | Issue 4 | Oct - Dec -2017

Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of controlled porosity osmotic pump for oral delivery of valsartan

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ABSTARCT

The aim of the present study was to design a controlled porosity osmotic pump tablet of Valsartan. The controlled porosity osmotic pump tablet contains opdry CA as semipermeable coat form contact with water, dissolve, resulting in an in situ formation of a microporous structure. The dosage regimen of Valsartan is 80-350mg tablet 2-3times a day. The plasma of life ranges from 6-7hrs.Hence Valsartan was chosen as a model drug with an aim to develop a controlled release system for a period of 24hrs.The effect of different formulation variables. It was found that drug release was directly related to the amount of osmogent and level of pore former. The optimized formulation was subjected to stability studies as per international conference on harmonization (ICH) guidelines and formulation was stable after 3 months study.

Keywords: Valsartan, Controlled porosity Osmotic pump tablet, Anti hypertensive.

INTRODUCTION

Osmotically controlled drug delivery systems (ODDS) are a type of NDDS which based on osmotic pressure for controlled delivery of active agent. These systems are used for both oral administration and implantation. These systems utilize osmosis as the major driving force for drug release. Adequate water solubility of the drug is essential for osmotic drug delivery system. Osmotic drug delivery devices are composed of an osmotically active drug core, which is surrounded by a rate controlling membrane. The release of drug(s) from osmotic systems is affected by various formulation factors such as osmotic pressure of the core component(s), solubility and size of the delivery orifice, and nature of semi permeable membrane. Different types of osmotic systems have been developed implantable and oral. Controlled-porosity osmotic pump (CPOP) is one type of osmotic tablets in which the delivery orifices are formed by incorporation of a leachable component into the coating solution. After coming into contact with water, this soluble additive dissolves resulting in an in situ formation of a microporous semipermeable membrane [1]. The method to create the delivery orifice is relatively simple with the elimination of the common laser drilling

technique. The mechanism of drug release from these systems was found to be primarily osmotic with simple diffusion playing a minor role. The release rate depends upon the solubility of the drug in the tablet core, the osmotic pressure gradient across the membrane, the coating thickness, and the level of leachable component in the coating [2].

Valsartan is a (2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5 yl) phenyl] phenyl] methyl] amino] butanoic acid. Valsartan is an orally active nonpeptide triazole-derived antagonist of angiotensin (AT) II with antihypertensive properties. Valsartan selectively and competitively blocks the binding of angiotensin II to the AT1 subtype receptor in vascular smooth muscle and the adrenal gland, preventing AT II-mediated vasoconstriction, aldosterone synthesis and secretion, and renal reabsorption of sodium, and resulting in vasodilation, increased excretion of sodium and water, a reduction in plasma volume, and a reduction in blood pressure [3].

MATERIAL AND METHODS

Materials

Valsartan was obtained as gift sample from similax Laboratories Ltd., Hyderabad. Other chemicals were used of analytical standard.

METHODS

Method of preparation of controlled porosity osmotic pump of valsartan tablet

All the controlled porosity osmotic pump of valsartan tablets, each containing 80 mg of valsartan, was prepared by wet granulation method. All the ingredients of the formulation were passed through sieve no# 60 and were blended in a mortar with a pestle to obtain uniform mixing [4].

Wet granulation

Controlled porosity osmotic pump of valsartan are prepared as per the formulae given in Table 1.

For this study different polymers like Polyox N 80,Polyox N 205and Osmogen like Nacl and PVPK30,Talc,Magnesium stearate ,Isopropyl alcohol, were selected to formulate the controlled porosity osmotic pump tablets of valsartan by employing wet granulation method. The required quantities of Drug and the Micro crystalline Cellulose (diluents), PVP K-30, were sifted through sieve# 40 manually and mixed well in a mortar by following geometric dilutions to ensure the uniformity of premix blend. The granulating fluid (Ethanol) was added and mixed thoroughly to form dough mass. The mass was passed through sieve #20 and Sieve #16 to obtain wet granules [5].

The wet granules were dried at 45°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through sieve #10, #12, #14, #16, #20 to break aggregates. The Glidant talc and lubricant magnesium stearate were passed through sieve #100 on to dry granules and were blended in a closed polyethylene bag. The tablet granules were compressed into tablets on an 8 station rotary tablet punching machine equipped with flat-faced, round punches of 8-mm diameter to a hardness of 6-7 kg/cm^2.

Coating of Tablet core

Preparation of coating Solution

Coating solution was prepared by mixing required quantity Opadry CA in acetone and stirred on magnetic stirrer to get homogeneous coating solution. The coating composition for valsartan core formulation was listed in Table 1

Table 1 : Composition of formulations for Controlled Porosity Osmotic Pump tablets

Sr.No	Ingredients (mg)	Formulation Code													
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Core Tablet															
1	**Valsartan**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
2	**Polyox Leo N 80 WSR**	40	44	48	52	56	60	66							

3	**Polyox Leo N 205 WSR**								40	44	48	52	56	60	66
4	**Sodium Chloride**	14	14	14	14	14	14	14	14	14	14	14	14	14	14
5	**Micro Cystalline Cellulose**	50	46	42	38	34	30	26	50	46	42	38	34	30	26
6	**Poly Vinyl Pyrolidone K-30**	10	10	10	10	10	10	10	10	10	10	10	10	10	10
7	**Iso Propyl alcoshol (ml)**	q.s	q.s	q.s	q.s	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	**Talc**	4	4	4	4	4	4	4	4	4	4	4	4	4	4
9	**Magensium Sterate**	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Coating Solution															
10	**Opadry CA (%w/V)**	5	5	5	5	5	5	5	5	5	5	5	5	5	5
11	**Acetone (ml)**	95	95	95	95	95	95	95	95	95	95	95	95	95	95
12	**Water (ml)**	5	5	5	5	5	5	5	5	5	5	5	5	5	5
13	**% Weight gain (%)**	10	10	10	10	10	10	10	10	10	10	10	10	10	10
14	**Total Weight (mg)**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of Tablets

Hardness

The tablet hardness is defined as the force required breaks a tablet in a diametric compression test. To perform this test, a tablet was placed between two anvils, force is applied to the anvils & the crushing strength that just caused the tablet to break was recorded. The hardness was measured using Monsanto hardness tester [6]. It is expressed in $kg/cm^{2.}$

Friability Test

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Approximately 4 g (Wo) of dedusted tablets were subjected to 100 free falls of 6 inches in a rotating drum and were then reweighed (W) [7]. The friability is given by

F= 100 × (1 – Wo/W)

Weight Variation Test

Twenty tablets were weighed individually, average weight was calculated & individual tablet weights were compared to the average weight. The tablets met the USP test if no more than 2 tablets are outside the percentage limit & if no tablet differs by more than two times the percentage limit [8].

Drug Content

10 tablets were randomly selected and average weight was calculated and powdered in a glass mortar. Powder equivalent to 100 mg of drug was weighed and dissolved in 100 ml of distilled water, filtered and drug content analyzed spectrophotometrically at 251 nm wavelength [9].

Thickness

The thicknesses of ten tablets were measured using vernier calipers [10].

In Vitro Drug Release Characteristics

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 100 rpm in 900 ml 0.1N Hydrochloric acid for first 2 hours and 50rpm in phosphate buffer pH 6.8 from 3

to 22 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 251 nm [11].

RESULTS & DISCUSSIONS

Post-Compression Evaluation Tests (before coating)

Physical appearance

Tablets were white in color with good texture. Plane on one side and Debussed on other side.

Table 2: Physical Evaluation of Uncoated Valsartan osmotic pump Tablets

Formulation Codes	‡ Weight Variation (mg)	*Thickness (mm)	*Hardness (kg/cm ^{2})	*Friability (%)	*Drug Content Uniformity (%)
F1	200.0±0.966	4.34±0.09	6.06±0.15	0.5109±0.05	97.53±0.16
F2	201.5±1.17	4.45±0.07	6.09±0.15	0.3733±0.05	97.91±0.10
F3	200.5±1.03	4.12±0.04	6.03±0.15	0.5643±0.08	98.75±0.10
F4	200.00±1.08	4.33±0.03	6.1±0.17	0.4999±0.02	97.84±0.06
F5	200.13±1.03	4.22±0.09	6.13±0.15	0.4589±0.10	98.40±0.06
F6	200.0±1.32	5.10±0.09	5.96±0.20	0.5444±0.02	98.95±0.10
F7	200.1±1.09	4.17±0.06	5.86±0.05	0.4596±0.08	97.67±0.06
F8	200.02±0.95	4.65±0.07	6.01±0.17	0.4237±0.02	99.56±0.06
F9	200.1±1.05	4.62±0.05	6.02±0.11	0.5115±0.005	97.01±0.14
F10	199.6±0.74	4.19±0.01	6.4±0.16	0.5643±0.08	98.35±0.05
F11	199.4±0.88	4.16±0.18	6.4±0.16	0.4999±0.02	98.76±0.11
F12	200.12±0.94	4.5±0.05	6.04±0.13	0.4589±0.10	99.25±0.06
F13	199.99±1.06	4.12±0.04	6.3±0.12	0.5444±0.02	97.25±0.16
F14	200.13±0.93	4.08±0.06	6.2±0.16	0.4596±0.08	96.25±0.06

***** All the values represented as mean ± Standard Deviation (SD), n=3.

‡ All the values represented as mean ± Standard Deviation (SD), n=20.

Table 3: Physical Evaluation of coated Valsartan osmotic pump Tablets

Formulation Codes	‡ Weight Variation (mg)	*Thickness (mm)	*Hardness (kg/cm ^{2})	*Friability (%)
F1	220.0±0.966	4.55±0.09	6.10±0.15	0.6109±0.05
F2	220.15±1.17	4.69±0.07	6.23±0.15	0.4733±0.05
F3	220.055±1.03	4.38±0.04	6.13±0.15	0.7643±0.08
F4	220.00±1.08	4.54±0.03	6.2±0.17	0.5999±0.02
F5	220.013±1.03	4.43±0.09	6.16±0.15	0.6589±0.10
F6	220.00±1.32	5.36±0.09	6.1±0.20	0.6435±0.02
F7	220.01±1.09	4.38±0.06	6.0±0.05	0.5586±0.08
F8	**220.94±0.95**	**4.86±0.07**	**6.2±0.17**	**0.5136±0.02**
F9	220.01±1.05	4.91±0.05	6.12±0.11	0.6232±0.005
F10	219.96±0.74	4.43±0.01	6.5±0.16	0.7643±0.08
F11	219.94±0.88	4.4±0.18	6.6±0.16	0.5999±0.02
F12	220.01±0.94	4.43±0.05	6.14±0.13	0.6589±0.10
F13	219.99±1.06	4.33±0.04	6.4±0.12	0.6435±0.02
F14	220.013±0.93	4.32±0.06	6.3±0.16	0.5586±0.08

***** All the values represented as mean ± Standard Deviation (SD), n=3.

‡ All the values represented as mean ± Standard Deviation (SD), n=20.

In vitro Drug Release Studies

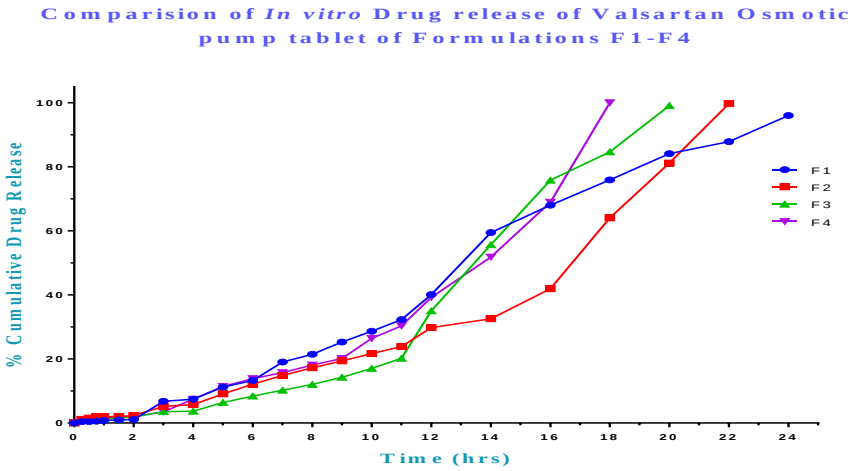

Fig 1: comparison of *In vitro* Drug release of valsartan osmotic pump tablet of formulation F1- F4

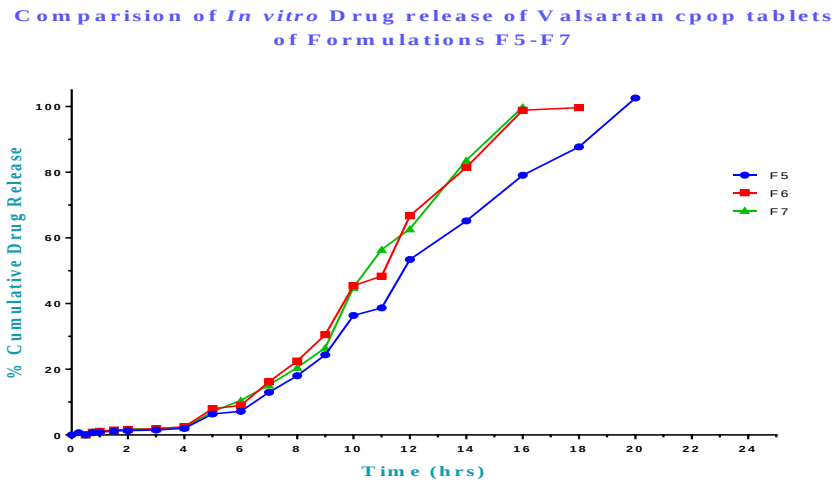

Fig 2: comparison of *In vitro* Drug release of valsartan osmotic pump tablet of formulation F5 - F7

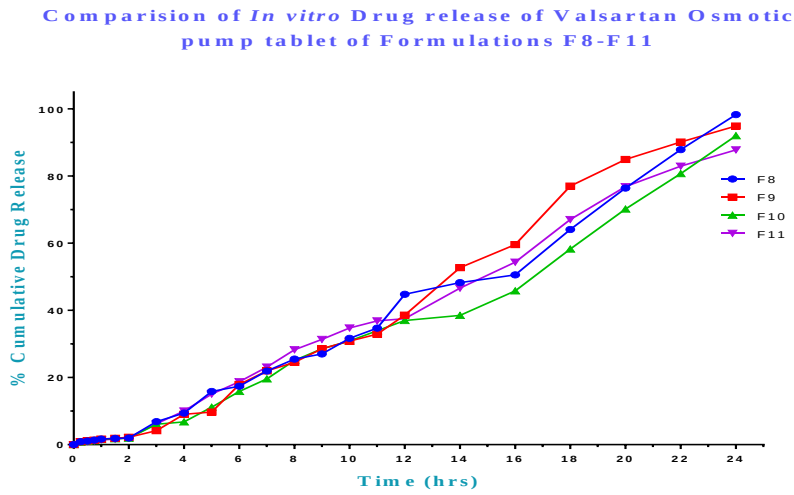

Fig 3: comparison of *In vitro* Drug release of valsartan osmotic pump tablet of formulation F8 - F11

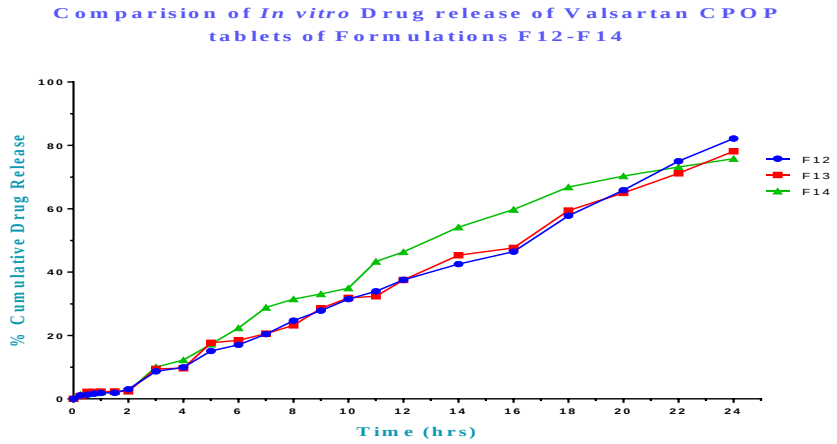

Fig 4: comparison of *In vitro* Drug release of valsartan osmotic pump tablet of formulation F12 - F14

Kinetic Analysis of Dissolution Data

Table 4: Comparison of Kinetic Data of Optimized Formulation F8

Formulation Code	Correlation Coefficient (r^2)				Diffusional Exponent (n)	Inference
F8	**Zero Order**	**First Order**	**Higuchi Equation**	**Korsmeyer -Peppas**	**Korsmeyer -Peppas**	**ZERO-ORDER& Super case II transport**
	0.975	0.7013	0.876	0.9602	1.2069	

CONCLUSION

Valsartan controlled Porosity Osmotic tablet was developed by doing Extensive literature survey. All The prepared Formulations of different and batches are evaluated for various pre compression & post compression parameters. The result suggests that all the values are within prescribed limits. Among the Several formulations prepared and investigated for various test, the formulation (F8) containing Polyox wsr N205 %. Opadry CA in the semipermeable has came out successfully to comples with the requirements for controlled formulations so F8 formulation was selected as optimized formulation. Formulation F8 *In vitro* day Release data the optimized was fitted into various kinetic modelling & data showed best fit evaluation for Zero order kinetics and mechanism of day release to be diffusion as super case II transport system .The optimized formulation as also subjected for Accelerated stability studies for 3 months and data showed no significant changes in formulation at elevated temperature and Relative Humidity.

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