INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

IJPAR |Vol.4 | Issue 1 | Jan-Mar-2015
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of valsartan pulsincap drug delivery system

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ABSTRACT

The purpose of study was to formulate and evaluate Pulsincap drug delivery system of Valsartan for time release. Several functions such as Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Formulation with (programmable delivery) PDDS make it possible to delivery drug at specific time in chronopharmacokinetic studies. Valsartan prepared with a view to release the Valsartan around 5am with a lag time of 8hr after administration. The basic design consists of an insoluble hard gelatin capsule body filled with physical mixture of Valsartan granules and sealed with HPMC K100. We found that the type and amount of polymers influenced the drug release. Valsartan granules are prepared with different ratios of polymers like HPMC and/or EC by geometric mixing method. The lag time was dependent on the compassion of these polymers. Granules are filled in the formaldehyde treated insoluble capsule body and plugged with the HPMCK100. The finished dosage forms were subjected to various QC tests like uniformity of weight, drug content and *in-vitro* release. Promising results indicated Val F7 shows 99.58% of drug released with 8 hrs lag time. Thus this approach can provide a useful means for timed release of Valsartan and may be helpful for patients with morning surg.

Keywords; Valsartan, Hard gelatin capsules, Ethyl cellulose, HPMC, HPMC K100.

INTRODUCTION

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. Several pulsed-release formulations have been developed recently. Tablet-based or capsule-based pulsatile/delayed-release formulation is the basis of the new drug delivery technology that addresses emerging chronotherapeutic requirements.

The Pulsincap is one of such system which is capable of releasing its drug at a predetermined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydro gel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and the hydro gel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released into the small intestinal fluid.

The aim of present study is to formulation and evaluation of Valsartan pulsincap for pulsatile drug delivery system . Valsartan pulsincap will be prepared to release the drug after predetermined lag period, to meet the therapeutic requirement of the body.

METHODOLOGY

PREPARATION OF THE STANDARD CALIBRATION CURVES OF VALSARTAN

Standard calibration linearity curve of Valsartan in 0.1N HCl

Valsartan (100mg) was dissolved in 10ml of methanol and volume was made up to 100 ml in volumetric flask using 0.1N HCl. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml. Absorbance of each solution was measured at 250 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with 0.1N HCl as a reference standard.

Standard calibration linearity curve of Valsartan in pH 6.8 Phosphate buffer

Valsartan (100mg) was dissolved in 10 ml of methanol and volume was made up to 100 ml in volumetric flask using Phosphate buffer pH 6.8. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml. Absorbance of each solution was measured at 250 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with Phosphate buffer pH 6.8 as a reference standard.

FORMULATION DESIGN AND PREPARATION OF VALSARTAN PULSINCAP

A series the formulations were prepared according to the formulation design as given in the Table 1 and 2. Briefly in each formulation accurately weighed quantity of drug, polymer along with other ingredients the used in were passed through # 60. All the ingredients were mixed together in a mortar to obtain a homogeneous mixture by using geometric dilution technique. Mixture is filled in the insoluble capsule body by hand filling method. HPMC K100 is used as the plug for the insoluble capsule body.

Table-1 Composition of Valsartan capsules formulations (Val F1 to Val F6)

S.No	Ingredients	Val F1 (mg)	Val F2 (mg)	Val F3 (mg)	Val F4 (mg)	Val F5 (mg)	Val F6 (mg)
1	Valsartan	80	80	80	80	80	80
2	MCC	126.25	113.75	120	107.5	132.5	126.25
3	PVP	6.25	6.25	12.5	12.5	6.25	6.25
4	Magnesium Stearate	6.25	6.25	6.25	6.25	6.25	6.25
5	Talc	6.25	6.25	6.25	6.25	6.25	6.25
6	HPMC	25	37.5	25	37.5	--	--
7	EC	--	--	--	--	18.75	25
8	Total Weight	250	250	250	250	250	250

Table-2 Composition of Valsartan capsules formulations (Val F7-Val F12)

S.No	Ingredients	Val F7 (mg)	ValF8 (mg)	Val F9 (mg)	ValF10 (mg)	ValF11 (mg)	ValF12 (mg)
1	Valsartan	80	80	80	80	80	80
2	MCC	126.25	120	120	107.5	113.75	113.75
3	PVP	12.5	12.5	12.5	12.5	12.5	12.5
4	Magnesium Stearate	6.25	6.25	6.25	6.25	6.25	6.25
5	Talc	6.25	6.25	6.25	6.25	6.25	6.25
6	HPMC	--	--	12.5	18.75	18.75	12.5
7	EC	18.75	25	12.5	18.75	12.5	18.75
8	Total Weight	250	250	250	250	250	250

RESULTS AND DISCUSSION

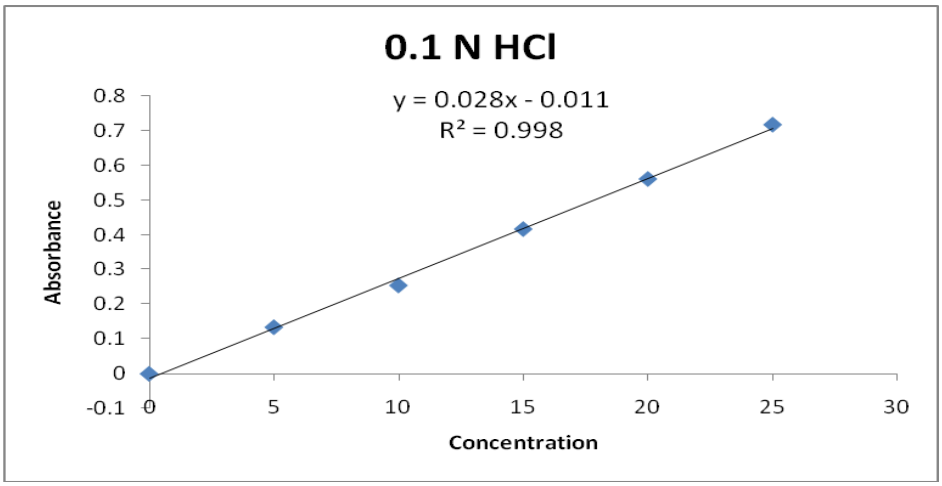


Fig-1 Calibration curve of Valsartan in 0.1N HCl

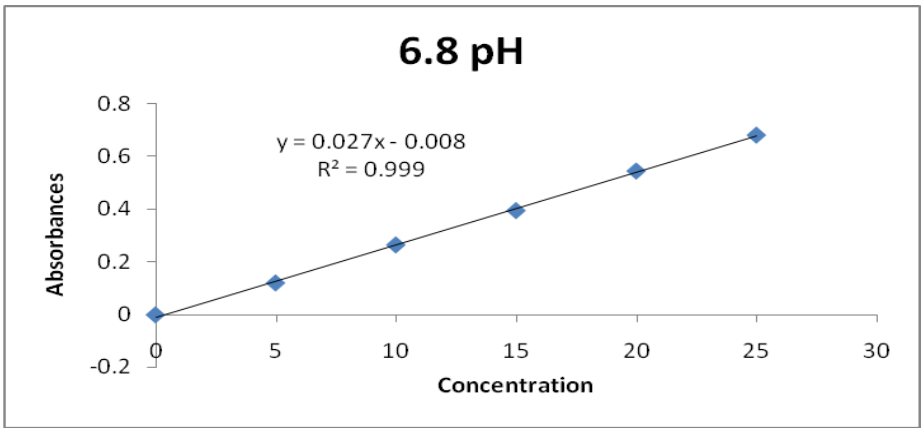


Fig-2 Calibration curve of Valsartan in 6.8 pH **Phosphate buffer**

Qualitative chemical test for free formaldehyde capsules

Formaldehyde reacts with gelatin forming an irreversible complex. The primary amine group present in gelatin reacts with formaldehyde making it irreversibly bound. In the present investigation the bodies of the hard gelatin capsules were exposed to formaldehyde vapors for different periods of time in closed desiccators in which vapor is equilibrated with formaldehyde liquid containing approximately 38% w/v formaldehyde.

Test for the solubility of the formaldehyde exposed capsule

The hardened capsules were tested for their dissolution using disintegration tester in purified water medium. The hardened bodies of the capsules which were exposed to formaldehyde vapor for 6, 8, 10, and 12 hours. The hardened bodies of the capsules which were exposed to formaldehyde vapors for 6, 8, were did not disintegrate for more than 24 hours. But 8 hours exposed capsules are taking more time for disintegration compared to 6 hours. However the bodies of the capsules, which were exposed to 10, and 12 hours formaldehyde vapors, were softened and became very sticky masses on exposure to the formaldehyde vapors. Hence in the present study the capsule bodies exposed to formaldehyde vapors for 8 hours were used in further studies

Dissolution studies of formaldehyde exposed capsules

The hardened capsules were tested for their dissolution using 0.1N HCl and pH 6.8 Phosphate Buffers. The effect of dissolution studies on the hardened bodies of the capsules which were exposed to formaldehyde vapors for 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 12 hours were shown in Table 13. The results indicated that the dissolution time was little shorter in acidic medium i.e. 0.1N HCl than the corresponding that is pH 6.8 Phosphate Buffer. As the time of exposure was increasing the time taken for dissolution was also increased for the hardened bodies of the capsules. The results indicated that the capsule bodies exposed to formaldehyde vapors for 8 hours were intact up to 18 hours and did not dissolve even up to 36 hours in both 0.1N HCl and in pH 6.8 Phosphate Buffer. So capsules that were exposed for 8 hours to formaldehyde vapors were selected for further studies. The cap of treated capsule was dissolved within 15 minutes, but in case of untreated capsules both the body and cap were dissolved within 15 minutes.

Table -3 Dissolution studies of formaldehyde treated capsule bodies.

S.No	Time of expose (hrs)	Observation in the dissolution medium	
		0.1N HCl	**Phosphate Buffer** pH **6.8**
1	2	Shaped out in 4 hrs	Shaped out in 5 hrs
2	4	Shaped out in 10 hrs	Shaped out in 10 hrs
3	6	Softened in 10 hr	Softened in 10 hrs
4	8	Intact up to 18 hr	Intact up to 20 hrs

Dissolution studies

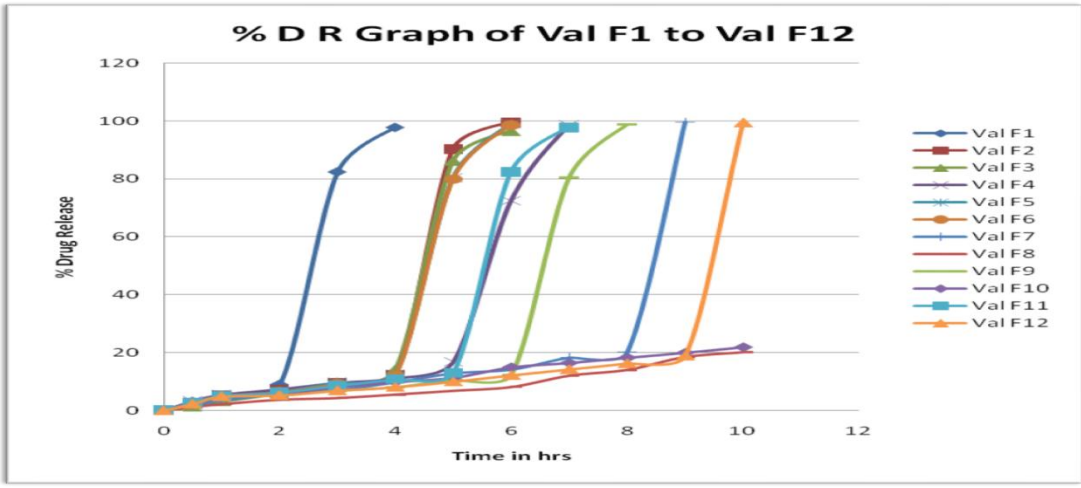
The results of in vitro dissolution studies indicated that the release of the drug Valsartan from the all the Pulsatile capsules was uniform and extended for a period of 10 hours. This may be due to hardening of the capsule body extending the release of the drug. The drug release from the capsules prepared by using Hydroxy propyl methyl cellulose and Ethyl Cellulose showed extended release over a period of 10 hours. In our present study the polymer in both the cases of Hydroxy propyl methyl cellulose and Ethyl Cellulose were used in three methods. In one case (Formulation F1 to F 4) the Hydroxy propyl methyl cellulose was blended with other excipients and filled in to capsules. In other case (Formulation F5 to F8) the blend was prepared with Ethyl Cellulose filled in to capsules. In another case (Formulation F9 to F12) the blend was prepared with both Hydroxy propyl methyl cellulose and Ethyl Cellulose filled in to capsules, and then the HPMC K100 was placed over the filled blend to form a slug over the filled material.

Formulation F1 to F4 contains Hydroxy propyl methyl cellulose(10%,15%,10%,15%) and PVP(2.5%,2.5%, 5%,5%) in different concentrations. The *in-vitro* dissolution data showed that increasing the polymer and binder concentration decreased the drug release and incising the lag time but not reach the goal.

Formulation F5 to F8 contains Ethyl Cellulose (7.5%, 10%, 7.5%, 10 %,) and pvp (2.5%, 2.5%, 5%, 5%) in different concentrations. The *in-vitro* dissolution data showed that increasing the polymer the rate of drug release is increased and complete drug was released within the lag time of 8 hrs in the 7th formulation. In this case increase binder concentration decreased the drug release and incising the lag time but not reach the goal.

Formulation F9 to F12 contains Hydroxy propyl methyl cellulose (5%, 7.5%,5%,7.5%), Ethyl Cellulose (5%, 7.5%, 5%, 7.5 %,) and PVP (5%, 5% 5%, 5%) in different concentrations. The *in-vitro* dissolution data showed that increasing the Hydroxy propyl methyl cellulose the rate of drug release is increased and increasing the Ethyl Cellulose the rate of drug release is increased. In the case binder concentration is constant.

In the total formulations ethyl cellulose is efficient than the HPMC. By the above studies depending up on the polymer and binder concentrations Val F7 shows the good results and 99.58% drug was released within 8 hrs lag time.



Among all the formulations are performed to pre formulation studies and quality studies. The valsartan pulsincap formulation is fallows all the micrometric and evaluation testes. In micromeritic properties the formulation shows excellent values in angle of repose, true density, bulk density, carrus index and hesunar's ratio.

In FT-IR studies there is no known chemical reaction in between drug and excipients. By this result there is compatibility in between drug and excipients. In the in vitro dissolution studies performed all the formulations up to 10 hours. Started with 0.1N HCl after 2 hrs changes the pH with 6.8 Phosphate Buffer as a dissolution medium. Samples are collated at time intervals and maser the absorbance values. In the dissolution study of Val F1 using 2.5% binder (PVP) and 10% polymer (HPMC) rate of drug release is 97.91% within 4 hrs. In the Val F2 formulation by increasing the polymer (15%) concentration 99.58% drug released within 6 hrs. By the above result in the Val F3 formulation by increasing the binder concentration (5%) 99.58% drug released within 6 hrs

In the formulation Val F4 increase polymer (5%) and binder (15%) concentrations then the rate of drug release is 99.33% within 7 hrs. In the formulation Val F5 change the polymer EC instead of HPMC. In this case 2.5% binder and 7.5% polymer is used by this the rate of drug release is 98.33% within 6 hrs. In the formulation Val 6 increase the polymer concentration (10%) the rate of drug release is 98.75% within 6 hrs.

In the formulation Val F7 binder concentration (5%) is increased but polymer concentration (7.5%) is decreased compared to Val F6. By this formulation the rate of drug release is 99.58% within 9 hrs. In the formulation Val F8 5% binder and 10% polymer is used by this formulation only 20.20% drug was released up to 10 hrs

In the formulation Val F9 5% binder, and two polymers (5% HPMC, 5% EC) is used. The rate of drug release is 98.75% in 8 hrs. In the formulation Val F10 5% binder and polymer concentrations are 7.5% HPMC, 7.5% EC were used the rate of drug release is 21.83% drug was released within 10 hrs. In the formulation Val F11 5% binder and 7.5% HPMC and 5% EC are used. In this formulation 97.9% drug was released within 7 hrs

In the formulation Val F12 5% binder and 5% HPMC and 7.5% EC are used. In this formulation 99.16% drug was released within 10 hrs

Above all the 12 formulation Val F7 shows 99.58% drug was released within 9 hrs this formulation is fallows 8 hrs lag time so Val F7 is the optimized. Val F12 shows 99.16% drug was released within 9 hrs but it shows 9 hrs lag time. It will be used for early drug administration g persons.

Stability Studies

The results of accelerated stability studies, carried out according to ICH guidelines, indicated that Val 7 (SA) capsules did not show any physical changes (appearance) during the study period and the drug content (n=3; mean ±SD) was found above 97% at the end of 90 days (0 day: 99.58±0.31%; 15 days: 99.28±0.83%; 30 days: 99.05±0.38%; 60 days: 98.73±0.16%; 90 days: 98.09±0.56%;). This indicates that Val 7 (SA) capsules exhibited good physical stability and acceptable potency at accelerated storage

condition for 3 months. Also there was no change in the release profile of the capsules under accelerated storage conditions. 25^0

Table-19 Stability Studies of Valsartan

S.No	Sampling interval	25^0C/60%RH	30^0C/60%RH	40^0C/75%RH
1	0^{th} Day	99.58	99.58	99.58
2	15^{th} Day	99.28	99.28	99.27
3	30^{th} Day	99.05	99.03	99.04
4	60^{th} day	98.73	98.71	98.74
5	90^{th} day	98.09	98.05	98.07

CONCLUSION

The summary of the present study was to formulation and evaluation of Valsartan pulsincap drug delivery system. Pulsatile Drug Delivery System (PDDS) is design for drug release at predetermine time profile. In the present study an attempt has been made to formulate Valsartan pulsincap by using various hydrophilic and hydrophobic polymers. Valsartan is an angiotensin-receptor blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure.

In order to solve the objective of the study suitable analytical methods was established in 0.1N HCl and 6.8 pH phosphate buffer. By carry out the drug and polymer compatibility studies by FT-IR spectroscopic studies, it was conclude that there was no interaction between drug and polymers as the principle peaks of the drug were found unaltered in the IR spectrum. Valsartan pulsincap were prepared successfully by pulsincap technique using different polymers in different ratios using HPMC and Ethyl cellulose. HPMC k 100 is used as the plug of the capsule.

The prepared Valsartan Pulsincaps were uniform in weight. The prepared Valsartan Pulsincaps were analyzed for estimated drug content in 6.8 pH phosphate buffer and the drug content was estimated in all the results shown uniformity of drug loaded in all the formulations was observed.

All the formulations were subjected to in vitro drug release studies and the formulation Val F7 shows complete and timed release with 99.58% in the lag time of 8 hrs. Val F12 shows complete and timed release with 99.58% in the lag time of 9 hrs. So Val F7 selected as the best formulation.

Valsartan capsules were prepared successfully by using HPMC, EC polymers individually and in both combination by pulsincap technique. In this study pulsing cap delivery of Valsartan formulation by using EC (Val 7) was effective in providing 99.58% of drug released. The system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 8 h and thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours that is at the time of symptoms. The release of drug was rapid and complete after the lag time. Thus this approach can provide a useful means for pulsatile/programmable release (with single pulse) of Valsartan and may helpful for patients with morning surge.

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