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Design and Characterization of Valsartan Loaded Press Coated Pulsatile Tablets

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Research Article

ABSTRACT

Valsartan (Diovan) is an antihypertensive drug belonging to the family of angiotensin II receptor antagonists. At a dose of 40 mg/d, its antihypertensive effect is inconsistent. At 80 mg/d its effect on blood pressure, its adverse effects, and its contraindications (mainly pregnancy and renal artery stenosis) are similar to those of angiotensin-converting enzyme (ACE) inhibitors, except that coughing is rarer with valsartan than with ACE inhibitors. Valsartan has no demonstrated advantage over losartan, another angiotensin II antagonist. Valsartan has not been shown to prevent complications of arterial hypertension, and its use is, therefore, less well validated than that of diuretics and beta-blockers.

Keywords: Valsartan, Pulsatile tablets, Coated tablets, Cross povidone, Aerosol, HPMC, Eudragit

INTRODUCTION

Controlled drug delivery is one which delivers the drug at a predetermined rate for locally or systematically for a specified period of time. Continuous oral delivery of drugs at predictable and reproducible kinetics for predetermined period throughout the course of gastro intestinal tract [1-4]. Pulsatile Drug Delivery Systems (PDDS) are gaining a lot of interest as they deliver the drug at the right place, at the right time and in the right amount, thus providing spatial, temporal, and smart delivery and increasing patient compliance.

The use of pulsatile release of the drugs is desirable where constant drug release is not desired [5-8]. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect, and irradiation [9,10]. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, current situation and future scope, recent advances in PDDS and PDDS product currently available in the market [11].

Press Coated

An oral press-coated tablet was prepared by using direct compression and wet granulation methods to achieve predetermined lag time. This press-coated tablet containing the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer and hydrophilic polymer.

The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time [7]. The aim is to formulate, evaluate and optimize press coated pulsatile formulation of Valsartan for oral drug delivery.

Valsartan is a potent, orally active non-peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension [11-13].

It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. The drug is a very good target for the generic industries. It is soluble in the neutral pH range. It belongs to the BCS class III drug classified as low permeability and high solubility drug.

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MATERIALS AND METHODS

The drug Valsartan, microcrystalline cellulose, SSG, Crosscarmellose, Crosspovidone was purchased from Signet Chemical Corporation, Mumbai, India. Hydroxy propyl methylcellulose (K4M) and Eudragit LS-100 were obtained from Fine Chem Industries, Mumbai, India.

Construction of calibration curve of Valsartan Standard stock solution was prepared by dissolving 100 mg of Valsartan in 100 ml of methanol to get concentration of 1 mg/ml. The prepared stock solution was further diluted with buffer to get working standard solution of 2 to 30 mcg of Valsartan to construct Beer's law plot for the pure drug, the absorbance was measured at λmax at 250 nm, against blank. The standard graph was plotted by taking concentration of drug on X-axis in the concentration range of 2 mcg to 30 mcg and absorbance on Y axis.

Method of Preparation

Formulation of pulsatile tablets

The inner core tablets were prepared by using direct compression method. Powder mixtures of Valsartan, microcrystalline cellulose (MCC, Avicel PH-102), citric acid, sodium bicarbonate and croscarmellose sodium (Ac-Di-Sol) were dry powdered for 20 min, followed by addition of magnesium stearate and talc as lubricants [5].

Table 1. Formulation table for preparing core tablets of Valsartan.

Ingredient	F1	F2	F3
Drug	20 mg	20 mg	20 mg
Crospovidone	1%	-	-
Croscarmellose sodium	-	1%	-
Sodium starch glycolate	-	-	1%
Magnesium stearate	0.25%	0.25%	0.25%
Aerosil	0.5%	0.5%	0.5%
Microcrystalline cellulose	0.5%	0.5%	0.5%
Total weight (mg)	150 mg	150 mg	150 mg

The mixtures were then further blended for 10 min., 150 mg of resultant powder blend was manually compressed using Rotary Tablet compression machine (Cemach Machineries Ltd., Model No: R&D 20, Ahmedabad, India) at a pressure of 1 ton, with 8 mm punch and die to obtain the core tablet **(Table 1).**

Table 2. Results of evaluation of powder blend for core tablets of Valsartan.

Parameter	F1	F2	F3
Bulk density (g/cm^3)	0.67 ± 0.23	0.55 ± 0.11	0.43 ± 0.12
Tapped Density (g/cm^3)	0.80 ± 0.19	0.66 ± 0.21	0.59 ± 0.13
Hausner's ratio	1.19	1.19	1.17
Carr's index (%)	16.12	16.28	14.56
Angle of Repose(ϵ)	23.04 ± 0.10	25.45 ± 0.11	25.56 ± 0.21

Flow properties of powder blend

The flow properties of powder blend were characterized in terms of angle of repose, compressibility index and Hauser ratio. Angle of repose was performed using funnel method by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface.

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The funnel bottom was closed and 2 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured.

The tan-1 of the height of the pile/radius of its base gave the angle of repose. Bulk density (ρb) and tapped densities (ρt) were determined and there by Hausner's ratio (HR) and compressibility index were calculated according to the following equations **(Table 2).**

Characterization studies

Thickness and diameter: It is measured by using Vernier caliper in mm.

Weight variation test: The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average.

Hardness: Hardness of the tablets was tested using a Monsanto hardness tester (Labtech, AVI-PH-4522, India). Thickness was determined by electronic Vernier caliper (Sealey professional tools, Model No: AK962EV.V2, UK).

Friability: Friability of the tablets was determined in a friability test apparatus (Ketan, Koshish Industries, Bombay, India, Model No: SS153).

Drug content: For drug content (without enteric coating) the tablets were estimated by the spectrophotometrically at 250 nm (Shimadzu 1800, Japan).

Disintegration: Disintegration time of the tablets was determined using a tablet disintegration test apparatus (Serve well Instruments Pvt. Ltd., Electrolab ED-2L, India) using distilled water as fluid **(Tables 3-6).**

Table 3. Results of evaluation of core tablets of Valsartan.

Formulation Code	Hardness ($kg.\ cm^{-2}$)	Friability (%)	Average Weight (mg)	Thickness (mm)	%Drug Content
F1	4 ± 0.3	0.413 ± 0.011	149.9 ± 0.66	2.1 ± 0.01	99.07 ± 0.94
F2	3.5 ± 0.09	0.386 ± 0.020	150.05 ± 0.66	2.1 ± 0.05	98.89 ± 1.5
F3	5 ± 0.4	0.319 ± 0.021	151.05 ± 2.66	2.1 ± 0.04	100.66 ± 1.8

Table 4. Disintegration time of the core tablet of Valsartan.

Batch	Disintegration time in dissolution medium		
	0.1 N HCl (pH 1.2) (sec)	pH 6.8 Buffer (sec)	pH 7.4 buffer (sec)
F1	57 ± 6.4	44 ± 3.8	42 ± 1.6
F2	59 ± 4.3	48 ± 6.2	50 ± 4.5
F3	58 ± 1.8	57 ± 4.1	49 ± 1.1

In vitro drug release of core tablets

In vitro dissolution studies were carried out using USP Type II (paddle method) apparatus (Electrolab TDT-08LIndia). Distilled water was used as dissolution medium.

Release pattern was studied by taking sample of 5 mL at the specific time intervals and analyzed at 250 nm using a UV spectrophotometer (Shimadzu 1800, Japan).

From the four formulations F1, F2, F3, F4, the formulation F1 is selected as best formulation and press coated with the various compositions containing HPMCK4M, Eudragit LS 100 with their compositions and the formulations were renamed as PCT1, PCT2, PCT3, PCT4, PCT5, PCT6.

The prepared tablets were undergone the following the following evaluation tests as specified earlier: Thickness and diameters, Weight variation test, Hardness, Friability, Disintegration, and Drug Content.

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Table 5. Results showing dissolution studies for core tablets.

Time (mins)	% Cumulative Drug Release (% CDR)		
	F1	F2	F3
0	0	0	0
5	20.2	29.7	17.5
10	40.2	43.2	43.9
15	59.1	75.6	68.1
25	67.8	98.4	84.2
35	73.1	101.7	91.1
45	84.6	-	99.7

Table 6. Formulation table for preparing press coated pulsatile tablets using core tablets (F2) of Valsartan.

Ingredient	F1	F2	F3	F4	F5	F6
Core Tablet	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg
HPMC E50	0.5%	-	1.0%	-	0.5%	1.0%
Eudragit LS 100	-	0.5%	-	1.0%	0.5%	1.0%
Talc	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Magnesium stearate	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Lactose	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Total weight (mg)	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

In vitro drug release of enteric coated tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus (Electrolab TDT-08L, India). In order to simulate the pH changes along with the gastro intestinal tract (GIT), dissolution media with 0.1 N HCl and phosphate buffer (pH 6.8) were sequentially used.

When performing the experiment, 0.1 N HCl medium was used for 2 h (since the average gastric emptying time is 2 h) **(Figure 1).** Then removed and fresh phosphate buffer (pH 6.8) was added for subsequent hours. 900 mL of the dissolution medium was used at each time and stirred at 50 rpm at 37°C ± 0.5°C. 5 mL of dissolution media was withdrawing at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 250 nm using a UV spectrophotometer **(Tables 7-9).**

The second stage of the work constitutes the formulation and evaluation of Valsartan with all the polymers individually and coded from; F1 F2 F3 respectively.

The following parameters were evaluated for prepared SST and the results proved that the drug loading and Entrapment efficiency was high in HPMC, followed by Croscarmellose and Crospovidone. The *In vitro* drug release studies showed better controlled and prolonged release with all the Pulsatile press coated tablets for about 11 hrs while PCT2 formulation showed better release from all.

Six different formulations (PCT1- PCT2 PCT3; PCT4 PCT5 PCT6) were prepared from the best formulation stated above (PCT 2) by same method changing the concentration of cross linking agent, speed and time of agitation and they were evaluated as above to obtain an optimized formulation. From all the evaluated parameters, it was concluded that the formulation PCT6 showed good morphology, high drug loading, high entrapment efficiency as well as best controlled and prolonged release of drug up to 11 hrs.

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Table 7. Evaluation of core and compression coated tablets of batches PCT1 to PCT6.

Test	Type of tablet	PCT1	PCT2	PCT3	PCT4	PCT5	PCT6
% Friability	*CT	0.41 ± 0.01	0.35 ± 0.05	0.42 ± 0.01	0.35 ± 0.02	0.34 ± 0.02	0.35 ± 0.05
	*PCT	0.42 ± 0.05	0.35 ± 0.04	0.42 ± 0.05	0.35 ± 0.02	0.41 ± 0.04	0.42 ± 0.05
Hardness (Kg/cm2)	*CT	6.2 ± 0.07	6.2 ± 0.11	5.3 ± 0.09	5.6 ± 0.04	5.9 ± 0.05	5.4 ± 0.05
	*PCT	04 ± 0.10	04 ± 0.1	04 ± 0.1	3.5 ± 0.09	05 ± 0.4	04 ± 0.1
Thickness (mm)	*CT	2.66 ± 0.02	2.00 ± 0.005	2.1 ± 0.05	2.66 ± 0.02	2.1 ± 0.056	2.1 ± 0.05
	*PCT	4.27 ± 0.01	4.22 ± 0.03	4.09 ± 0.003	4.17 ± 0.02	4.20 ± 0.02	4.2 ± 0.01
Average weight (mg)	*CT	150.05 ± 0.6	152.1 ± 1.3	149.9 ± 0.6	155.05 ± 2.6	150.05 ± 0.6	149.9 ± 0.6
	*PCT	250.02 ± 0.6	247.1 ± 0.6	250.05 ± 0.6	249.9 ± 0.6	253 ± 0.5	250 ± 0.5
Note: *CT – Core Tablet; *PCT – Press Coated Tablet							

Table 8. Results showing dissolution studies for press coated pulsatile tablets.

Time (Hrs)	% Cumulative Drug Release (% CDR)					
	PCT1	PCT2	PCT3	PCT4	PCT5	PCT6
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	0	0	0	0	0	0
4	0	0	0	0	0	0
5	20.2	19.7	17.5	22.1	29.1	0
6	40.2	32.1	43.9	35.6	47.1	43.2
8	59.1	47.8	51.4	48.2	54.2	59.3
10	67.8	59.5	68.1	59.1	69.8	61.2
12	73.1	78.9	84.2	74.1	77.9	75.6
14	84.6	84.2	91.1	85.2	84.1	88.4
16	99.2	98.3	99.7	98.2	98.7	97.7

Table 9. Results of optimized press coated Pulsatile tablets (PCT 6).

S. No	Zero Order	Higuchi	Cross Meyer Peppas	Peppas slope value
CODE	R^2	R^2	R^2	n value
PCT 6	0.9996	0.8595	0.9448	1.171

Thus, from the above parameters it was concluded that the formulation code PCT6 was an optimized formulation. From the above observation, it was concluded that the morphological characters, other evaluated parameters, and *in vitro* drug release profile for PCT 6 formulation showed the best results. Therefore, it was thought to compare the evaluated parameters along with *in vitro* drug permeation studies for % cumulative drug release.

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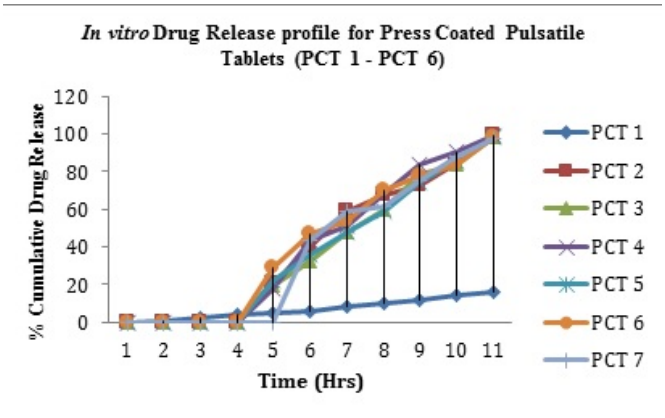

Figure 1. Graph showing the results for *in vitro* drug dissolution profile for press coated Pulsatile tablets (PCT 1-PCT 6).

CONCLUSION

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place, at the right time and in the right amount, thus providing spatial, temporal, and smart delivery and increasing patient compliance. The use of pulsatile release of the drugs is desirable where constant drug release is not desired. Thus, form all the above parameters and results, it was concluded that Valsartan formulated with HPMC, crospovidone croscarmellose polymers showed good results out of which Pct6 was found to be a promising formulation as pulsatile press coated tablets drug delivery by which the bioavailability of the drug is increased by bypassing the first pass metabolism, reducing total dose and frequency of drug administration may be considerably reduced there by bowel syndrome asthma Disease.

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