K.Kannan et al /J. Pharm. Sci. & Res. Vol.4(6), 2012, 1866 - 1871

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Development and Evaluation of Valsartan Film Coated Tablets

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Abstract
Valsartan is a FDA approved drug for the treatment of hypertension belongs to a class of drug known as angiotensin II receptor antagonists, which helps to control high blood pressure. Angiotensin II is a substance in the body that increases blood pressure. Valsartan works by blocking the effect of angiotensin II, as a result, blood vessels relaxes and blood pressure is lowered. The aim of the present study is to formulate and evaluate immediate release tablets of Valsartan. Preformulation studies were performed prior to compression. Tablets were formulated by direct compression, wet granulation and slugging techniques. The fabricated tablets were evaluated for various pre compressional parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and post compressional parameters like average weight, thickness, hardness, friability, assay, disintegration time and dissolution studies. Comparatively, slugging technique exhibited the good flow property than direct compression technique. The stability studies were carried out for the optimized batch for six months. The results of the present study showed that among all the formulations, F8 was better in all terms of pre compression and post compression parameters and showed comparably a good dissolution profile with that of the marketed product.

Keywords: Valsartan, Hypertension, Angiotension II, Slugging technique, Immediate release.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration [1]. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects [2, 3]. For many substances, conventional immediate release formulation provide clinically effective therapy maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patients [4].

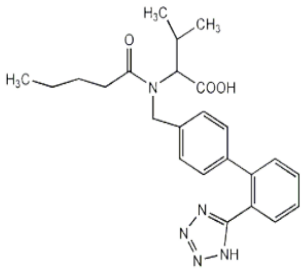

Figure 1: Chemical structure of Valsartan

Hypertension is one of the most prevalent chronic adult illnesses today and cannot be cured, but can be controlled. The pharmacological treatment for control of hypertension utilizes various drug therapies such as single doses or associations of diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor (AT1) antagonist (ARA) [5,6].
Valsartan (VAL) is a potent and specific competitive antagonist of the angiotensin-II AT1-receptor [7, 8] by blocking the action of angiotensin. Valsartan dilates blood vessels and reduces blood pressure [9]. Valsartan (VAL) is chemically 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazoyl-5-yl)phenyl]phenyl]methyl]amino] butanoic acid is an orally active specific angiotensin II receptor blocker effective in lowering blood pressure in hypertensive patients [9].
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Valsartan blocks the vasoconstricton and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis [10, 11].
Formulation of potent drug molecules as a dosage form still draws continuous interest and challenges against optimization towards pharmacokinetic parameters like absorption, on set of action, bio-availability and also economic factors. The main objective is to formulate an oral solid dosage form of valsartan tablets which is considered to be a stable with robust quality along with reduced cost and pharmaceutically equivalent to that of the marketed product for the treatment of hypertension.

MATERIALS AND METHODS

Valsartan (Dr. Reddy's laboratories, India) was received as a gift sample. Lactose monohydrate (Signet pharma agencies, Mumbai), Microcrystalline cellulose (Signet pharma agencies, Mumbai), PVP K-30 (Boai Nky pharmaceuticals, India), Crospovidone XL (Anshul Agencies, India), Aerosil (Carboit samnol pharma agencies, India), Magnesium stearate (Signet pharma agencies, Mumbai), talc (Signet pharma

agencies, Mumbai) and opadry brown (Ideal curves pvt. Ltd. India) were commercially procured and used for this study.

FORMULATION OF TABLETS

Formulation of Valsartan tablets were prepared by direct compression, wet granulation and slugging technique employing various excipients as mentioned in Table 1. Valsartan, microcrystalline cellulose PH102, crospovidone or croscarmellose sodium were passed through 40 # mesh and mixed well for 10 minutes. The blend was lubricated with 50% of magnesium stearate and talc after passing through 40 # mesh. The above lubricated blend was compressed using 18×8 mm oblong shaped punches by increasing hardness for slugging. The tablets were slugged by milling and sifted through 18 # mesh. Crospovidone or croscarmellose sodium, colloidal silicon dioxide were added to the granules obtained after slugging by passing through 40 # mesh. The blend was lubricated with remaining amount of magnesium stearate and talc after passing through 40 # mesh. The tablets were compressed using 27 station tablet compression machine with 18 × 8 mm oblong shaped punches (Rimek, Ahmedabad). The compressed tablets were coated using instacoat brown (coating material).

Evaluation of Tablets [3, 12, 14, 15]

The formulated tablets were evaluated for the following physicochemical parameters.

Weight variation [16, 17]

Composite samples of tablets (usually 10) were taken and weighed throughout the compression process. The composite weight divided by 10 which gives average weight but contain usual problems of averaged values. Within the composite sample that has an acceptable average weight, there could be tablets excessively over weight or underweight. To alleviate this problem the united states of pharmacopeia provides limits for the permissible variations.

Content Uniformity [16, 17]

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Thickness [16, 17]

The thicknesses of 10 tablets were recorded during the process of compression. This is generally due to the differences of density of granules, pressure applied for compression and the speed of compression. It was measured by vernier caliper (Mitutoyo, Japan).

Table 1: The formulation composition of valsartan tablets

Sl. No	Ingredients	Quantity per tablet (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Valsartan	320	320	320	320	320	320	320	320
2	Croscarmellose sodium	64.00	64.00	-	-	89.6	76.8	51.2	64.00
3	Microcrystalline cellulose pH102	228.6	211.8	-	228.6	203	215.8	241.4	228.6
4	SSG	-	-	64.00	-	-	-	-	-
5	Crospovidone XL	-	-	-	64.00	-	-	-	-
6	Aerosil	12.80	12.80	12.80	12.80	12.80	12.80	12.80	12.80
7	Magnesium stearate	6.40	6.40	6.40	6.40	6.40	6.40	6.40	6.40
8	Talc	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
9	PVPK-30	-	20	-	-	-	-	-	-
10	Water	-	-	q.s.	-	-	-	-	-
11	Opadry coat	3%	3%	3%	3%	3%	3%	3%	3%

Table 2: Compressibility Index, Hausner's Ratio, Angle of repose with corresponding Flow characters.

Type of Flow	Compressibility Index	Hausner's ratio	Angle of repose (θ)
Excellent	1 – 10	1.00 – 1.11	25 – 30
Good	11 – 15	1.12 – 1.18	31 – 35
Fair	16 – 20	1.19 – 1.25	36 – 40
Passable	21 – 25	1.26 – 1.34	41 - 45
Poor	26 – 31	1.35 – 1.45	46 – 55
Very Poor	32 – 37	1.46 – 1.59	56 – 65
Extremely Poor	> 38	> 1.60	> 66

Table 3: Weight Variation Tolerance for Tablets

Average weight of the tablet (mg)	Percent difference
130mg or less	10
More than 130mg to 324mg	7.5
More than 324mg	5

Hardness [16, 17]
Tablets require a certain amount of strength or hardness and resistance to friability and to withstand mechanical shocks from handling in manufacture packaging and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer. Tablet hardness has been defined as force required to break a tablet in a diametric compression tester. To perform this test, a tablet is placed between two anvils, force is applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed the tablet crushing strength.

Friability [16, 17]
The laboratory friability tester is known as the Roche friabilator. It subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 100rpm dropping the tablets at a distance of six inches for each revolution. Normally a pre weighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Some chewable tablets are most effervescence tablets undergo high friability weight losses, which accounts for the special stack packaging that may be required for these types of tablets. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.
The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test
W_2 = Weight of tablets after test

Disintegration [16, 17]
For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 # mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Assay (By HPLC method) [18, 19]
Instrument
High performance liquid chromatography equipped with UV-Detector and data handling system

Chromatographic conditions
Chromatographic separations were achieved by using X-Terra RP- 18 (100 x 4.6mm), 5µm analytical column. The mobile phase consists of mixture of distilled water, Acetonitrile and glacial acetic acid in the ratio of 550:450:1 v/v respectively. The flow rate was maintained at 2.0 ml/min with injection volume of 20µl and the absorbance was measured at 248nm for Valsartan. The column and the HPLC system were kept in ambient temperature.

Preparations
Mobile phase preparation
Mobile phase was prepared by filtering and degassing the mixture of distilled water, Acetonitrile and glacial acetic acid in the ratio of 550:450:1v/v.
Blank preparation
5ml of methanol was transferred into 50ml volumetric flask and diluted to volume with mobile phase.
Standard preparation
25.6mg of Valsartan working standard was accurately weighed and transferred into a 100mL volumetric flask. 60ml of methanol was added and sonicated to dissolve. The solution was cooled to room temperature and diluted to volume with methanol.
5 ml of the above solution was transferred into 50ml volumetric flask and diluted to volume with diluent.
Sample preparation [19]
20 tablets were weighed and finely powder and an accurately weighed portion of the powdered tablet, equivalent to 320mg of Valsartan was transferred into 250ml volumetric flask. 150ml of methanol was added and sonicated for 30 minutes with occasional shakings and the solution was cooled to room temperature and diluted to volume with methanol and mixed well. The solution was filtered through 0.45µm membrane filter. 2.0mL of the above solution was transferred into a 100ml volumetric flask and diluted to volume with mobile phase.
Calculation

% Content of Valsartan:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{5}{25} \times \frac{1000}{1} \times \frac{20}{5} \times \frac{P}{100} \times \frac{100}{320}$$

Where,
TA- Peak area response due to Valsartan from sample preparation
SA- Peak area response due to Valsartan from standard preparation
SW- Weight of Valsartan working standard taken in mg
TW- Weight of sample taken in mg
P- Purity of Valsartan working standard, taken on as is basis.
Avg. wt - Average weight of tablet.
LA- Label Amount.

Dissolution
Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability.

***Estimation by HPLC method** [19]*

Instrument

High performance liquid chromatography equipped with UV-Detector and data handling system.

Dissolution conditions

The release rate of valsartan from the tablets was determined using USP dissolution testing apparatus II (Electro lab, India). The dissolution testing was performed using 1000ml of 0.067M Phosphate buffer, pH 6.8 at 37±0.5°C temperature and speed 50 rpm. Sample of 10ml was withdrawn at regular interval of 10^{th}, 20^{th}, 30^{th} and 45^{th} minutes and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using HPLC.

Preparations

0.2M Sodium hydroxide solution

8.0g of sodium hydroxide was dissolved in water and diluted to 1000 ml with water.

Preparation of Dissolution medium (0.067M Phosphate buffer, pH 6.8)

9.12g of Potassium dihydrogen phosphate was dissolved in 1000ml of water, and the pH of solution was adjusted to 6.8 with 0.2M sodium hydroxide solution

Chromatographic conditions

Chromatographic separations were achieved by using X-Terra RP- 18 (100 x 4.6mm), 5µm analytical column. The mobile phase consists of mixture of purified water, Acetonitrile and glacial acetic acid in the ratio of 550:450:1 v/v respectively. The flow rate was maintained at 2.0 ml/min with injection volume of 20µl and the absorbance was measured at 248nm for valsartan. The column and the HPLC system were kept in ambient temperature.

Mobile phase preparation

Mobile phase was prepared by filtering and degassing the mixture of purified water,

Acetonitrile and glacial acetic acid in the ratio of 550:450:1 v/v. respectively

Standard Stock preparation

40mg of Valsartan working standard was accurately weighed and transferred into a 100ml volumetric flask. 60ml of methanol was added and sonicated to dissolve. The solution was cooled to room temperature and diluted to volume with methanol.

Standard Preparation

5.0ml of the above solution was transferred into 50ml volumetric flask and diluted to volume with diluent.

Sample Preparation [19]

One tablet was placed in each of six dissolution flasks containing 1000ml of dissolution medium, previously maintained at 37°C ±0.5° C. After completion of specified time interval, a portion of solution was withdrawn from the zone of midway between the surface of dissolution medium and top of the rotating blade not less than 1cm from vessel wall and filtered through 0.45 µ membrane filter. 5.0ml of the above solution was transfer into a 20ml volumetric flask and diluted to volume with dissolution medium. Dissolution sample was directly injected into the HPLC system.

Calculation:

% of Labeled amount of Valsartan dissolved:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{5}{25} \times \frac{1000}{1} \times \frac{20}{5} \times \frac{P}{100} \times \frac{100}{320}$$

Where,

TA - Peak area response due to Valsartan from sample preparation

SA - Peak area response due to Valsartan from standard preparation

SW - Weight of Valsartan working standard taken in mg

P- Purity of Valsartan working standard, taken on as is basis

Stability Studies as per ICH guidelines [20, 21, 22, 23]

In order to determine the change on storage, stability study was carried out a 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples were withdrawn at regular intervals during the study of 60 days. Formulation was evaluated for changes in Assay and *in vitro* release studies.

RESULTS AND DISUCUSSION

Preformulation studies

Compatibility test between the drug and tablet components was carried out at 40°C ± 2°C / 75±5% and 25°C ± 2°C / 60 ±5% for three months. The mixture does not show any visible change, thus indicating drug and other tablet components do not have any incompatibility.

Evaluation of tablets

Micrometric properties

Bulk Density for valsartan blend was found to be in the range of 0.414 to 0.682. Tapped density for granules were found to be between 0.535 and 0.543. Compressibility index and Hausner's ratio were obtained in the range of 14.60 to 23.61 and 1.17 to 1.30 respectively. Angle of repose was observed in the range of 26.10' to 41.15' (Table 4).

Post-compression parameters

Prepared blends were compressed and these compressed tablets were evaluated for weight variation, thickness, friability, hardness, disintegration, assay and dissolution. The average percentage deviation of 20 tablets of each tablet was less than 3%. The thickness and hardness of the tablet ranged from 6.17 – 6.93 mm and 10.1 – 12.2 kg/cm2 respectively. The percentage friability of all batches ranged from 0.170 to 0.71 %W/W. The disintegration time was ranged from 9 minute 15 seconds to 19 minutes 57 seconds for coated tablets (Table 5).

Table 4: Pre-compression Parameters of Valsartan Tablet Blend

Parameters	Formulation Trials							
	F1	F2	F3	F4	F5	F6	F7	F8
Bulk Density(gm/ml)	0.414	0.635	0.440	0.682	0.460	0.462	0.462	0.463
Tapped Density(gm/ml)	0.542	0.543	0.535	0.540	0.541	0.542	0.542	0.543
Compressibility Index (%)	23.61	22.65	17.75	15.74	14.97	14.76	14.60	14.73
Hausner's ratio	1.30	1.29	1.21	1.18	1.17	1.17	1.17	1.17
Angle of repose (θ)	41°15'	28°23'	32°21'	31°14'	27°17'	28°12'	27°15'	26°10'

Table 5: Evaluation of Post-Compression parameters of Valsartan tablets

Parameters	Formulation Trials						
	F2	F3	F4	F5	F6	F7	F8
Average weight (mg)	640.5	641.2	648	642	649.5	644.8	642.8
Thickness (mm)	6.17	6.48	6.41	6.93	6.45	6.59	6.58
Friability (%)	0.18	0.32	0.17	0.53	0.29	0.71	0.22
Hardness (Kg/cm^2)	10.58	14.36	10.1	12	10.18	11.6	12.20
Assay (%)	92.1	94.21	110.2	99.17	98.57	94.35	94.32
Disintegration Time (min)	9min 15sec	15min 10sec	10min 30sec	9min 45sec	10min 35sec	19min 57sec	5min 37sec

Table 6: Stability data for F - 8 Film Coated Valsartan Tablets

Characteristics Tested	Time intervals				
	Initial	1 month 25°C / 60% RH, 40°C / 75% RH	2 months 25°C / 60% RH, 40°C / 75% RH	3 months 25°C / 60% RH, 40°C / 75% RH	6 months 25°C / 60% RH, 40°C / 75% RH
Description	*	*	*	*	*
Hardness (Kg/ Cm^2)	12.20	12.15	12.10	12.10	12.00
Disintegration Time	5 Mins 37 secs	5 Mins 30 Secs	5 Mins 20 Secs	5 Mins 18 Secs	5 Mins 10 Secs
Dissolution (%)	100.3	100.2	100.2	100.1	99.8

***Light brown to brown, ovoid with beveled edges**

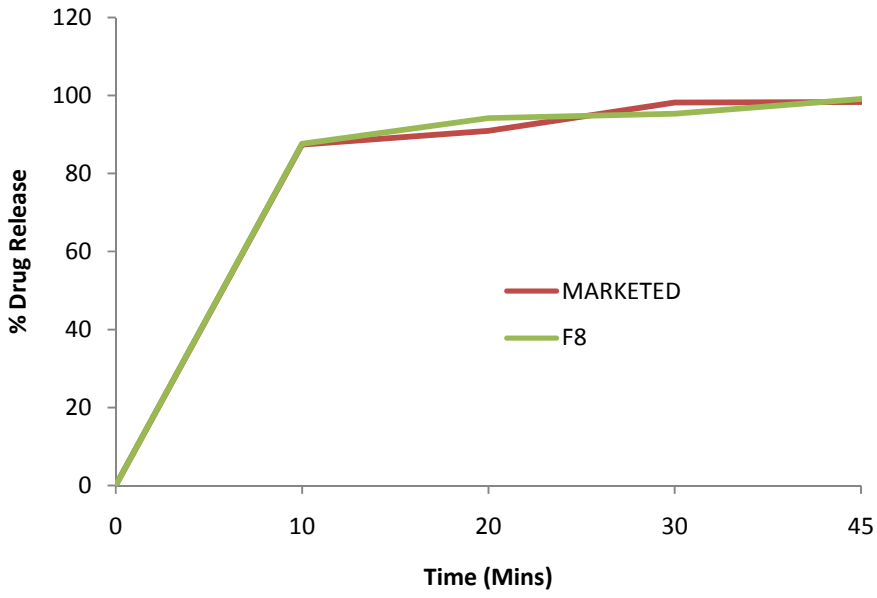

Figure 2: Comparison of dissolution curves of optimized batch and Marketed product

CONCLUSION

The immediate release tablets of valsartan have been developed with slugging technique and it was compared with that of marketed product. Compared to the direct compression and wet granulation technique, slugging technique was found to be the best method of choice for formulation of these tablets. Various trials were performed to optimize the disintegrants and its concentration of sodium starch glycolate, crospovidone and croscarmellose sodium. The *in vitro* drug release profile of Valsartan tablets from each batch (formulation 2 to 8) prepared by different methods were carried out in 0.067 M Phosphate buffer having pH 6.8 for 45 minutes using paddle type apparatus. Results from these experiments shown that *in vitro* dissolution data was highly significant in F8 formulation, and this promising formulation F8 was compared with marketed product. Formulation trial F8 on stability studies does not show any remarkable changes in their characteristics. Therefore, it was concluded that the F8 trial was the satisfactory formulation that could perform therapeutically, with improved efficacy and better patient compliance like that of the marketed product.

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