Research Article

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Development and characterization of valsartan and hydrochlorothiazide film coated tablet

Satyam Pandey*, Aditya Nath Pandey, Dinesh singh, Ankit mishra[1] and Manisha Kawadkar

Millennium College of Pharmacy, Bhopal, (M.P.) - India

1, VNS College of Pharmacy, Bhopal, (M.P.) - India

Abstract

Tablets are solid unit dosage form of medicaments with or without suitable diluents and prepared either by molding or compression. They are solid, flat or biconvex disc in shape. They vary greatly in shape, size and weight which depend upon amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics and in other aspects depending upon their intended use and method of manufacture. Tablets are the most widely used solid dosage form of medicament. Because of their advantages their popularity is continuously increasing day by day. Hypertension is a very common disorder, particularly past middle age. It is not a disease in itself, but it is an important risk factor for cardiovascular mortality and morbidity. The WHO-ISH guidelines defined it to 140 mm Hg systolic and 90 mm Hg diastolic, through risk appears to increase even above 120/90 mm Hg. The present paper deals with development characterization of valsartan and hydrochlorothiazide film coated tablet

Key-Words: Valsartan, Film coated, Development

Introduction

Only approximately 40% to 50% of hypertensive patients will achieve goal blood pressures of <140/90 mm Hg with monotherapy, regardless of the medication used. Fixed-dose combination therapy with two different classes of antihypertensive agents will achieve goal pressures in more than 70%. The sixth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure has suggested that the use of combination therapy is appropriate as initial treatment.[1]

Valsartan reduces blood pressure to a similar extent as other angiotensin II-receptor antagonists. If blood pressure is not controlled by valsartan 80 mg, add a second drug rather than increasing the dose to 320 mg. increasing the dose from 80 mg to 320 mg provides marginal additional blood pressure reduction. Establish the effective dose using individual drugs before prescribing the appropriate combination.[2]

*** Corresponding Author:**
Mob.: 08898675733

Valsartan is an angiotensin II-receptor antagonist that has been available overseas for several years. Angiotensin II-receptor antagonists have similar blood pressure reducing effects to those of other major antihypertensive drug classes. This class of drugs is an option for initial therapy for people with hypertension and may be useful for those with particular comorbidities (e.g. diabetic nephropathy) or intolerances (e.g. angiotensin-converting enzyme [ACE] inhibitor-induced cough). Other options for initial therapy include low-dose thiazide diuretics, dihydropyridine calcium-channel blockers or angiotensin-converting enzyme inhibitors. The aim of Present work to prepare valsartan and hydrochlorothiazide coated tablet. This combination therapy gives better result than the monotherapy. The invention relates to a solid pharmaceutical composition comprising valsartan and a process for its preparation. Similar combination is also in the market (marketed by novartis) having more cost.[1-3] Our aim is to prepare lower cost formulation, prepare a good strength and stability of dosage form. Thus the aim of valsartan and hydrochlorothiazide combination therapy is to prevent morbidity and mortality associated with other preparation; by lowering it to an acceptable level with minimum inconvenience to the patients.

Material and Methods[4-9]

The following materials that were either AR/LR grade or the best possible Pharma grade available were used as supplied by the manufacturer.

Materials	Supplier
Vaisartan	Hetero labes limited
Hydrochlorothiazide	Unicham laboratories Ltd
Microcrystalline cellulose	Siguchi Chlorochem
Lactose	Dynamic Diary Industries
Colloidal silicon dioxide	Cabot Sanmar Ltd.
PVP –K -30	Siguchi chlorochem
Avical pH 102	Siguchi Chlorochem
Avical pH 200	Siguchi Chlorochem
Avical-CS-183	Siguchi Chlorochem
Cross carmellose sodium	Ross Wall Industries
Magnesium Stearate	Nitika Chemicals
Cross povidone	Huzhouzhanwan Chemicals & Pharma
Sodium Lauryl Sulphate	Galaxy
Talc	Neelkanth Mine
Isopropyl Alcohol	Deepak fartilisers
Iron Oxide Red	Roha dye

Preformulation studies

Preparation of 6.8 Phosphate buffer

Place 50.00ml of 0.2ml potassium Dihydrogen phosphate in a 200ml volumetric flask adds the specified volume of 0.2 M sodium hydroxide and then add water to volume

Preparation of 0.2 M Potassium Dihydrogen phosphate:

Dissolve 27.281gm of Potassium Dihydrogen phosphate in water and dilute with water to 1000 ml.

Preparation of 0.2M sodium hydroxide

Dissolve sodium hydroxide in water to produce a 40 to 60 w/v solution and allow to stand. Taking Precaution to avoid absorption of carbon dioxide. Siphon off the clear supernatant liquid and dilute with carbon dioxide free water a suitable volume of the liquid to contain 8.0 gm NaOH in 1000ml.

Spectroscopic studies

UV spectroscopy: (Determination of λ max.)

Valsartan and Hydrochlorothiazide was accurately weighed and dissolved in distilled water to make 1 mg/ml. This solution was then suitably diluted to 100ml using distilled water to get a final solution of concentration 100µg/ml. UV spectrum was recorded in the wavelength range 200- 400 nm.

Construction of calibration curve for Valsartan(in6.8Phosphate buffer solution)

(i) Preparation of standard stock solution: A standard stock solution of valsartan of concentration 1000 µm/ml was prepared in pH 6.8 phosphate buffer.

(ii)Working stock solution: The standard stock solution was then appropriately diluted with pH 6.8 phosphate buffer, to obtain a series of Valsartan solution in the concentration range of 5-30 µm/ml. The absorbance of all the solutions was measured against blank (pH 6.8 phosphate buffer) at 250 nm using double beam spectrophotometer (V-530, Jasco). A standard plot of absorbance v/s concentration of drug in µg was plotted.

Construction of calibration curve for valsartan(pH 6.8 phosphate buffer)

Similarly calibration curve of valsartan (pH 6.8 phosphate buffer) was prepared.

Construction of calibration curve for Hydrochlorothiazide(in6.8Phosphate buffer solution)

(i) Preparation of standard stock solution: A standard stock solution of Hydrochlorothiazide of concentration 1000 µm/ml was prepared in pH 6.8 phosphate buffers.

(ii)Working stock solution: The standard stock solution was then appropriately diluted with pH 6.8 phosphate buffer, to obtain a series of Hydrochlorothiazide solution in the concentration range of 2-20 µm/ml. The absorbance of all the solutions was measured against blank (pH 6.8 phosphate buffer) at 272 nm using double beam spectrophotometer (V-530, Jasco). A standard plot of absorbance v/s concentration of drug in µg was plotted.

Construction of calibration curve for valsartan(pH 6.8 phosphate buffer)

Similarly calibration curve of valsartan(pH 6.8 phosphate buffer) was prepared.

Compatibility studies b/w active and excipients:-

Valsartan and hydrochlorothiazide Raw material mix 1:1 ratio then kept on 55ºC within 15 day with 5% moisture or without moisture in amber color 5ml bottle . This process also mix 1:1 both drug and all excipients kept on same condition and visual evaluation after 15 day.

IR Spectroscopy (FTIR)

Appling method By KBr Pressed pellet technique. Taken drug and mix with KBr and triturate with the help of mortar pastel and place in chamber of FTIR and evaluate the IR curve of Valsartan. Hydrochlorothiazide IR evaluates same process like that valsartan. After that valsartan and hydrochlorothiazide taken 1:1 ratio and evaluate with

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IR Curve. Then all excipients and both drug are evaluate same process.

Solubility studies

Solubility of valsartan and Hydrochlorothiazide studied in different solvent like water, alcohol (Ethyl alcohol and methyl alcohol), and Phosphate buffer. **Valsartan**: Valsartan soluble in ethyl alcohol, slightly soluble in water and Soluble in ether. **Hydrochlorothiazide**: Slightly soluble in ethyl alcohol, Soluble in sodium hydroxide and sparingly soluble in water.

Composition of Valsartan and hydrochlorothiazide

Intra granular composition

Ingredients(mg)	Formulation Code(mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Valsartan	80	80	80	80	80	81.6	81.6	81.6	84	83.2
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	-	12.5	12.5	12.5	12.5
Avical-102	81.04	-	-	-	-	-	-	-	-	-
Avical-200	-	81.04	-	-	-	-	-	-	-	-
Avical-183	-	-	77.49	-	-	-	-	-	-	-
Microcrystalline cellulose	-	-	-	54.5	78.4	43.4	43.4	41.3	38.9	39.68
PVP -K -30	-	-	-	4	-	-	-	-	-	-
Colloidal silicon dioxide	0.51	0.51	0.51	2	0.90	1	1	1	1	1
Cross povidone	4.25	4.25	6.8	-	-	3.2	33.2	3.2	3.2	3.2
Cross carmellose sodium	-	-	-	6	1.80	-	-	-	-	-
Magnesium Stearate	1.7	1.7	1.7	1.0	0.90	0.8	0.65	0.8	0.8	-
Lactose	-	-	-	20	-	-	-	-	-	-
Isopropyl Alcohol	-	-	-	-	16		-	-	-	-

Extra granular composition

Ingredients(mg)	Formulation Code(mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hydrochlorothiazide	-	-	-	-	-	12.5	-	-	-	-
Microcrystalline cellulose	-	-	-	-	-	11.7	11.7	11.7	11.7	11.7
Colloidal silicon dioxide					-	1	1	1	1	1
Cross povidone	-	-	-	-	-	4	4	4	4	4
Cross carmellose sodium	-	-	-	-	3.60	-	-	-	-	-
Talc	-	-	-	-	0.90	-	-	-	-	-
Sodium Lauryl Sulfate	-	-	-	-	-	-	-	2.1	2.1	2.12
Magnesium Stearate	-	-	-	-		0.8	0.8	0.8	0.8	

Evaluation of Tablets

I. Pre-compression parameters

Micromeritic evaluation, Angle of repose, Bulk density, Percentage Compressibility, Hausner Ratio

II. Post-compression parameters

Shape and color of tablets, Uniformity of thickness, Hardness test, Friability test, Drug content uniformity, Weight variation test, *In vitro* disintegration, *In vitro* dissolution studies, Stability studies

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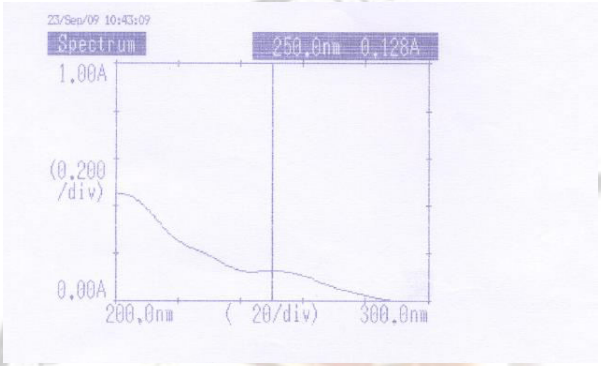
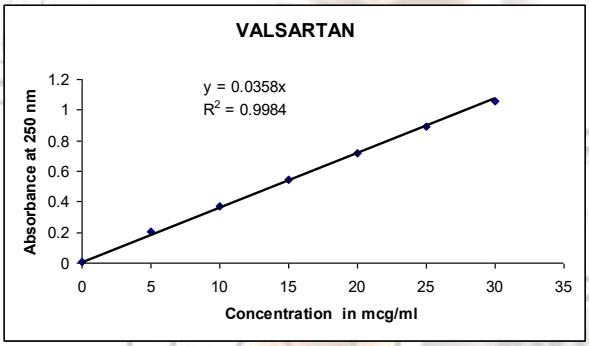
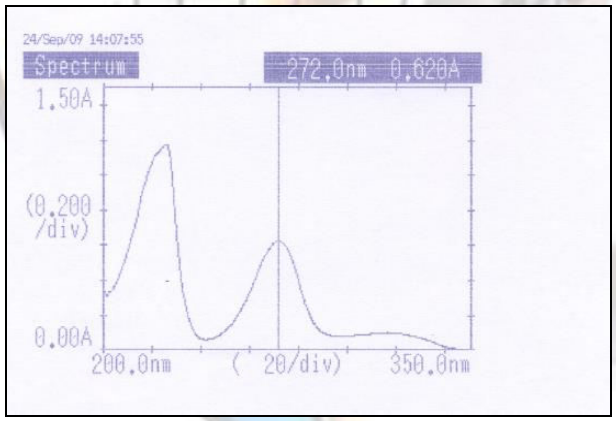
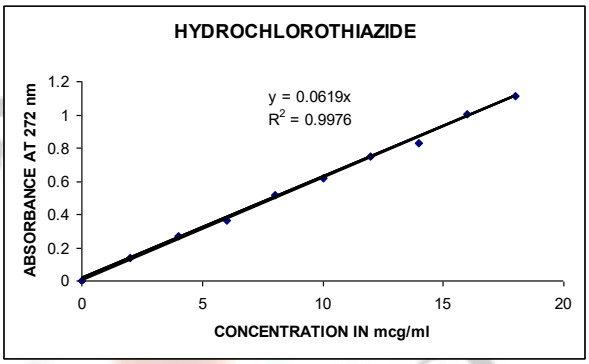
Results and Conclusion

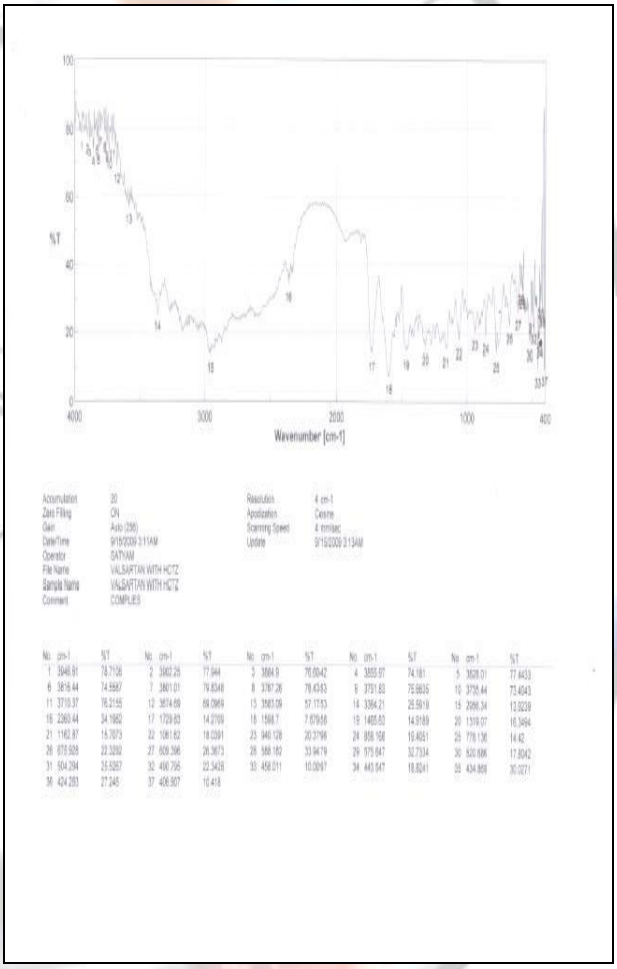
Preformulation studies were conducted prior to the development of rapidly disintegrating tablets of Valsartan and Hydrochlorothiazide. It was found that the estimation of Valsartn by spectrometric method at 250 nm and Hydrochlorothiazide by spectrometric method at 272 nm.











IR spectroscopic curve Valsartan with Hydrochlorothiazide

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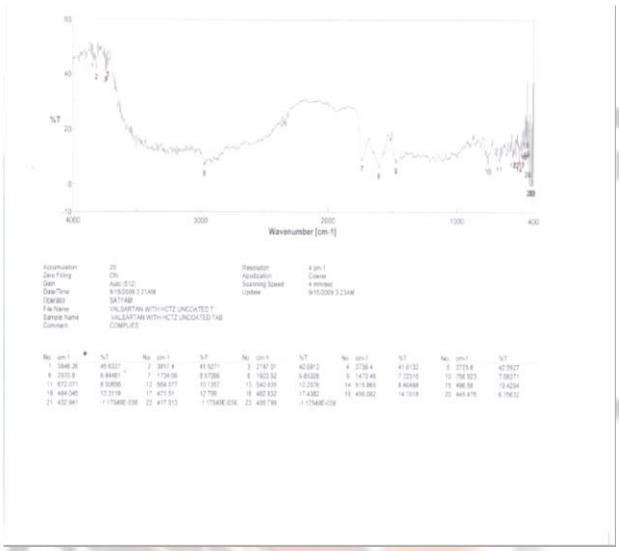
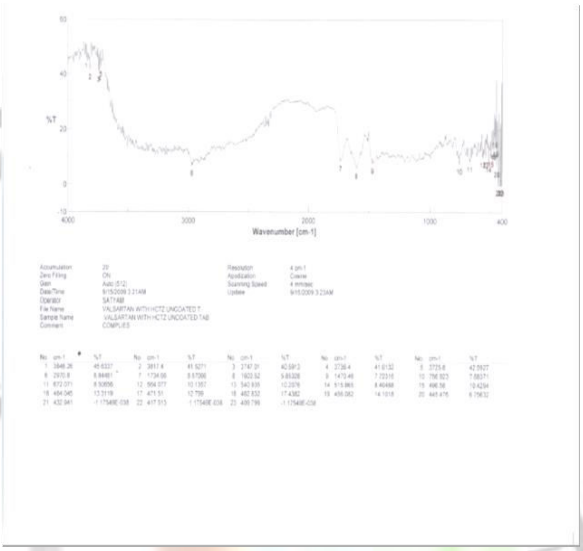


IR spectroscopic curve Valsartan with Hydrochlorothiazide uncoated formula



IR spectroscopic curve Valsartan with Hydrochlorothiazide coated formula

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Table 1: Precompression parameter according to formula:

Formula	Angle of repose(degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	% Compressibility	Hausner Ratio
F1	26	0.23	0.41	43.90	1.78
F2	29	0.24	0.45	46.67	1.88
F3	35	0.48	0.57	15.78	1.19
F4	22	0.35	0.45	22.22	1.29
F5	28	0.35	0.41	14.63	1.17
F6	34	0.60	0.71	15.492	1.18
F7	33	0.50	0.71	29.58	1.42
F8	30	0.58	0.68	14.71	1.17
F9	23	0.54	0.69	21.74	1.28
F10	28	0.35	0.41	14.63	1.17

Table 2: Thickness and Diameter

Formulation Code	Diameter(mm)	Thickness(mm)
F1	8.0±0.5	4.30 ±1.17
F2	8.0±0.5	4.41 ±1.19
F3	8.0±0.5	4.70 ±1.17
F4	8.0±0.5	4.14 ±1.18
F5	8.0±0.5	4.12 ±1.15
F6	8.0±0.5	3.80±1.12
F6	8.0±0.5	3.80±1.15
F8	8.0±0.5	3.80±1.17
F9	8.0±0.5	3.80±1.19
F10	8.0±0.5	3.80±1.15

Table 3: Friability and Weight variation

Formulation Code	Friability	Weight variation(mg)
F1	0.470%	180±3.0%
F2	0.348%	180±2.0%
F3	0.658%	180±3.0%
F4	0.265%	180±3.0%
F5	0.309%	180±3.0%
F6	0.340%	160±7.5%
F7	0.210%	160±7.5%
F8	0.167%	160±7.5%
F9	0.375%	160±7.5%
F10	0.220%	160±7.5%

Table 4: Disintegraton Time and Hardness

Formulation Code	Disintegraton Time(min)	Hardness (kg/cm2)
F1	8.30	4.00
F2	9.20	5.00
F3	7.00	3.00
F4	2.00	3.00
F5	9.30	7.00
F6	2.45	6.5
F7	1.50	6.00
F8	0.50	4.90
F9	1.40	5.50
F10	1.30	5.00

Table 5: Dissolution and Content Uniformity Of valsatan

Formulation Code	Dissolution (%)	Content uniformity
F1	83.50	89.53
F2	81.58	84.31
F3	84.21	89.40
F4	86.31	88.90
F5	69.60	82.48
F6	88.40	103.90
F7	90.50	103.97
F8	84.5	91.52
F9	97.50	98.04
F10	99.50	99.70

Table 6: Dissolution and Content Uniformity Of Hydrochlorothiazide

Formulation Code	Dissolution (%)	Content uniformity
F1	80.20	78.50
F2	86.50	91.10
F3	85.88	90.30
F4	88.40	94.70
F5	78.50	80.21
F6	84.40	98.41
F7	107.1	97.99
F8	82.10	80.48
F9	83.80	97.51
F10	90.53	99.54

Stability studies

The stability studies of the optimized formulation of tablets revealed that no significant changes in the physical parameters when stored at temperature and humidity conditions of 30 ± 2ºC/ 75 ± 5 % RH and at room temperature.

No significant reduction in the content of the active drug was observed over a period of two months hence shelf life of the formulation could extrapolate to a minimum of two years. However, storage temperature not exceeding 45ºC and moisture proof packaging are essential to ensure stability of these formulations.

The optimum formulation did not show any significant change in disintegration time, % release after 30 minutes and drug content when kept at different condition and periods.

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