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FORMULATION AND EVALUATION OF VALSARTAN FAST DISSOLVING TABLETS

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ABSTRACT

The aim of the study was to formulate and evaluate orally disintegrating tablet of Valsartan. Direct compression method was used to formulate orally disintegrating tablet of Valsartan by employing sodium starch glycolate and crospovidone as superdisintegrants, microcrystalline cellulose as filler and magnesium stearate (lubricant), Talc. The powder blends were evaluated for flow property and compressed into tablets by direct compression technique. These prepared FDTs were evaluated for physicochemical properties and parameters such as average weight, thickness, weight variation, hardness, friability, disintegration time, drug content and dissolution profile. Dissolution and drug content tests were performed using USP apparatus II and ultraviolet spectrophotometry, respectively. Effect of superdisintegrant on disintegration behaviour of tablet and effect direct compression method on drug release profile were studied using artificial saliva. Among all the formulations, F3 has taken least time for disintegration and also release profiles of F3 were found to be satisfactory comparative to other formulations. So F3 Formulation was found to be the best for the preparation of valsartan orally disintegrating tablets as it has exhibited faster disintegration and best dissolution profile when compared to other formulations.

KEYWORDS: Valsartan, superdisintegrants, direct compression technique, in vitro drug release studies.

INTRODUCTION

Orally disintegrating tablets (ODTs) rapidly disintegrate in the mouth without chewing on oral administration and without the need for water, unlike other drug delivery systems and conventional oral solid immediate-release dosage form.[1,2] ODT dosage forms, also commonly known as fast melt, quick melts, fast disintegrating and orodispersible systems have the unique property of disintegrating the tablet in the mouth in seconds. The desired criteria for the FDT they should have a pleasing mouth feel, leave minimal or no residue in the mouth after oral administration and not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.[3]

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction and in the management of heart failure.[4,5] Valsartan is rapidly absorbed after oral dose with a bioavailability of about 23%. Peak plasma concentrations occur 2-4 hrs, and its plasma half-life is about 7.5 hrs after an oral dose. In the management of hypertension, Valsartan is given in a dose of 80 mg once daily.[6] The aim of the proposed work was to formulate and characterize fast dissolving tablets of valsartan for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension in elderly patients.

2. MATERIALS AND METHOD[7,8,9]

Materials

Valsartan was collected as a gift sample from Hetero labs, Hyderabad, and Crospovidone, sodium starch glycolate, Microcrystalline cellulose and talc were purchased from AR chemicals.

Method

Drug excipient compatibility studies

The IR absorption spectra of the Valsartan drug and with different superdisintegrants and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc

of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to presence superdisintegrants, natural gums, polymers and exipients.

Formulations Table

Table 1: Formulation of core tablets of Valsartan.

Ingredients(mg)	V1	V2	V3	V4
Valsartan	80	80	80	80
Crospovidone	2	4	-	-
Sodium starch glycolate	-	-	2	4
Microcrystalline cellulose	113	111	113	111
Talc	2	2	2	2
Magnesium Stearate	3	3	3	3
Total	200	200	200	200

Preparation of matrix tablets by Direct compression method

Different matrix embedded formulations of valsartan were prepared by direct compression method using varying proportion of polymers. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, super disintegrant and filler (MCC) was mixed thoroughly. Magnesium stearate and talc was added as lubricant and glidant the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 8 mm flat-faced punches at a compression force required to produce tablets of about 4–6 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Evaluation studies[10,11,12]

i) Pre compression parameters

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3.

Bulk density = W/V_o

Tapped density = W/V_f

c) Compressibility index

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inte rparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

d) Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

ii) Post compression parameters

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Valsartan. Dissolve the weighed quantity of powder into 100 ml of buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the

volume with distilled water. Immediately analyze the drug by taking absorbance at 268nm using reagent blank.

Disintegration time

Disintegration time was measured in 900 ml artificial saliva (pH 6.8) according to the USP method without disc at 37 ± 0.5^{o}C temperature. The disintegration time of 6 individual tablets were recorded and the average was reported.

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 period of time. Temperature maintained at 37±5. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at 268 nm against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared tablets of Valsartan were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 30 days.

3. RESULTS AND DISCUSSION

Drug excipient compatibility studies

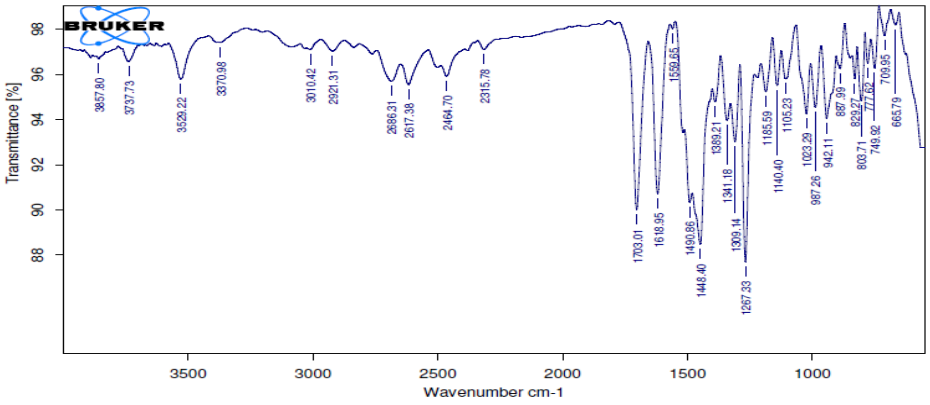

Fig. 1: FT-IR Sample for Valsartan.

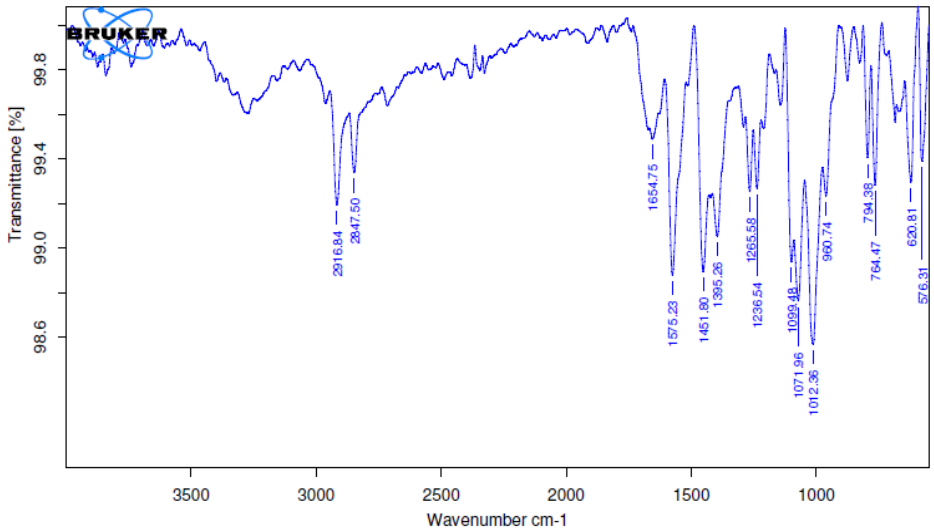

Fig. 2: FT-IR Sample for Optimaized Formulation.

Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.448-0.464

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.520-0.549.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to31^0

d) Compressibility index: Compressibility index was carried out, it was found between 10% to 17.66% indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table 2: Pre compression parameters of Valsartan fast dissolving tablets.

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(^{0})
F1	0.464	0.520	10.76	1.12	30^{0}c
F2	0.448	0.539	16.88	1.12	29^{0}c
F3	0.452	0.549	17.66	1.21	28^{0}c
F4	0.451	0.543	16.94	1.20	31^{0}c

Post compression parameters

Weight variation

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation range was 198-200mg which is within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness (n=3) were uniform in F1 to F4 formulations and were found to be in the range of 2.1 mm to 2.5 mm.

Hardness

The measured hardness of tablets of each batch ranged between 3.12 to 3.32 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability range was 0.48-0.51% that is less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F4 was found to be between 95.20% and 98.55% of Valsartan, it complies within the official specifications.

In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 maintained at 37±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Range was 26.18-29.15sec i.e., <1min for all. Among all, F3 found to show faster disintegration (i.e., least disintegration time of 27sec) when comparative to other formulations.

Table 3: Evaluation parameters of Valsartan fast dissolving tablets.

B. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)	Disinte-gration time(sec)
F1	200	2.4	3.12	0.48	95.15	28.96
F2	198	2.5	3.19	0.51	94.98	27.58
F3	200	2.2	3.20	0.50	98.10	26.18
F4	199	2.1	3.32	0.49	96.24	29.15

Dissolution studies

All the four formulation of Valsartan fast dissolving tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time with 50rpm. The formulation F3 containing sodium starch glycolate as super disintegrant in 1% conc. (i.e., 2mg in 200mg tablet weight) was found to be most effective as it has shown maximum drug release among all the four formulations.

Table 4: Dissolution Profiles of all formulations.

%Drug Release				
Time (min)	F1	F2	F3	F4
0	0	0	0	0
2	24.29	25.40	26.10	23.80
4	39.28	38.21	40.15	39.65
6	52.45	51.46	53.46	49.10
8	65.74	62.80	62.30	64.65
10	72.82	71.19	73.35	71.29
15	81.40	83.85	83.19	79.96
20	87.19	90.63	89.46	88.30
30	92.88	95.35	97.98	95.50

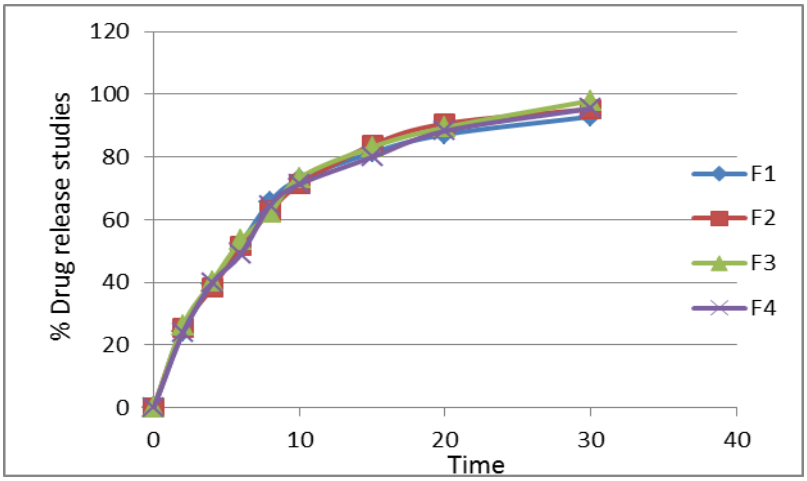

Fig. 3: Percentage drug release of all formulations.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 30 days. Parameters quantified at various time intervals were shown.

Table 5: Stability study parameters for F-3.

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	97.98	97.45	Not less than 85 %
F-3	30^0C/75% RH % Release	97.98	97.58	Not less than 85 %
F-3	40^0C/75% RH % Release	97.98	97.61	Not less than 85 %

4. SUMMARY AND CONCLUSION

Present work was done with an aim to formulate Fast dissolving tablet dosage form of valsartan and to evaluate the tablets for various parameters including in vitro drug release studies. Valsartan was subjected to preformulation studies; based on the results obtained, Valsartan fast dissolving tablets were successfully formulated. Four Formulations were prepared by using crospovidone and sodium starch glycolate as super disintedrants, magnesium stearate as lubricant, microcrystalline cellulose as filler. These formulated powder blends were evaluated for physical parameters such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose. and were found to lie within the specifications. The powdered blends were compressed into tablets by direct compression method and were evaluated for the parameters such as average weight, weight variation, thickness, friability, hardness, disintegration time, drug content and dissolution rate. All the parameters viz: Friability, Hardness, Thickness, Weight variation and drug content were also found to be within limits. Among all the formulations, F3 containing sodium starch glycolate as super disintegrant in 1% conc. (i.e., 2mg in 200mg tablet weight) has taken least time of 26sec for disintegration and also release profiles of F3 were found to be satisfactory comparative to other formulations. The formulation F3 was found to be most effective as it has shown faster disintegration and maximum drug release among all the four formulations.

Stability studies of the optimized formulation were done and found that there was no significant change in the physical and chemical properties.

It was also observed that to further increase the drug release from FDTs, solubility enhancement of valsartan is required and is under investigation.

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