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Formulation and In-vitro Evaluation of Valsartan Fast Dissolving Tablets by Sublimation Technique

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ABSTRACT:

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. The purpose of this investigation was to develop fast dissolving tablets (FDTs) of Valsartan by sublimation technique using camphor as subliming agent together with crospovidone (CP) as superdisintegrant. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, the results revealed that there was no interaction between dug and other excipients. Effect of subliming agent camphor and superdisintegrant crospovidone on disintegration time, wetting time, Water absorption ratio, drug content in-vitro release and stability parameters have been studied. Disintegration time and dissolution parameters (t50% and t90%) decreased with increase in the level of camphor and crospovidone. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly ($p<0.05$). It is concluded that fast dissolving tablets of Valsartan could be prepared by sublimation technique.

KEY WORDS: Valsartan, fast dissolving tablet, crospovidone, camphor, super disintegrant.

INTRODUCTION:

Valsartan (Fig.1) 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.

Valsartan is rapidly absorbed after oral dose with a bioavailability of about 23%. Peak plasma concentration occur 2 to 4 hrs and its plasma half life is about 7.5 hrs after an oral dose. In management of hypertension, Valsartan is given in a dose of 80mg once daily.[1]

Compare to other orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiology function associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy[2]. The pediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[3] and fast-disintegrating tablets[4] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying / Lyophilization[4,] tablet molding[6] and direct-compression methods[7]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva

into the pores when placed in oral cavity[8]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentration of active drug[3]. Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern[9]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of tablet[10]. The oral fast dissolving dosage forms, also known as fast melt, fast disintegrating dosage forms, are relatively novel dosage technology that involves rapid disintegration or dissolution of the dosage forms, into a solution or suspension in the mouth without need of water[11-15]. The dosage form begins to disintegrate immediately after coming into contact with saliva, the complete disintegration normally occurring within 30 to 50 seconds[16]. The solution containing active ingredients is swallowed, and the active ingredients are then absorbed through gastrointestinal epithelium to reach the target and to produce the desired effect[17].

In the present study, an attempt was made to develop dissolving tablets of Valsartan by sublimation technique to investigate the effect of subliming agent on the release profile of the drug in the tablets.

MATERIALS AND METHODS

Valsartan was gift sample from Dr. Reddy's Laboratary. (AP). crospovidone, aspartame, camphor, mannitol, talc, magnesium stearate and all the other chemicals used were of pharmaceutical grade.

Fourier transform infrared (FTIR) spectroscopy

The Fourier-transform infrared spectra of Valsartan and mixture Valsartan with excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400 -4600 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in Fig. 2.

Preparation of tablet

Fast dissolving tablets of Valsartan were prepared by sublimation technique. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg 10-station rotary tablet machine (Rimek Mini Press-1). A batch of 50 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions are given in table 1. After compression the tablets were collected and vacuum dried at 60^0C until the constant weight is obtained to ensure the complete removal of sublimable component to make a tablet porous.

Evaluation of tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus using 900 ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper, wetting time study, a piece of tissue paper folded twice was kept in culture dish containing 6 ml of distilled water. A tablet having small amount of amaranth powder on upper surface was kept on tissue paper. A time required to develop a red color on upper surface of tablet was recorded as the wetting time. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 40 mg of Valsartan was taken and dissolved in phosphate buffer 7.4. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 231 nm. Using 900 ml of buffer monitored *in vitro* dissolution of Valsartan from tablets at 37 ± 0.5^0 C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 min time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 231 nm. The stability study of the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40 ± 2^0 C / 75 ± 5% RH for 3 months.

RESULTS AND DISCUSSION

In the IR Spectrum of Valsartan (Fig-2), a broad band at 3500^{-cm} indicates the presence of an N-H Functional group. The band at 2962.90 $^{-cm}$ indicates C-H group streaching vibration. Bonds in the range of 1204.82-1025^{-cm} confirm the presence of a tetrazole (-CN_4) ring. The presence of a band at 1502^{-cm} indicates an N-N bond. The peak at 1371^{-cm} is due to C=N. The peak at 1731^{-cm}

confirms the presence of a carboxylate functional group. The characteristic peak at 1602^{-cm} is for stretching of a C=O functional group present in the structure. The peak at 1065^{-cm} indicates the presence of C-N bond. The complex region of $900\text{-}600^{-cm}$ indicates skeletal vibration and an aromatic ring in the drug substance. All these prominent peaks of Valsartan were also present in drug and other excipients, clearly indicates that the drug has retained its character without interacting with croscormellose sodium used in the development of Valsartan fast dissolving tablets.

The flow properties of the powder mixture are important for the uniformity of mass of tablets; the flow of powder mixture was before compression of tablets. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post-compressional parameters results are shown in table 3 and 4. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be high (≥ 99.01 %) and uniform in all formulations. The tablet thickness was found to be 2.65 to 3.10 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The disintegration time decreased significantly with increase in concentration of croscarmellose sodium. The wetting time of all formulations were found to be in the range of 29 to 68 sec. The dissolution profiles of all formulations are shown in Fig. 4. Out of four formulations, the formulation VS_4 shows faster drug release within 11 min. *In vitro* release profiles of different formulations are shown in Fig. 5 and in table 5. The $t_{50\%}$ and $t_{90\%}$ values changed with changing concentration of croscarmellose sodium. The formulations VS_1, VS_2, VS_3 and VS_4 50 % of drug released in 8.05, 7.54, 6.04, 5.50 min, and 90 % of drug released in 16.89, 14.97, 12.07 10.01 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage decrease in disintegration and wetting time was noticed. This may be due to the removed trance amount of camphor during stability study. Drug content of all the promised formulations were not changed after stability study (Table 5).

CONCLUSION

The release of drug from the VS_4 formulation was quick when compare to other formulations. It can be concluded that fast dissolving tablets with improved Valsartan dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

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Table 1: Formulation of Valsartan fast dissolving tablets

Ingredients (mg)	Formulation code			
	VS_1	VS_2	VS_3	VS_4
Valsartan	40	40	40	40
Camphor	2.5	5	7.5	10
Crospovidone	6	6	6	6
Mannitol	49.5	47	44.5	42
Magnesium stearate	1	1	1	1
Talc	1	1	1	1
Total Weight	150	150	150	150

Table 2: Pre-compressional parameters of direct compression method

Formulation code	Bulk density* (g/cc) ± SD	Tapped density* (g/cc) ± SD	Angle of repose*(degree) ± SD	Carr's index* (%)± SD
VS_1	0.49 ± 0.003	0.70 ± 0.02	23.12 ± 1.49	21.42
VS_2	0.53 ± 0.01	0.71 ± 0.02	23.04 ± 1.71	23.72
VS_3	0.55 ± 0.03	0.72 ± 0.003	24.31 ± 1.68	27.62
VS_4	0.56 ± 0.03	0.72 ± 0.02	27.77 ± 1.65	19.16

* Average of three determinations

Table 3: Post-compressional parameters of Valsartan fast dissolving tablets

Formulation code	Hardness* (kg/mg^2) ± SD	Thickness* (mm) ± SD	Friability (%) ± SD	Weight variation* ± SD
VS_1	3.8 ± 0.09	2.34 ± 0.09	0.45	99.56 ± 0.03
VS_2	3.8 ± 0.06	2.45 ± 0.07	0.81	101.4 ± 0.06
VS_3	3.9 ± 0.04	2.12 ± 0.04	0.54	100.08 ± 0.05
VS_4	3.4 ± 0.07	2.17 ± 0.06	0.12	99.24 ± 0.06

* Average of three determinations

Table 4: *In- vitro* disintegration time, wetting time, water absorption ratio and drug content of Valsartan fast dissolving tablets

Formulation Code	Disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Water absorption ratio* ± SD	Drug content* (%) ± SD
VS_1	45 ± 0.23	45 ± 0.89	61.53 ± 0.67	96.34 ± 0.09
VS_2	34 ± 0.14	32 ± 0.78	64.91 ±0.54	97.78 ± 0.89
VS_3	21 ± 0.26	19 ± 0.45	69.23 ± 0.19	97.67 ± 0.78
VS_4	14 ± 0.38	12 ± 0.25	72.22 ± 01.23	99.91 ± 0.37

* Average of three determinations

Table 5: Results of stability study

Formulation code	Disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Drug content* (%) ± SD
VS_4	12 ± 1.22	10 ± 1.32	99.49 ± 1.42

* Average of three determinations

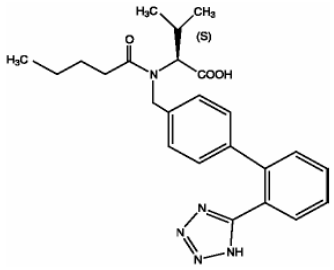

Fig. 1:Valsartan structure

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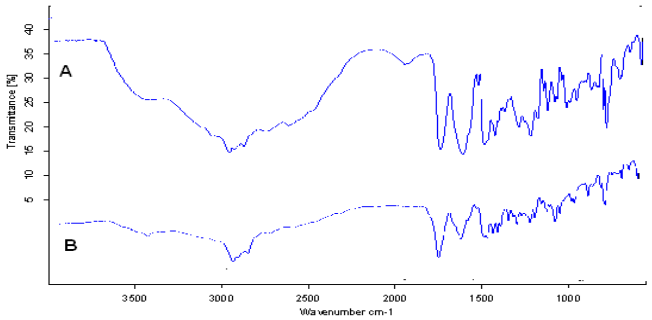

Fig. 2: IR spectrum of pure Valsartan (A) and Formulation VS_4 (B)

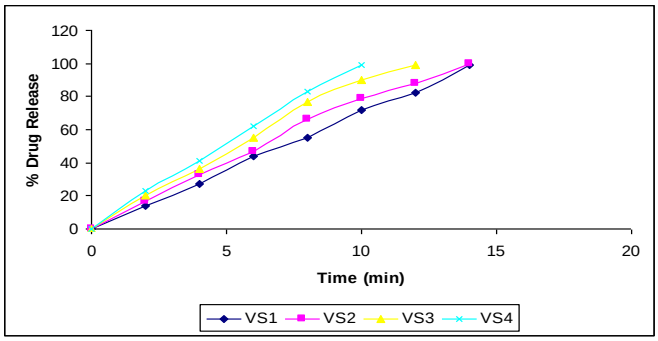

Fig.3: Dissolution profile of formulations Valsartan fast dissolving tablets

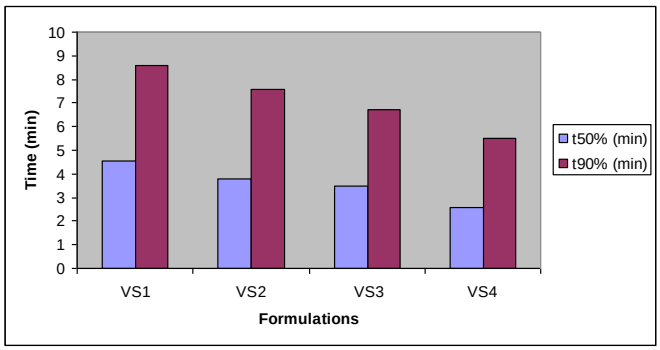

Fig. 4: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different formulations