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Research Article

FORMULATION AND EVALUATION OF VALSARTAN FAST DISINTEGRATING TABLETS BY VACUUM DRYING TECHNIQUE

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ABSTRACT

Objective: The main objective present research work an attempt has been made to prepare fast dissolving tablets of Valsartan by using vacuum drying technique. Camphor, Urea and Menthol are used as a sublimating agent. Valsartan is an oral antihypertensive agent, with problems of variable bioavailability and bioequivalence related to its poor water solubility. Valsartan is an angiotensin II type 1 receptor antagonist indicated in the treatment of hypertension.

Methods: The prepared tablets Valsartan fast dissolving tablets were evaluated for various parameters like weight variation, hardness, friability, disintegration time, drug content, water absorption ratio, wetting time, in- vitro drug release, FTIR, DSC studies and short term stability studies. The blend was examined for the pre-compressional and post-compressional parameter.

Results and Discussions: The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. All the post-compressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. Based on the in-vitro disintegration time and dissolution studies formulations SC2 and SC3 were found to be promising and showed a disintegration time of 24 sec and 16 sec respectively. Formulation SC3 containing camphor showed highest drug release 99.4% within 10 min. IR spectral analysis and DSC study showed that there was no drug interaction with formulation additives of the tablet as there is no variation and shift in the position of characteristic absorption bands it can be justified there is no interaction between drug and polymer. Short term stability studies on the formulations indicated that there are no significant change in hardness, friability, drug content and in-vitro drug release ($p<0.05$).

Conclusion: The results concluded that fast dissolving tablets of Valsartan showing enhanced dissolution may lead to improved bioavailability and effective therapy by using sublimation method.

Keywords: Fast dissolving tablet, Valsartan, Crospovidone, Camphor, Urea, Disintegration time.

INTRODUCTION

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. 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 [1-3].

Most pharmaceutical forms for oral administration are formulated for direct ingestion, for chewing, for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth. Elderly individuals have difficulty in swallowing when prescribed in conventional tablet and capsule form [4-6]. The problem of swallowing is also evident in pediatrics, psychiatric as well as traveling patients who may not have ready access to water [7]. The rapidly disintegrating tablet in the mouth or orodispersible tablets overcome all the above problems and thus offer an alternate form of oral medication, which provide patients with a more convenient means of taking their medication [8]. Addition of super disintegrating agent in the formulation is one of the approaches to formulate orodispersible tablets [9-15]. 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. 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 [16,17]. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization [18] tablet molding [19] and direct compression methods [20]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in the oral cavity [18,21]. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern [22]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [23]. Therefore, direct compression appears to be a better option for manufacturing of tablets. The key to the rapid disintegration of fast dissolving tablets (FDT) is the preparation of a porous structure in the tablet matrix. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation [24-26]. Highly volatile ingredients such as camphor, menthol, and urea may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. In present research work, an attempt has been made to prepare FDT of Valsartan by using vacuum drying technique.

METHODS

Materials

Valsartan was procured from Gift sample from Dr. Reddy's Lab, Hyderabad. Mannitol, MCC, aspartame, talc, and magnesium stearate purchased from S.D. Fine chem., Mumbai. All other materials were of analytical reagent grade.

Preparation of FDT by direct compression technique [27]

The basic principle involved in preparing FDT by sublimation technique shown in Fig. 1 using inert solid ingredients (urea, camphor, and menthol) and crospovidone were added to other tablet excipient and the blend was compressed into a tablet. Removal of volatile material by sublimation generated a porous structure. Accurately weighed ingredients were sifted through sieve no. 44 and thoroughly mixed for 10 minutes and magnesium stearate and other ingredients were added to the blend and thoroughly mixed. The tablets were compressed using Rimek tablet punching machine. The composition of the tablets was given in Table 1. The compressed tablets were than subjected to sublimation at 50°C for 60 minutes.

Evaluation of Valsartan tablets

Micromeritic properties of powder blend of tablets before compression

The prepared tablet blends are evaluated for different tests such as the angle of repose, apparent bulk density, tapped density, percent compressibility, and Hausner ratio.

Evaluation of Valsartan FDT [28-31]

Weight variation

The average weight of 20 tablets is calculated using an electronic balance. Individual weight of each tablet is calculated and compared with the average weight. The mean±standard deviation (SD) and relative SD were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

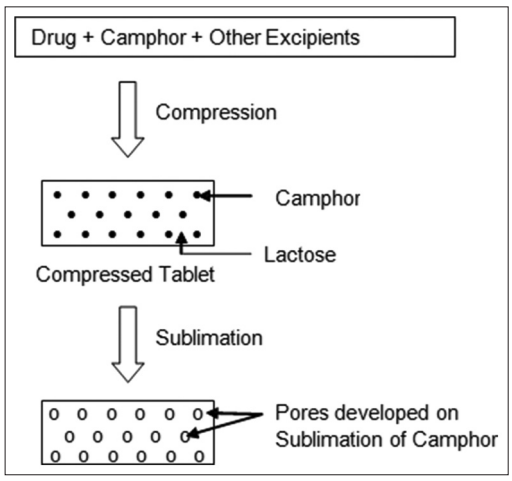

Fig. 1: Schematic diagram of vacuum drying technique for design of fast dissolving tablets

Tablet thickness

Randomly 10 tablets should be taken, and thickness was measured for each tablet by placing it between two anvils and rotating the sliding knob until the tablet was tightly fitted and the reading was noted.

Hardness and friability

Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test." Hardness of tablet was determined using a Pfizer tablet hardness tester. Friability of 10 tablets from each formulation was determined using the Roche friabilator (Campbell Electronics, Mumbai, India). This device subjects a no of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. A pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed. Percentage friability of tablets <1% was considered acceptable.

It was calculated using following formula:

$$\% \text{ friability} = \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets})}{\text{Initial wt. of tablets}} \times 100$$

Content uniformity

6 tablets from each formulation were taken randomly and powdered. A quantity of powder equivalent to the weight of one tablet was transferred into a 100 mL volumetric flask, containing phosphate buffer pH 5.8, and mixed thoroughly for few minutes, and the volume was made up to 100 ml with phosphate buffer pH 5.8. The solution was filtered through Whatman filter paper and suitably diluted with the same medium, and the drug content was estimated from the standard plot by measuring the absorbance at 250 nm using a UV-Visible spectrophotometer.

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 5.8 (simulated saliva fluid) maintained at 37±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 5.8 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.

Wetting time and water absorption ratio

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a petri dish with a 10 cm diameter. About 10 mm of water containing a water-

Table 1: Formulation of Valsartan fast dissolving tablets prepared by sublimation method (1-tablet)

Ingredient (mg)	Formulation code								
	SU1	SU2	SU3	SC1	SC2	SC3	SMI	SM2	SM3
Valsartan	80	80	80	80	80	80	80	80	80
Crospovidone	16	16	16	16	16	16	16	16	16
Urea	10	20	30	-	-	-	-	-	-
Camphor	-	-	-	10	20	30	-	-	-
Menthol	-	-	-	-	-	-	10	20	30
Aspartame	2	2	2	2	2	2	2	2	2
D-Mannitol	54	44	34	54	44	34	54	44	34
MCC	20	20	20	20	20	20	20	20	20
PVP	15	15	15	15	15	15	15	15	15
Talc	1	1	1	1	1	1	1	1	1
Mg stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Note: MCC: Microcrystalline cellulose (Avicel PH-102), PVP: Poly vinyl pyrrolidone, MgSt: Magnesium stearate

soluble dye was added to the petri dish. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out (n = 6), and the mean value was calculated.

The weight of the tablet before keeping in the petri dish was noted (W_b). The wetted tablet from the petri dish was taken and reweighed (W_a). The water absorption ratio, R, was determined according to the following equation:

$$R = 100 (W_a - W_b)/W_b$$

Where, W_b and W_a are the weight before and after water absorption, respectively. Measurement of wetting time of a tablet was shown in Fig. 2.

In-vitro dissolution studies [32]

Dissolution rate was studied using USP Type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900 ml of buffer pH (5.8) (simulated saliva fluid) as dissolution medium. Temperature of the dissolution medium was maintained at 37±2°C, an aliquot of dissolution medium was withdrawn at every 2 minutes interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 250 nm, and concentration of the drug was determined from the standard calibration curve.

***In-vitro* drug release studies details**

Apparatus used**:** USP XXIII dissolution test apparatus

Dissolution medium: 5.8 pH phosphate buffer solution

Dissolution medium volume**:** 900 ml

Temperature: 37±0.5°C

Speed of basket paddle**:** 35 rpm

Sampling intervals**:** 2 minutes

Sample withdrawn**:** 5 ml

Absorbance measured**:** 250 nm

Compatibility studies

Infrared (IR) studies

IR spectra for pure drug Valsartan and SC2 and SC3 powdered tablets were recorded in Infrared spectrophotometer with KBr pellets.

Differential scanning calorimetry (DSC) studies

DSC studies were carried out pure drug Valsartan and best formulations such as SC2 and SC3. DSC scan of about 5 m accurately weighed Valsartan and optimized formulations were performed by an automatic thermal analyzer system (DSC60 Shimadzu Corporation, Japan). Sealed and perforated aluminum pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/minutes from 50°C to 300°C.

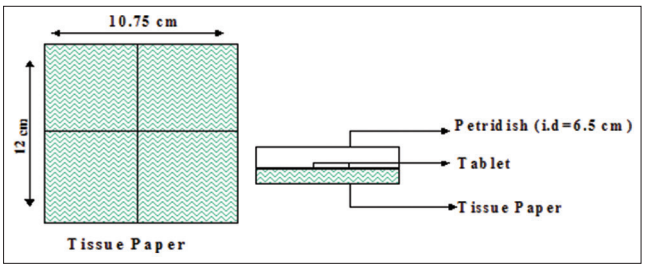

Fig. 2: Simple method for the measurement of wetting time of a tablet

Stability studies [33-34]

- Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications
- The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods, and shelf lives to be established
  ICH specifies the length of study and storage conditions:
- Short-term testing 25±2°C/60% RH±5% for 12 months
- Accelerated testing 40±2°C/75% RH±5% for 6 months

The present study, stability studies were carried out at 25°C/60% and 40°C/75% RH for a specific time period up to 3-month for the selected formulations.

RESULT AND DISCUSSION

Valsartan is an oral antihypertensive agent, with problems of variable bioavailability and bioequivalence related to its poor water solubility. In the present research work, an attempt has been made to prepare FDT of valsartan using vacuum drying technique. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results were shown in Table 2.

All the post-compressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. Results were shown in Table 3. In all the formulations, hardness test indicated good mechanical strength ranges from 2.6 to 3.3 kg/cm^2. The friability range is 0.63-0.74% to be well within the approved range (<1%) indicated that tablet had good mechanical resistance. The weight variation was found in all designed formulations in the range 195-200 mg. All the tablets passed weight variation test as the average percentage weight variation was within 7.5%, i.e., in the pharmacopeia limits. The thickness was almost uniform in all the formulations and values ranged from 3.48 mm to 3.74 mm. The standard deviation values indicated that all the formulations were within the range.

The *in-vitro* disintegration time is measured by the time taken to undergo complete disintegration. Rapid disintegration within 2 m was observed in all the formulations. The *in-vitro* disintegration data is tabulated in Table 4. The *in-vitro* disintegration time of FDT was found to be 16-55 seconds which is in the range of fulfilling the official requirements. By the addition of super disintegrants, the disintegration time increased significantly ($p<0.05$) tablets prepared. The disintegration time decreased significantly regardless of the diluents used. It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrate the tablet rapidly. Above results shows that tablets prepared with crospovidone and camphor (sublimation method) showed least disintegration time in comparison with the all other formulations because of their lowest hardness and the porous structure.

Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in Table 4. The wetting time of valsartan tablets prepared by sublimation method were found to be in the range of 17.18-53.37 seconds. Promising formulation SC3 (camphor) showed a wetting time of 17.18 seconds, which facilitate the faster dispersion in the mouth. The water absorption ratio in the range 46.45-71.48%. The percentage drugs content of the tablets were found to be between 97.46 and 99.66% of Valsartan. The results were within the range, and that indicated uniformity of mixing. The wetting

Table 2: Pre-compression parameters of powder blend of vacuum drying technique

FC	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Angle of repose (θ)*	Hausner's ratio*	Carr's index (%)*
SC1	0.47±0.24	0.55±0.12	28.14±0.21	1.14±0.02	14.54±0.26
SC2	0.44±0.22	0.49±0.14	22.05±0.17	1.09±0.02	10.20±0.42
SC3	0.54±0.25	0.62±0.11	26.92±0.12	1.13±0.02	12.90±0.26
SU1	0.49±0.03	0.70±0.02	23.12±1.49	1.13±0.03	21.42±0.23
SU2	0.53±0.01	0.71±0.02	23.04±1.71	1.13±0.04	23.72±0.14
SU3	0.55±0.03	0.72±0.03	24.31±1.68	1.13±0.05	27.60±0.26
SM1	0.56±0.03	0.72±0.02	27.77±1.65	1.13±0.06	17.24±0.23
SM2	0.51±0.17	0.58±0.14	27.85±0.21	1.13±0.01	21.76±0.14
SM3	0.43±0.18	0.49±0.34	22.36±0.14	1.13±0.01	22.24±0.23

*Average of three determinations

Table 3: Post-compression parameters Valsartan fast dissolving tablets

FC	Hardness* (kg/cm^2)±SD	Friability (%)±SD	Thickness* (mm)±SD	Weight variation* (mg)±SD
SC1	2.9±0.09	0.45±0.07	2.34±0.09	199.63±1.7
SC2	2.8±0.06	0.81±0.09	2.45±0.07	197.18±1.0
SC3	2.4±0.04	0.54±0.12	2.12±0.04	200.37±0.6
SU1	2.9±0.2	0.53±0.07	2.22±0.03	198.33±1.1
SU2	3.1±0.1	0.67±0.09	2.33±0.09	200.14±1.5
SU3	3.0±0.1	0.65±0.08	3.10±0.09	199.82±1.9
SM1	3.2±0.07	0.17±0.29	2.17±0.06	202.22±0.9
SM2	3.4±0.13	0.62±0.05	2.62±0.07	199.59±1.3
SM3	3.3±0.22	0.16±0.07	2.65±0.05	199.56±1.7

*Average of three determinations

Table 4: Post-compression parameters Valsartan fast dissolving tablets

FC	Disintegration time* (seconds)±SD	Wetting time* (seconds)±SD	Water absorption ratio*±SD	Drug content* (%)±SD
SC1	29.16±1.2	29.15±1.4	51.28±1.2	99.20±0.5
SC2	24.16±1.2	23.23±1.5	53.63±1.2	99.55±0.7
SC3	16.16±1.4	17.18±1.2	71.48±1.1	98.76±0.8
SU1	31.92±1.6	34.73±1.4	64.26±1.2	99.20±0.5
SU2	35.44±1.2	30.03±1.6	67.56±1.5	99.55±0.7
SU3	46.61±1.4	44.32±1.5	71.14±0.4	98.76±0.8
SM1	55.12±1.2	49.68±1.6	74.35±0.9	99.92±1.2
SM2	43.92±1.6	42.85±1.8	46.45±0.91	100.08±0.8
SM3	48.20±1.4	53.37±0.82	47.58±1.3	99.38±1.3

*Average of three determinations

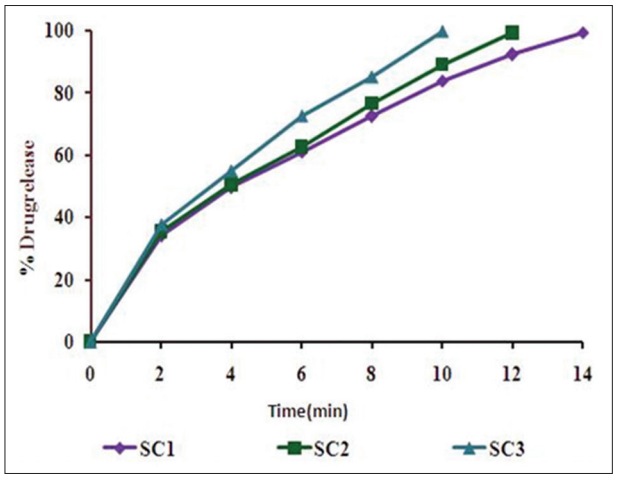

Fig. 3: Release profile of formulation containing camphor (SC1-SC3)

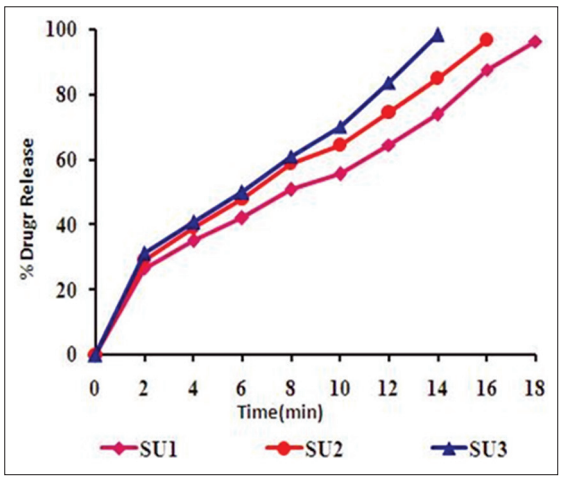

Fig. 4: Release profile of formulation containing urea (SU1-SU3)

time, water absorption ratios, and drug content results were tabulated in Table 4.

The dissolution rate was studied by USP Type-II apparatus (USP XXIII Dissolution Test Apparatus at 35 rpm) using 900 ml of phosphate buffer pH (5.8) as dissolution medium. The dissolution release profiles of valsartan from the tablets are shown in Figs. 3-5. The tablet prepared by sublimation technique and the dissolution rate of the tablet was increased with increase in the concentration of camphor. Formulation SC3 containing camphor showed the highest drug release 99.79% in 10 minutes. This may be due to their lowest hardness, and the

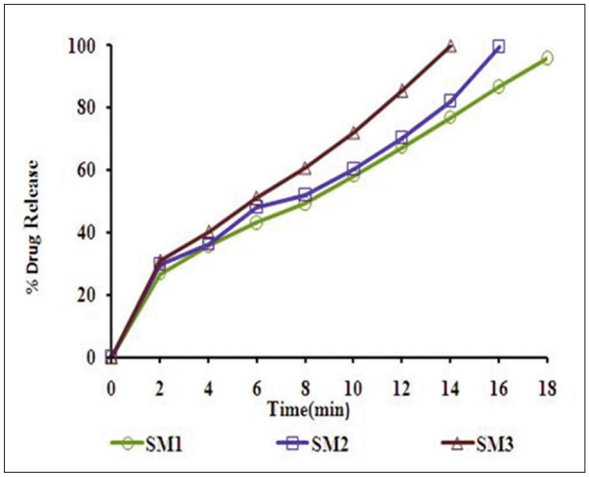

Fig. 5: Release profile of formulation containing menthol (SM1-SM3)

porous structure was responsible for faster water uptake. Hence, it facilitates the wicking action of crospovidone in bringing about faster disintegration.

Based on the *in-vitro* disintegration time and dissolution studies formulations SC2 and SC3 were found to be promising and showed a disintegration time of 24 seconds and 16 seconds, respectively. Formulation SC3 containing camphor showed the highest drug release 99.4% within 10 minutes. This may be due to their lowest hardness, and the porous structure was responsible for faster water uptake. Hence, it facilitates the wicking action of crospovidone in bringing about faster disintegration.

Compatibility studies

IR studies

IR spectra for pure drug Valsartan and SC2 and SC3 powdered tablets were recorded in an infrared spectrophotometer with KBr pellets (Fig. 6). During the present research, the pure drug Valsartan was taken for study. The IR of this drug is collected which exhibited presence of various functionalities by their presence indicating the characteristic absorption peaks. The drug Valsartan exhibited a broad peak around 3400/cm indicating the probable presence of characteristic absorption peak due to carboxylic acid. In this molecule, there is also N-H absorption almost in the same region hence resulting in the presence of broadening of the peak. This molecule contains a number of aromatic C-H peak by exhibiting a number of peaks around 2962/cm. C=0 peaks due to the carboxylic acid group as well as amide are absorbed at 1732/cm, and 1600/cm suggesting that the drug taken for the present study contains functionalities such as N-H, COOH, C-H, C=0. In the next experiment, the formulation SC2 was taken. The resulting formulation is subjected for IR measurements. The spectrum obtained as indicated the presence of all characteristic features of the drug as well as excipients. At 3397 cm^{-1} the broad peak due to the drug molecule was observed, and C-H absorption peak of the aromatic ring system of the drug is also noticed at 2950/cm C=0 peaks of the drug were found to be present at 1729/cm and 1632 cm. These data established that during the process of formulation no chemical reactions have taken place between drug and excipients. All the characteristic absorption peaks of the drug and excipients have remained intact. In SC3 formulation as there is no variation and shift in the position of characteristic absorption bands it can be justified, there is no interaction between drug and polymer.

DSC studies

The DSC thermograms of pure drug Valsartan and formulations SC2 and SC3 were shown in Fig. 7. The pure drug Valsartan is taken for DSC studies which started melting at 72°C has completed the melting process completely at 79°C the melted liquid disappeared at 88°C.

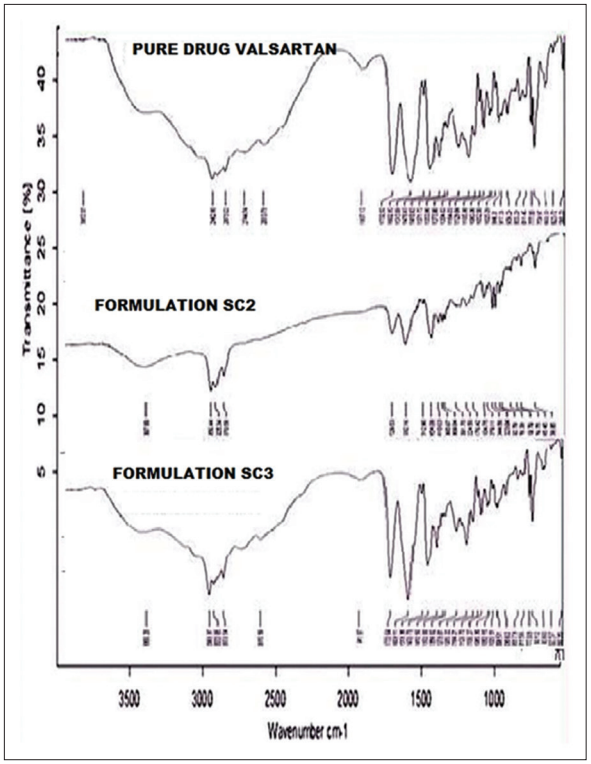

Fig. 6: Fourier transform infrared spectra of pure drug Valsartan and formulations SC2 and SC3

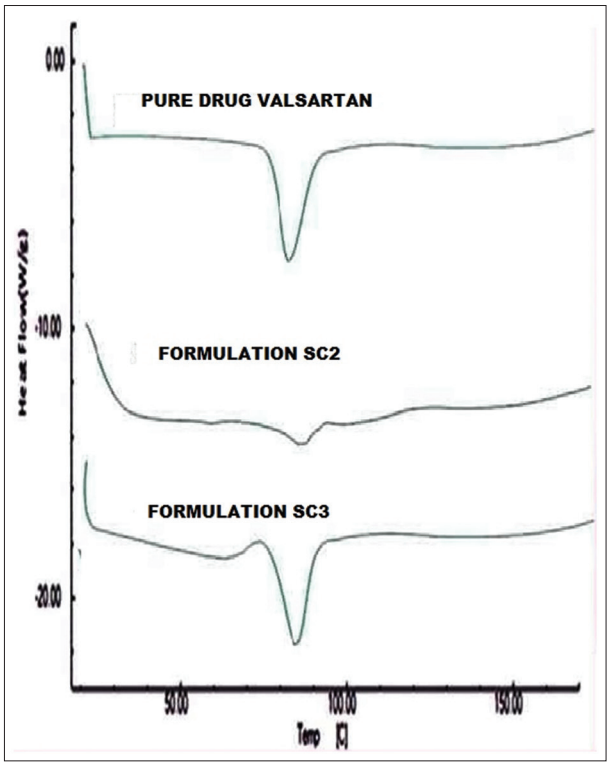

Fig. 7: Differential scanning calorimetry thermograms of pure drug Valsartan and formulations SC2 and SC3

The sharp melting peak at 78°C indicates that compound is pure, and there is no mixture in it. In our sec experiment, i.e., formulation SC2 thus obtained was taken for DSC studies but in this case, it is found that the melting process of the formulated product was delayed, and

Table 5: Result for promising Valsartan fast dissolving tablets at (25°C/60% RH) and (40°C/75% RH) for 3 months

S. No.	FC	Month	Hardness kg/cm²	Drug content* (%)	Disintegration time* (sec)
(25°C/60% RH)					
1	SC2	1st	2.8	99.55	24.16
		2nd	2.7	99.32	24.14
		3rd	2.5	99.65	24.06
2	SC3	1st	2.4	98.76	16.16
		2nd	2.3	98.66	16.02
		3rd	2.1	98.67	15.94
(40°C/75% RH)					
3	SC2	1st	2.8	99.55	24.16
		2nd	2.6	99.44	24.02
		3rd	2.6	99.12	23.78
4	SC3	1st	2.4	98.76	16.16
		2nd	2.2	98.32	15.82
		3rd	2.1	98.12	15.64

sharp melting peak could not be obtained. It started at 89°C continued at 102°C. This indicates the physical mixture has been obtained during the process of formulation but not any reaction takes place. Next formulation SC3 similar observation is observed wherein the melting process has started at 88°C continued up to 105°C. Another hump was obtained at 126-138°C. Such nature of peaks indicates that constituents of the formulation have remained un-reacted resulting in delayed melting process. All these data suggest that during the process of formulation no interaction between drug and excipients. Only physical mixture is produced.

Table 5 shows the parameters of the tablets after stability study. After stability study of promised formulations, their hardness, drug content, and disintegration time were performed to detect the shelf life of promised formulations. In the case of tablet prepared by sublimation was decreased in disintegration time 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 was not changed after stability study.

CONCLUSION

The above results concluded that the FDT of Valsartan showing enhanced dissolution may lead to improved bioavailability and effective therapy using sublimation method. Based on the *in-vitro* disintegration time and dissolution studies formulations SC2 and SC3 were found to be promising and showed a disintegration time of 24 sec and 16 sec, respectively. Formulation SC3 containing camphor showed the highest drug release 99.4% within 10 min. Overall results indicate that formulation SC3, which contain 15% crospovidone, and camphor was a better one and satisfies all the criteria as fast dissolving tablet.

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