ORIGINAL ARTICLE

Development and Evaluation of Valsartan Fast Disintegrating Films

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Abstract

Objective: The aim of the present work was to develop and evaluate the fast disintegrating films (FDF) of valsartan which is used for the treatment of hypertension and heart failure. **Method:** The valsartan fast disintegrating films were prepared by solvent casting method using hydroxylpropyl cellulose, poly vinyl alcohol (PVA), HPMC E5 as film forming agents, Polyethylene glycol 400 as plasticizers and dimethylsulfoxide as penetration enhancer. **Results:** Valsartan FDF were developed and evaluated for weight uniformity, drug content, film thickness, and folding endurance, the results obtained were within the specified limits. The *in vitro* diffusion studies were performed using Franz diffusion cell apparatus containing 6.8 pH phosphate buffer as a dissolution media. **Conclusion:** The FDF prepared with HPMC E5 at 1:3 ratio released the drug up to 98.7% within 5 min which showed the increased solubility, dissolution rate flexibility, and tensile strength of the films when compared to formulation prepared with hydroxypropyl cellulose and PVA. The Fourier-transform infrared studies were conducted for pure drug, polymers and optimized formulation V9 which indicated that were no incompatibilities found between the drug and polymers used in the present studies. Scanning electron microscopy analysis was performed for pure drug, polymers, and optimized formulation V9 which showed that they were no surface fractures and cracks in the films.

Key words: Valsartan, Fast disintegrating films, Solvent casting method, Polymers, Plasticizers, Penetration enhancer and superdisintegrants

INTRODUCTION

Fast disintegrating films (FDF) are a sort of solid dosage form that was developed based on the technology of transdermal patches for medication delivery via the oral route. This delivery device consists of a thin film that is simply applied on the patient's tongue or mucosal tissue and quickly dissolves when wet by saliva. The medicine is then rapidly disintegrated and dissolved for oral mucosal absorption.[1-3] The huge surface area of the film, which wets quickly when exposed to the moisture environment, contributes to the fast-dissolving activity. FDF is made with a hydrophilic polymer that dissolves quickly on the tongue or in the buccal cavity, allowing the medicine to enter the systemic circulation through the buccal mucosa.[4] For the increase of bioavailability, quick-dissolving drug delivery systems are specifically designed for medicines with substantial first-pass metabolism and low dosage.[5,6]

In the shape of breath strips, this technology evolved over the last few years from the confection and oral care businesses, becoming a novel and well-accepted form by consumers. These films have the ability to administer the medication systemically through intragastric, sublingual, or buccal routes of administration, as well as for local action.[7-9] Valsartan is an antihypertensive that is exclusively soluble in alcohols since it has a BCS Class II moiety. VAL is an angiotensin II receptor antagonist with a high affinity for the type I (AT1) angiotensin receptor pharmacologically.[10,11] As a result, it necessitates rapid absorption and high bioavailability from

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the standpoint of the patient. Valsartan takes 4 h to absorb and has a bioavailability of only 20–25%. Valsartan absorption is delayed in fed circumstances.[12] Blood pressure often rises in chronic hypertension individuals, necessitating quick drug reduction. VAL is an effective antihypertensive with fewer adverse effects than angiotensin II receptor antagonists and the ability to treat hypertension with frequent dosage.

In the present studies, valsartan is taken as a drug candidate for the development of FDF which were prepared by using hydroxylpropyl cellulose, PVA, HPMC E5 as film-forming agents, dimethylsulfoxide as a penetration enhancer, polyethylene glycol 400 and crospovidone were used as plasticizers and superdisintegrants, and they were prepared by solvent casting method to improve the solubility and dissolution rate of valsartan.

MATERIALS AND METHODS

Valsartan is a gift sample from M/S Aurobindo Pharma Ltd, Hyderabad. HPC, HPMC E5, and PVA were obtained from Mylan Pharma limited Hyderabad. PEG 400 and dimethyl sulfoxide were obtained from SD Fine Chem., Ltd., and Mumbai.

Preparation of valsartan FDF

The solvent casting method was used to make valsartan fast-dissolving oral thin films. To obtain transparent solutions, film-forming polymers such as HPC PVA and HPMC E5 were dissolved in alcoholic solutions individually in 100 ml beakers. Specified amounts of valsartan, crospovidone, dimethyl sulfoxide, and PEG 400 were weighed and dissolved in the alcoholic solution, then well mixed to obtain a homogenous solution. The resulting solution was cast on a non-adhesive base plate and cured for 24 h under an infrared lamp. The films were trimmed into desired sizes once they had dried completely. Several attempts were conducted to improve the formula for making valsartan fast-dissolving oral thin films.[13-16] The composition of valsartan fast-dissolving oral thin films is given as follows. The compositions of prepared films are given in Table 1.

Evaluation of physical parameters for valsartan FDF

The valsartan oral thin films were evaluated for physical parameters such as weight uniformity, drug content, film thickness, and folding endurance. The results are given in Table 2.

Weight uniformity

The weight uniformity of the films can be done manually using a digital electronic balance.

Uniformity of drug content

An UV visible spectrophotometric method was used to assess the drug content uniformity of the films, measuring their absorbance at a wavelength of 250 nm. The percentage drug content of various films was determined and is given in Table 2.

Film thickness

At various locations on the film, the thickness of the film was measured using a screw gauge with a least count of 0.01 mm. The average weight was calculated after measuring the film thickness at three separate locations. The obtained results are given in Table 3.

Folding endurance

Folding endurance was determined by repeatedly folding a tiny strip of film in the same spot until the film cracked, at that spot, the number of times the film could be folded in the same area was noted as folding endurance. The film was folded at an angle of 1800° in the same location until it broke, or it was folded 100 times without breaking. The experiments were completed in a timely manner, and the average mean was computed.

Dispersion test

Strips of film equivalent to 10 mg of drug are placed in 200 ml of pH6.8 phosphate buffer and stir with glass rod for 3 min

Table 1: Composition of valsartan fast disintegrating films

Ingredients (w/w)	V1	V2	V3	V4	V5	V6	V7	V8	V9
Valsartan	40	40	40	40	40	40	40	40	40
HPC	40	80	160	-	-	-	-	-	-
Polyvinyl alcohol	-	-	-	40	80	160	-	-	-
HPMC E5	-	-	-	-	-	-	40	80	160
PEG 400	50	75	100	50	75	100	50	75	100
Dimethyl sulfoxide	5	5	5	5	5	5	5	5	5
Crospovidone	20	20	20	20	20	20	20	20	20
Methanol	QS	QS	QS	QS	QS	QS	QS	QS	QS

and pass through 22 meshes the film is passed dispersion test only when no residue left on the mesh.

In vitro diffusion studies

In vitro diffusion studies were conducted on all the valsartan FDF using Franz diffusion cell apparatus containing pH 6.8 phosphate buffer as dissolution medium. The dissolution studies were carried out over a period of 15 min for all the formulations. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of samples was withdrawn at regular time intervals, filtered, and assayed spectrophotometrically at 250 nm. The drug release profiles for all the film formulations are shown in Figure 1.

Evaluation of various *in vitro* dissolution parameters

Dissolution parameters such as T_{50}, T_{90}, $DE_{5\%}$, and first-order rate constants were calculated from the dissolution data obtained, and the results are given in Table 3.

Characterization of valsartan FDF

Based on the diffusion studies performed on all the formulations, the optimized formulations were selected and the following characterization studies were done on pure drug, polymers, and optimized formulation.

Fourier-transform infrared (FTIR) spectroscopy

To investigate the interaction between drug and carrier in films, the FTIR spectra of valsartan, HPC, PVA, and HPMC were acquired using a Bruker FTIR spectrophotometer. The samples were produced on KBr discs (2 mg of sample in 200 mg of KBr), with a sampling range of 400-4000/cm and a resolution of 4/cm. The FTIR spectra are shown in Figures 2-5.

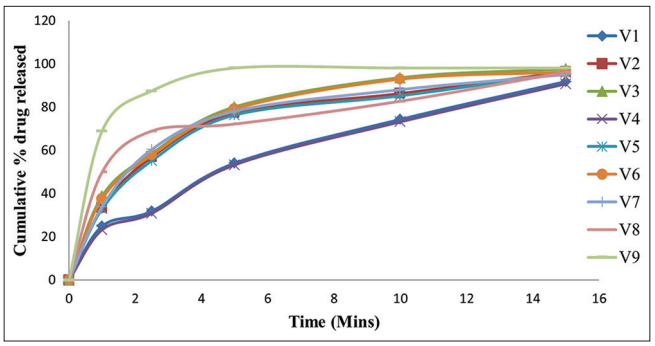

Figure 1: Drug release profiles for valsartan fast disintegrating films

Table 2: Evaluation of physical parameters for valsartan fast disintegrating films

Formulation	Weight uniformity (mg)	Drug content (mg/film)	Film thickness (mm)	Folding endurance (no)	Dispersion test
V1	149	37.21	0.030	97	Passed
V2	188	38.64	0.032	98	Passed
V3	269	39.51	0.033	99	Passed
V4	148	37.11	0.031	90	Passed
V5	190	38.23	0.032	89	Passed
V6	271	39.09	0.033	92	Passed
V7	153	38.89	0.032	97	Passed
V8	192	38.90	0.033	98	Passed
V9	275	40.11	0.034	101	Passed

Table 3: Evaluation of *In vitro* Dissolution Parameters for valsartan fast disintegrating films

S.No	Formulation	T_{50} (min)	T_{90} (min)	$DE_{5\%}$	First order	
					K (min^{-1})	R^2
3.	V1	4.2	14.1	21.8	0.232	0.911
4.	V2	2.1	13.5	23.7	0.211	0.933
5.	V3	2.3	9.5	25.6	0.267	0.929
9.	V4	4.8	14.0	22.7	0.289	0.956
10.	V5	4.0	13.1	24.8	0.233	0.965
11.	V6	2.2	8.6	27.9	0.255	0.956
15.	V7	2.0	13.8	18.9	0.222	0.978
16.	V8	1.7	12.5	26.9	0.311	0.988
17.	V9	1.1	4.8	33.89	0.354	0.994

Scanning electron microscopy (SEM) analysis

The SEM photographs were taken for the optimized film formulation V9 and valsartan pure drug. The SEM photographs are shown in Figures 6 and 7.

RESULTS AND DISCUSSION

Preparation of valsartan FDF

Based on the physiochemical and biopharmaceutical properties, the aim of the present study was to prepare FDF of valsartan using the solvent casting method, which should possess a suitable approach in enhancing the disintegration and dissolution characteristics in more faster with increased bioavailability of poorly soluble valsartan drug. Hydroxylpropyl cellulose, PVA, and HPMC E5 were chosen as the film-forming agents, polyethylene glycol 400 as plasticizers, and crospovidone and dimethyl sulfoxide as superdisintegrant and penetration enhancer. The valsartan FDF formulations were prepared by 1:1, 1:2, and 1:3 ratios of drug and film-forming agents by solvent casting method. The composition of valsartan FDF formulations is shown in Table 1.

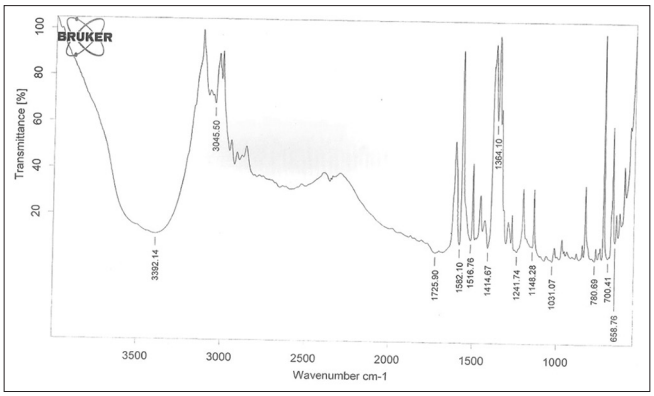

Figure 2: Fourier-transform infrared spectrum of hydroxylpropyl cellulose

Evaluation of physical parameters for valsartan FDF

The physical parameters such as weight uniformity, drug content, film thickness, and folding endurance were performed for all the valsartan FDF. The weight uniformity of all valsartan FDF prepared with hydroxylpropyl cellulose, PVA, and HPMC E5 were maintained in the range of 149–275 mg. The drug content of all valsartan FDF was maintained in the range of 37.21–40.11 mg. which indicates that the drug is evenly dispersed in all the FDF formulations. The film thickness of all FDF formulations was maintained at the range of 0.030 ± 0.034 mm. The folding endurance values for all the FDF formulations were maintained in the range of 89–101 folding, which indicates that the FDF formulations were found to be stable and should have good tensile strength. The dispersion test for all the prepared films were passed. The results of evaluated parameters such as weight uniformity, drug content, film thickness, and folding endurance are shown in Table 2.

In vitro diffusion studies of valsartan FDF formulations

Diffusion studies were conducted on all the valsartan FDF formulations using Franz diffusion cell apparatus containing pH 6.8 phosphate buffer as dissolution medium. The FDF formulations V1–V3 which were prepared by

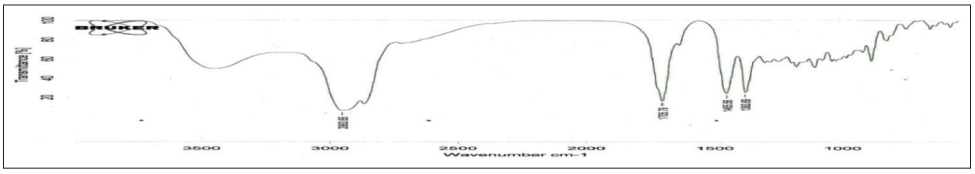

Figure 3: Fourier-transform infrared Spectrum of poly vinyl alcohol

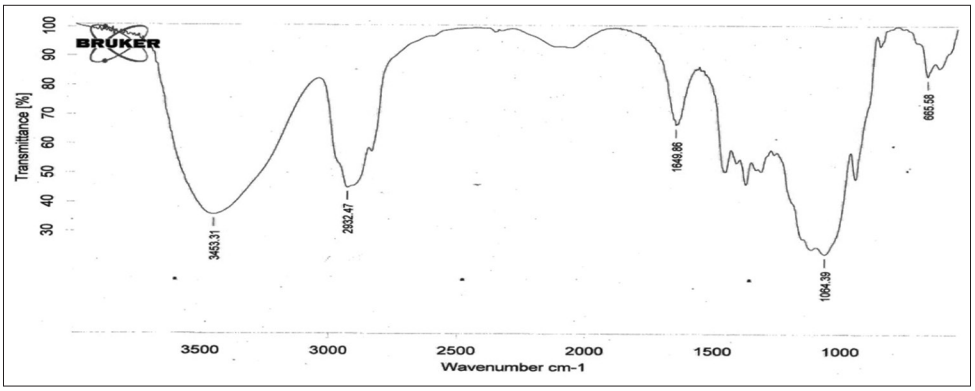

Figure 4: Fourier-transform infrared spectrum of HPMC E5

Table 4: Interpretation of FTIR Spectrum

Group	Valsartan	HPC	Poly vinyl alcohol	HPMC E5	Optimized Formulation (V9)
O-H Stretching	2613.05 cm^{-1}	2595.55 cm^{-1}	2581.72 cm^{-1}	2422.89 cm^{-1}	2522.45 cm^{-1}
C-H Stretching	2963.20 cm^{-1}	2927.53 cm^{-1}	2926.22 cm^{-1}	2728.77 cm^{-1}	2877.44 cm^{-1}
C≡N Vibration	1204.62 cm^{-1}	1198.42 cm^{-1}	1196.51 cm^{-1}	1218.12 cm^{-1}	1144.90 cm^{-1}
C=O Stretching	1732.41 cm^{-1}	1729.56 cm^{-1}	1728.85 cm^{-1}	1559.76 cm^{-1}	1768.32 cm^{-1}
N-H Bending	1602.40 cm^{-1}	1603.78 cm^{-1}	1602.52 cm^{-1}	1490.22 cm^{-1}	1640.11 cm^{-1}
Aliphatic 3^0 amine	1105.70 cm^{-1}	1068.98 cm^{-1}	1068.81 cm^{-1}	1447.18 cm^{-1}	1218.65 cm^{-1}

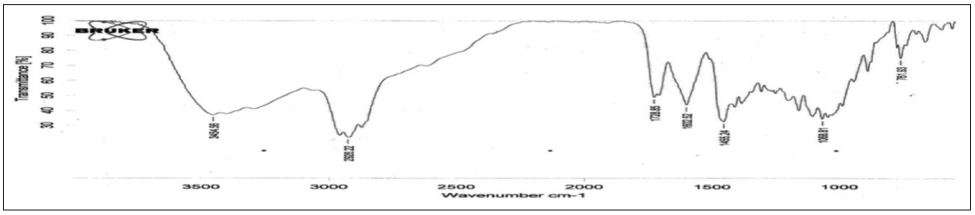

Figure 5: Fourier-transform infrared spectrum of optimized formulation (V9)

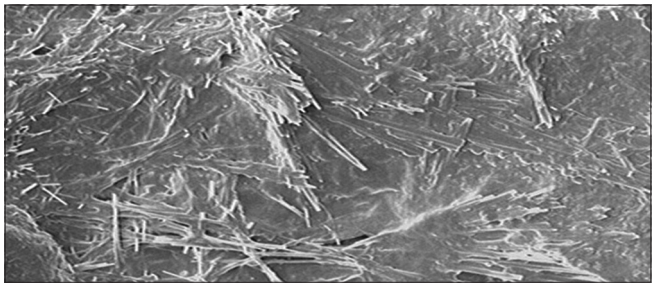

Figure 6: Scanning electron microscopy photograph of valsartan pure drug

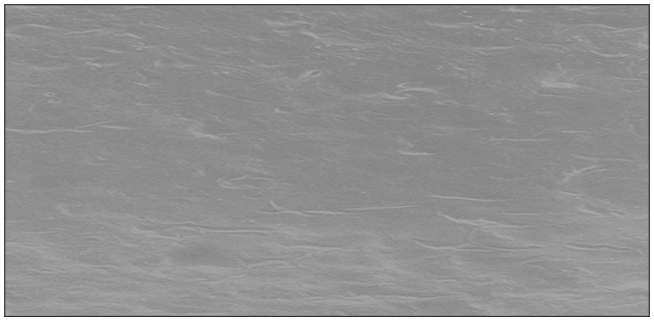

Figure 7: Scanning electron microscopy photograph of optimized formulation (V9)

using hydroxypropyl cellulose (HPC) showed an average drug release of 91.88 to 97.67 % within 15 min. The FDF formulations V4–V6, which were prepared by using PVA, showed an average drug release of 90.81–96.23% within 15 min. The FDF formulations V7–V8 which were prepared by using HPMC E5 showed an average drug release of 95.11–96.23% within 15 min. when compared to the entire FDF formulations, the FDF formulations that were prepared by using HPMC E5 at 1:3 ratio showed better drug release up to 98.11% within 5 min. The drug release profiles are shown in Figure 1.

Evaluation of various *in vitro* dissolution parameters

All the film formulations were found to be linear with first-order release rate with R^2 values in the range of 0.911–0.994. Thus, the rates of drug release from all the film formulations were concentration dependent and were linear with first-order release rate constant (K_1). The results of the evaluation of physical parameters for valsartan oral thin films are given in Table 3.

FT-IR spectroscopic analysis

The FTIR spectra of valsartan exhibited significant peaks at wave numbers of 2613 cm^{-1} (O-H), 2963 cm^{-1} (C-H), 1204 cm^{-1} (C≡N vibrations), 1732 cm^{-1} (C=O stretching), 1602 cm^{-1} (N-H bending), and aliphatic 3º amine 1105 cm^{-1}. For Hydroxypropyl cellulose, the peaks were observed at 2595 cm^{-1} (O-H), 2927 cm^{-1} (C-H), 1198 cm^{-1} (C≡N vibrations), 1729 cm^{-1} (C=O stretching), 1603 cm^{-1} (N-H bending), and aliphatic 3º amine 1068 cm^{-1}. For PVA, the peaks were observed at 2581cm^{-1} (O-H), 2926 cm^{-1} (C-H), 1196 cm^{-1} (C≡N vibrations), 1728 cm^{-1} (C=O stretching), 1602 cm^{-1} (N-H bending), and aliphatic 3º amine 1068 cm^{-1}. For HPMC E5, the peaks were observed at 2422 cm^{-1} (O-H), 2728 cm^{-1} (C-H), 1218 cm^{-1} (C≡N vibrations), 1559 cm^{-1} (C=O stretching), 1490 cm^{-1} (N-H bending), and aliphatic 3º amine 1447 cm^{-1}. For optimized formulation (V9), the peaks were observed at 2522 cm^{-1} (O-H), 2877 cm^{-1} (C-H), 1144 cm^{-1} (C≡N vibrations), 1768 cm^{-1} (C=O stretching), 1640 cm^{-1} (N-H bending), and aliphatic 3º amine 1218 cm^{-1}. The spectra of optimized formulation V9 exhibited all the principle peaks present in the valsartan pure drug. Thus, there was no appearance or disappearance of any characteristics peak which shows that there is no chemical interaction between the drug and the polymer used. The FTIR spectra of drug, polymers, and optimized formulation V9 are shown in Figures 2-5,8, and the interpretation is shown in Table 4.

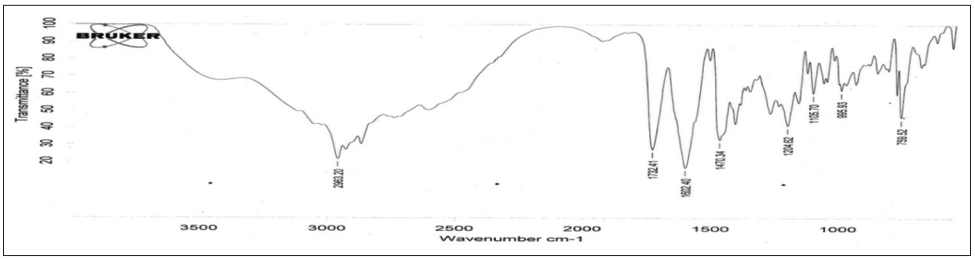

Figure 8: Fourier-transform infrared spectrum of valsartan Pure Drug

SEM analysis

The SEM analysis was performed for valsartan pure drug and optimized formulation V9. The results indicated that the optimized formulation V9 showed surface texture was smooth and uniform without any cracks on its surface. The SEM images are shown in Figures 6 and 7.

CONCLUSION

Valsartan oral thin films prepared by solvent casting method showed good flexibility and film characteristic properties. The optimized formulation V9 containing HPMC E5 at 1:3 ratio released the drug 98.11% within 5 min, which was desirable for faster dissolution and absorption. Valsartan oral thin films prepared by solvent casting technique were found to be suitable for the prevention and treatment of hypertension.

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AUTHOR CONTRIBUTIONS

T. Balakrishna has performed the basic methodology of this work. S. Vidyadhara has guided the entire formulation of the research work. Abhigna and Akhila have helped in the development of valsartan FDF. Sravanth and Vardhan helped in the interpretation of FTIR data. Anjali helped in the SEM analysis of valsartan FDF.

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