

Design and Characterization of Fast Dissolving Films of Valsartan

Rajesh KAZA^{1*}, Prasanna RajuYALAVARTHI², Nagaraju RAVOURU³

^{1*} Sri Padmavathi School of Pharmacy, Department of Pharmaceutics, Vaishnavi Nagar, Tiruchanoor, 517503 Tirupati, INDIA, ² Sree Vidyanikethan College of Pharmacy, Pharmaceutics Division, A. Rangampet, 517502Tirupati, INDIA, ³Institute of Pharmaceutical Technology, Sri Padmavathi Mahila Visvavidyalayam, 517502 Tirupati, INDIA

Recently researcher's focused on valsartan fast dissolving films (FDF) and their development. Valsartan films were prepared by solvent casting method using different grades of HPMC (E5, E50 and K4M). Six formulations (FV1-FV6) of valsartan films were prepared and evaluated for their physical characteristics such as thickness, tensile strength, elongation, weight variation, folding endurance, drug content uniformity and surface pH and gave satisfactory results. The compatibility of the drug in the formulation was confirmed by FTIR and DSC studies. The formulations were subjected to disintegration, *in vitro* drug release and pharmacodynamic studies on spontaneous hypertensive rats (SHR). Formulation FV5 was found to be best formulations which contain HPMC E5 and valsartan solid dispersion with guar gum at weight ratio of 1:4 showed excellent film forming characteristics such as disintegration time of 57 sec and percentage drug release 95.95% within 10 minutes. The optimized film formulation (FV5) showed excellent stability over 45 days when stored at 40°C/60% relative humidity. The pharmacodynamic study of valsartan FDF in SHR proved the better therapeutic efficacy.

Key words: Elongation, Folding endurance, Solvent casting, Systolic blood pressure, Tensile strength.

Valsartan'ın Hızlı Çözünen Filmlerinin Tasarımı ve Karakterizasyonu

Son zamanda araştırmacılar hızlı çözünen valsartan filmler (FDF) ve onların geliştirilmesine odaklandılar. Valsartan filmler, farklı HPMC'ler (E5, E50, K4M) kullanılarak çözücü döküm metodu ile hazırlandı. Altı valsartan film formülasyonu (FV1-FV6) hazırlandı ve kalınlık, gerilme gücü, uzama, ağırlık değişimi, katlanmaya dayanım, etken madde içerik tekdüzeliği ve yüzey pH'sı gibi fiziksel özellikleri değerlendirildi ve başarılı sonuçlar verdi. Etken maddenin formülasyondaki geçimliliği FTIR ve DSC çalışmaları ile onaylandı. Formülasyonlar dağılma, *in vitro* etken madde salımı ve spontan hipertansif ratlarda (SHR) farmakodinamik çalışmalara maruz bırakıldı. HPMC ve valsartanın guar gum ile katı dispersiyonunu ağırlıkça 1:4 oranında içeren FV5 formülasyonu 57 saniye dağılma süresi ve 10 dakikada %95.95 etken madde salımı ile mükemmel film oluşum özellikleri gösterdi ve en iyi formül olduğu bulundu. Optimize edilen film formülasyonu (FV5) 40 C°/%60 relatif nemde bekletildiğinde 45 günden fazla mükemmel stabilite gösterdi. FDF valsartan film'in SHR'lerde farmakodinamik çalışması daha iyi terapötik etkiyi kanıtladı.

Anahtar kelimeler: Uzama, Katlanmaya dayanım, Çözücü döküm, Sistolik kan basıncı, Gerilme gücü.

*Correspondence: E-mail: rajeshkaza5@yahoo.co.in; Tel: +91-9885943616

INTRODUCTION

Fast dissolving drug delivery is rapidly gaining interest in the field of formulation technology. These systems either dissolve or disintegrate within a minute, on contact little quantity of water or by chewing. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption (1, 2). They undergo disintegration in the salivary fluids of the oral cavity, where they release the active ingredient. The major portion of the active ingredient is swallowed orally along the saliva and absorption takes place in the gastrointestinal tract subsequently making them particularly suitable for pediatrics and geriatric patients. The fast dissolving films (FDF) were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form. These dosage forms offer specific advantages including accurate dosing, ease of transport, handling, acceptable taste, rapid onset of action and patient compliance (3). The transmucosal deliveries of metformin, dexamethasone and levocetizine hydrochloride have proved their enhanced bioavailability over the conventional formulations (4 - 6). Solvent casting was proved to be reliable technique for the manufacturing of FDFs. The film strips prepared by this method undergo instantaneous disintegration upon placing in buccal/oral cavity. The plasticizers present in FDF formulation, reduce the glass transition temperature and thereby enabling desired film qualities (6).

Valsartan (VAL), an antihypertensive and being a BCS Class II moiety, it is soluble only in alcohols. Pharmacologically VAL is an angiotensin II receptor antagonist with has high affinity towards the type I (AT₁) angiotensin receptor (7, 8). Hence, it requires rapid absorption and high bioavailability in patient point of view. VAL is absorbed over 4 hours, and its bioavailability is only about 20 to 25%. Fed conditions delay the absorption of VAL (9). In chronic hypertensive patients, blood pressure often shoot up and it require

rapid reduction with medication. VAL is effective antihypertensive without many side effects of angiotensin II receptor antagonists and offers the possibility of frequent dosing to deal with hypertension.

In order to enhance the solubility of valsartan and subsequently dissolution and absorption, this research work is undertaken. Solid dispersions of VAL with some natural polymers such as hupu gum, guar gum (GG) and xanthan gum were prepared. The polymers were selected as carriers since their natural abundance and biocompatibility. Solid dispersions were prepared by kneading technique at different drug: carrier weight ratios and were evaluated (10). The optimized formulation of solid dispersions, VAL:GG at 1:4 weight ratio was selected and used for further study. The optimized solid dispersion was used in preparation of VAL films by solvent casting method, which offers superiority over other practicing methods. The casted films were evaluated and *in vivo* therapeutic efficacy was assessed by comparing with that of conventional formulation.

MATERIALS AND METHODS

Valsartan was procured from M/s. A-Z Pharmaceuticals Pvt. Ltd., Chennai as gift sample. HPMC (E-5, E50 and K4M) were purchased from M/s. Hi media. Pvt. Ltd., Mumbai. Guar gum, citric acid anhydrous and propylene glycol was purchased from M/s. S.D. Fine Chem. Ltd., Mumbai. All other chemicals used were of analytical grade.

Solid dispersions

Solid dispersions of VAL with guar gum in the weight ratio of 1:4 were prepared using kneading technique. The appropriate weighed amounts of VAL and GG were moistened with methanol to get homogenous slurry. Methanol was removed by vacuum evaporation. The resulting mass was transferred to vacuum desiccator and dried to constant weight. The dried product was pulverized and sifted through sieve # 100. The samples prior to be used for the study were stored in the desiccator.

Preparation of fast dissolving films

Accurately weighed quantities of film forming polymers such as HPMC of various grades, plasticizers, sweetener, salivary stimulating agent and flavoring agent were dissolved in distilled water and resulting dispersion was stirred for 90 min at 70°C (11, 12). The resulting product was kept for drying for 24 hrs. The dispersion was casted onto the glass mould and allowed to dry under vacuum. The mould in size of 5×5 cm² and the mould capacity of 16 mL was used to obtain a thin flexible rapid dissolving film. In initial attempts placebo films were prepared by omitting VAL. Later, the optimized VAL: GG solid dispersion (1:4 ratio) with equivalent weight 40 mg of VAL was added to the formulation (Table 1) to obtain FDF of VAL. After sufficient drying, film was cut into 2×2 cm² square strips. The prepared square thin film strips were stored in a desiccator for further studies.

different strategic locations. Thickness test was to ascertain uniformity in the thickness of the prepared film, as thickness is proportional to the accuracy of dose in the strip (1). Ten film strips were randomly selected and their average weight of film strip was found out. Individual films were weighed and compared with the average weight for the deviation (11-13).

The surface pH of thin film strips was determined in order to find out the possible side effects. The film strip was placed in a petri dish and was moistened with 0.5 mL of distilled water and kept 1hr to equilibrate. The pH of the equilibrated film strip was measured with glass membrane electrode in contact with surface of the film strip (15-17). The procedure was repeated in triplicate.

Tensile strength and elongation

Mechanical properties of the film are important from packaging point of view. Tensile strength was performed to assess

Table 1. Composition of VAL fast dissolving films

Ingredients	FV1	FV2	FV3	FV4	FV5	FV6
VAL:GG (equivalent to 40 mg of VAL)	74.53	74.53	74.53	74.53	74.53	74.53
HPMC E5	--	--	--	--	100	120
HPMC E50	---	---	100	120	--	--
HPMC K4M	100	120	---	---	--	--
Propylene glycol	40	30	40	30	40	30
Aspartame	10	5	10	5	10	5
Citric acid	10	5	10	5	10	5
Water up to (mL)	16	16	16	16	16	16

*Evaluation of FDF**Tackiness, folding endurance and thickness*

Six films of final formulations were randomly selected. Each of the strips was pressed against the fingertips and tackiness was recorded. Results were noted in qualitative terms as tack and non-tacky (13). Folding endurance of prepared films was determined by repeatedly folding a small strip of film (2 × 2 cm²) at the same place until it breaks, was noted as the folding endurance value (14). The test was conducted for six film strips. Films were measured for their thickness using micro screw-gauge at

strength and elasticity of the developed formulations. Tensile testing was conducted using a texture analyzer, equipped with a 5N load cell. Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film broke (1). Percentage elongation (% E) of the films was computed with following equation:

$$D_f - D_0 / D_0 \times 100$$

Where, D_0 is distance between the tensile grips before the fracture of the film and D_f is a distance between the tensile grips after the fracture of the film.

Dissolving / Disintegration time

The time for films (for six strips) to dissolve was recorded using modified disintegration method. In this disintegration test, a petri dish was filled with 2 mL of distilled water and the film strip was carefully placed on the surface of water (17). Time required for the film strip to disintegrate/dissolve completely was noted.

Drug content uniformity

A film strip about $1 \times 1 \text{ cm}^2$ area was dissolved in 100 mL of methanol at 40°C . The content was passed through $0.4 \mu\text{m}$ membrane filter. The filtrate was assayed using UV spectrophotometer at 249 nm (11).

In vitro dissolution studies

In-vitro dissolution studies were carried out for the prepared films using USP dissolution type II apparatus. A strip of thin film was attached to the dissolution beaker of 1000 mL capacity, midway from the bottom with instant adhesive. After 2 min, the dissolution beaker was filled with 900 mL of simulated salivary fluid of pH 6.8 (SSF). A 5 mL of samples were withdrawn at different time intervals and filtered through $0.4 \mu\text{m}$ membrane and diluted suitably. The absorbance was read spectrophotometrically at 249 nm against blank. The percent drug dissolved was calculated using standard graphic. The mean of six observations was considered for dissolution profiles (3).

FTIR spectroscopy

The spectral measurements were performed using Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of $4000\text{--}400 \text{ cm}^{-1}$ at the spectral resolution of 2 cm^{-1} .

DSC thermal analysis

Thermal analysis of film strips were recorded with Netzsch DSC 200 PC (Netzsch, Selb, German). The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of $5/\text{min}$ was employed over a temperature range of $0\text{--}350^\circ\text{C}$ with nitrogen purging. The sample was weighed into an aluminium pan was used as reference.

Stability studies

The stability study of the prepared FDF was carried under different environmental conditions. The six film strips were first wrapped separately with butter paper and followed by aluminium foil. The film strips were stored in stability chamber at two different storage conditions of $40^\circ\text{C}/60\%$ relative humidity (RH) and $60^\circ\text{C}/75\%$ RH. The film strips were evaluated for the appearance, weight, drug content and *in vitro* drug release after 45 days.

Pharmacodynamic study

In this study, a film strip of $2 \times 2 \text{ cm}^2$ size, contains 40 mg of valsartan was subjected to the dissolution, (300 mL dissolution medium) so that it could release 0.133 mg of drug/mL. Hence, 1.3 mL contains 0.173 mg of the valsartan (6). The similar dosage of drug from the marketed conventional tablets was used in the study to have a similar dose with that of the drug in the film strip used.

Therapeutic efficacy of FDF-antihypertensive activity

Experimental animals, male Spontaneously Hypertensive (SH) rats aged about 10-12 weeks and weighing between 180–220 g were used in this study. The animals were bred and housed in the animal house, Sri Padmavathi School of Pharmacy, Tirupati, India. Animals were allowed a free access to food and tap water *ad libitum*. The animals were divided into following groups: Group 1, control untreated group which received normal saline. Group 2 received telmisartan (marketed tablet) 12.5 mg/kg , and group 3 received solution of valsartan film strips at predetermined doses respectively. All the preparations were administered orally and

once daily for 4 weeks. The experimental protocol was approved by the institutional animal ethical committee (Ref. No: 1016/a/06/CPCSEA/011/2012).

Noninvasive systolic blood pressure measurement

Systolic blood pressure (SBP) measurement of SH rats was carried out using tail-cuff method (18) plethysmography (INCO, Ambala, India) in conscious pre-warmed (27-29°C for 30 min) restrained rats (19). During the last week of treatment, the rats were allowed to acclimatize to the experimental conditions of noninvasive SBP measurements by allowing them to stand in rat restrainers for 30 min every day. SBP measurements were recorded 24 h after the last treatment dose. At least 8-10 recordings were taken for each rat and the mean of the lowest 4 values within less than 10 mmHg difference was taken as the mean SBP. The obtained data are statistically treated.

RESULTS AND DISCUSSION

Previously optimized valsartan guar gum solid dispersions (VAL:GG) at weight ratio of 1:4 prepared by kneading technique was selected for this study. It is proposed to formulate and develop the fast dissolving films of above solid dispersions to evaluate the efficacy of GG solid dispersions in the FDF formulation. The formulated FDFs were appeared to be clear, homogeneous, some are transparent and some are partially transparent. They were found to be physically flexible, non-tacky and dry.

The folding endurance was measured manually, by folding the FDF repeatedly at a point till it broke. The breaking time was considered as the end point. Folding endurance was found to be highest for FV4 and lowest for FV5. It was found that the folding endurance of the FDF was affected with increase of carrier concentration. The folding endurance values of the FDF were found to be optimum and therefore, the FDFs exhibited the good physical and mechanical properties. The folding endurance of films was found to be in the range of 66 to 90 (Table 2).

As all the formulations contain different amount of polymers, the thickness was gradually increased with the amount of polymers. All the film formulations were found to have thickness in the range of 0.198 to 0.205 mm and were observed within the limits. The compositional variation of selected polymer resulted with the varied thickness in FDFs and was not affected by the amount of HPMC as shown in Table 2.

Weight variation and surface pH

The randomly selected film strips about 1×1 cm² area were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 192.01 to 204.79 mg. The results indicated that selected carriers, solvent used in method of solid dispersion preparation, proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted films. The surface pH was found to be in the range of 6.11 to 6.88, which is closer to neutral pH indicating that FDFs may have less potential to irritate the sublingual mucous and hence, more acceptable by the patients.

Tensile strength and elongation

The tensile testing gives an indication of the strength and elasticity of the FDF, reflected by the parameters tensile strength, elastic modulus and elongation at break. A soft and weak carrier is characterized by a low tensile strength, elastic modulus and elongation at break. A hard and brittle carrier is defined by a moderate tensile strength, high elastic modulus and low elongation at break; a soft and tough carrier is characterized by a moderate tensile strength and high elongation at break. The tensile strength was found to be increased with increase of concentration of HPMC (E5, E50 and K4M) whereas the increase in the concentration of propylene glycol leads in the decrease in the tensile strength. The tensile strength of the valsartan films was ranging from 9.76 to 13.77 and is shown in Table 3.

Disintegration time

It was observed that *in vitro* dissolving/disintegration time varies from 54 to 87 sec for all the formulations (Table 2). *In*

in vitro disintegration time of FDFs was affected significantly slower than that of HPMC E5 and HPMC E50. This is attributed to the by polymers viz. HPMC E50, K4M and E5.

Table 2. Physicochemical parameters of valsartan fast dissolving films (mean±S.D.) (n=6)

Formulation Code	Weight variation (mg)	Thickness (mm)	Folding Endurance	Disintegration Time (sec)	% Drug content
FV1	192.01±1.23	0.201±0.93	74±1.81	87±0.82	62.43±0.76
FV2	201.53±0.92	0.211±1.08	66±1.98	72±0.65	61.65±0.84
FV3	202.65±0.98	0.207±0.89	82±0.76	69±1.78	67.44±0.93
FV4	195.41±1.53	0.198±1.06	90±1.07	66±0.91	57.52±0.87
FV5	204.79±0.59	0.205±0.66	66±0.79	57±0.78	80.76±0.73
FV6	203.85±1.08	0.189±0.95	75±1.56	54±0.96	73.32±0.88

Table 3. Physicochemical parameters of valsartan fast dissolving films (mean±S.D.) (n=6)

Formulation Code	Tensile strength (N/mm ²)	% Elongation	Surface pH
FV1	9.76±1.22	1.41±1.55	6.12±0.88
FV2	10.78±0.93	2.78±0.97	6.28±0.93
FV3	11.84±0.96	3.15±0.91	6.19±1.87
FV4	12.75±0.94	1.87±0.93	6.17±0.98
FV5	11.64±0.75	1.94±0.87	6.11±0.99
FV6	13.77±1.07	2.02±0.89	6.88±0.91

This is due to polymer's high water absorption and retention capacities.

Drug content

The prepared film formulations were assayed for their drug content. Results showed the more uniformity of the drug in the film strips and indicated the less drug loss in formulations as shown in Table 2. This could be due to the method employed in the formulation.

In vitro dissolution studies

The *in-vitro* drug release profiles of the formulations in SSF pH 6.8 show differences depending on their composition (Figure 1).

Three different grades of HPMC (E5, E50 and K4M) at the concentrations of 50 and 60% w/w each with respect to the total film composition (200 mg of 2×2 cm²) were used and it was found that the rate of valsartan released from the HPMC K4M films was

swelling of the high viscosity HPMC K4M upon contact with the dissolution medium, resulting in the formation of a thick matrix gel, thereby hindering the release of the drug from the film which shows the dissolution of 78 and 74% at the end of 10 min. Even though the viscosity is high for HPMC K4M when compared to HPMC E5 and HPMC E50 but it was showing the good dissolution profile and other reason attributed in this concern is the selection of plasticizer which is hydrophilic in nature and is used at high concentrations.

The low viscosity polymers such as HPMC E5 and HPMC E50 shown a superior dissolution rates in comparison with that of high viscosity polymer HPMC K4M because the loosely bound polymer molecules in these films were readily eroded, allowing the easy dissolution of valsartan upon contact with the dissolution medium. FV5 formulation containing HPMC E5 and propylene glycol at the concentrations of 15 and 20% w/w shows

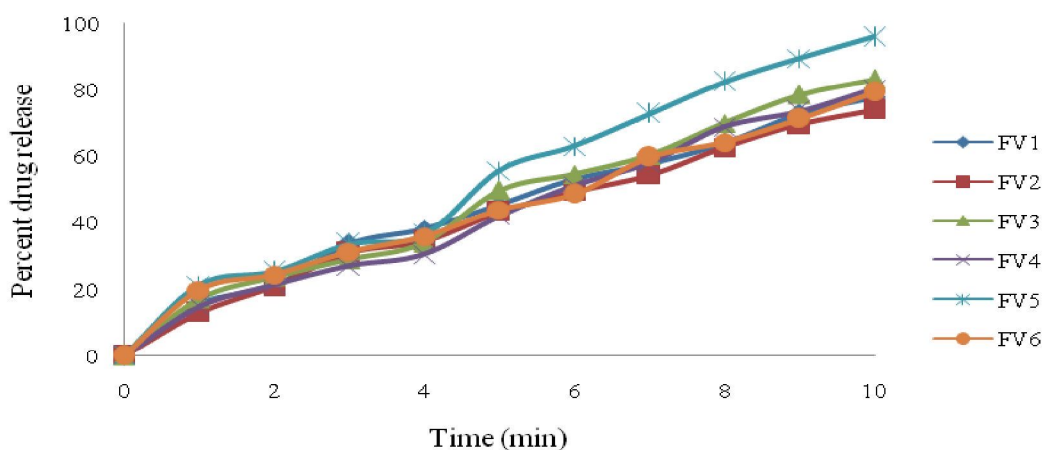


Figure 1. Comparative *in vitro* dissolution profile of valsartan fast dissolving films (n=6)

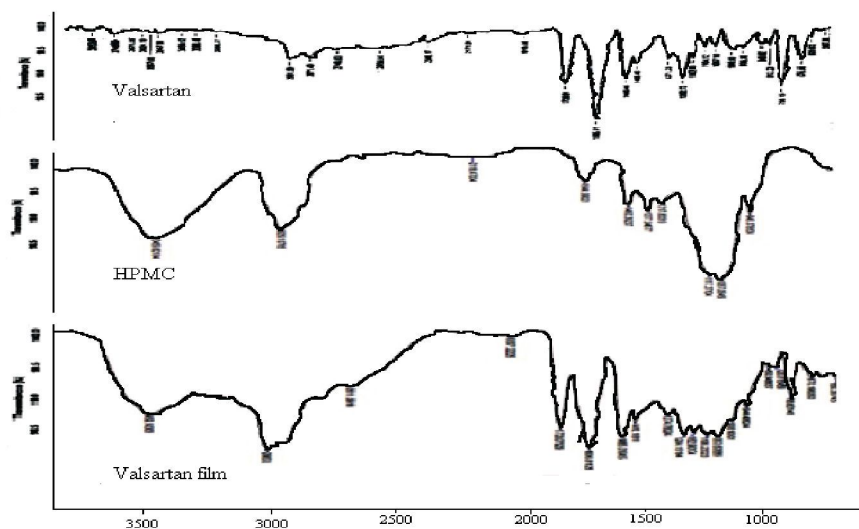


Figure 2. FTIR spectra of HPMC, valsartan and FV4 (FDF)

rapid dissolution of 95.95% within 10 min. FV6 formulation containing HPMC E5 and propylene glycol at the concentrations of 60% w/w and 15% w/w also showed rapid dissolution of 83% within 10 min. Both the FV6 and FV5 formulations showed quick dissolution profiles in comparison with that of FV3 and FV4 consisting of low viscosity polymer HPMC E50 which shows the drug release of 83 and 80% within 10 min.

FTIR spectroscopy

HPMC, a polymer with excellent film forming ability, was used in the formulations of fast dissolving films of VAL. The

interpretations of the FT-IR spectra of HPMC and FV4 of FDF are given in Figure 2.

The principal absorption peaks of HPMC were observed at 3459 cm^{-1} (OH-stretching) 2929 cm^{-1} (CH-stretching) and 1117 cm^{-1} (C-O-C-stretching). The principal peaks of VAL were observed at 1715.14 (C=O stretching), 1210.32 (C-N stretching), 1588.10 (N-H bending) and 1155.56 (N-N stretching). Same peaks of N-N and methyl bond were present without much shifting in the spectra of FV4 contains VAL and HPMC suggested no interaction between the drug and selected polymers.

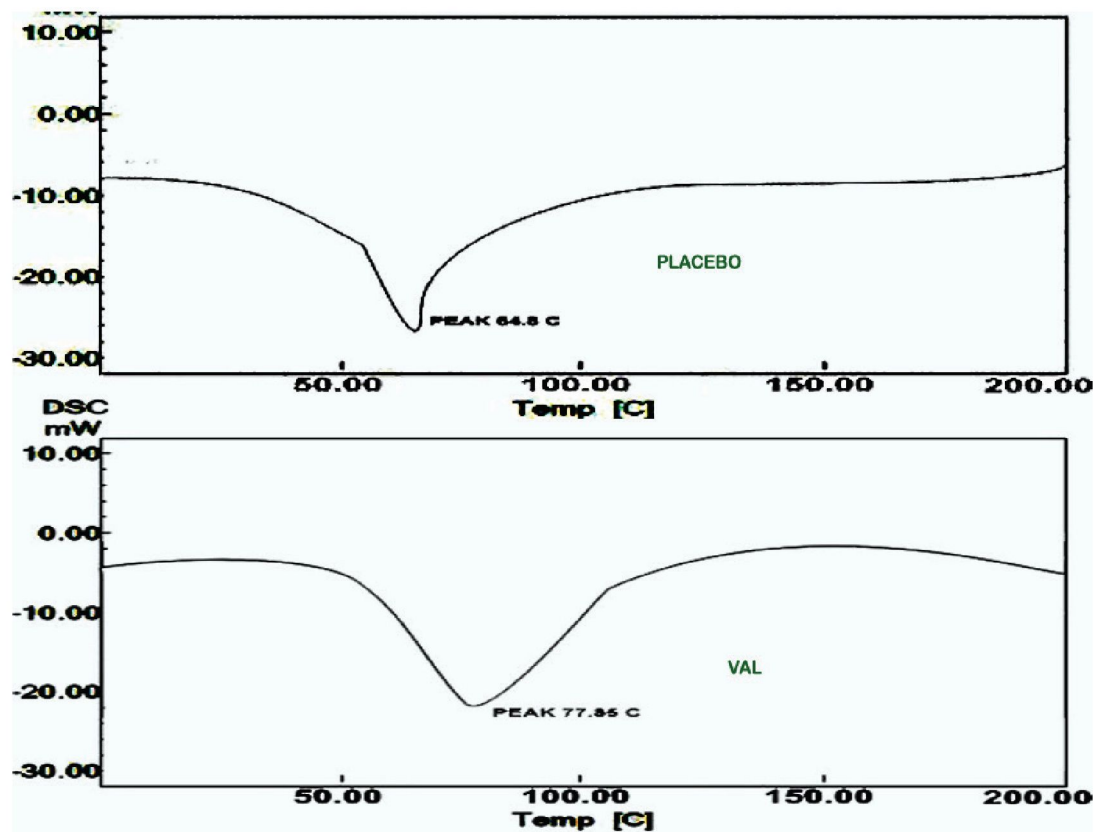


Figure 3. DSC thermograms of placebo film and valsartan film (FV5)

DSC studies

The DSC thermograms of prepared fast dissolving films are shown in Figure 3.

The thermograms of placebo film (HPMC as a major film former) shows melting endotherm at 64.8 °C. DSC thermogram of VAL fast dissolving film was found at 77.85°C. The DSC thermograms of prepared films indicated that there were no interaction between the drugs and excipients used in the film formulations.

Accelerated stability testing

The stability study was carried out for 45 days at 40 °C/ 60% RH and 60° C/ 75% RH. The films were observed for physical change, appearance, weight, drug content and *in-vitro* drug release. The optimized FDF formulations, FV5 of VAL were found to be physically and chemically stable as they showed no significant change in the shape, colour or flexibility, weight and drug content at applied stress conditions. However, when

stored at 60° C/ 75% RH for 45 days, all the films became brittle.

Therapeutic efficacy of FDF

The blood pressure/systolic pressure (SBP) were measured as an indication of the efficacy of the FDF formulations of selected drugs. The results showed clearly that there is significant difference between the telmisartan commercial tablet and FDFs. The angiotensin inhibitor (ACE) valsartan FDFs exhibited a considerable fall in SBP immediately which proved the therapeutic efficacy of the drug in FDF formulations (Table 4). These differences were found to be significant ($P < 0.05$ and $P < 0.01$ respectively). Thus, it is attributed that the prepared FV5 of VAL film formulations are considerably more efficient in lowering the blood pressure. The faster dissolving time/dissolution rate of the optimized FDF formulations could be the reason for the therapeutic action in lowering of SBP.

Table 4. Effect of systolic blood pressure of valsartan fast dissolving films on various treatment groups

Group	Treatment	SBP (mm Hg)
I (control)	vehicle (Tween 80)	162.0±6.75
II (standard)	telmisartan commercial tablet (12.5 mg/kg)	145.7±7.46*
III (test)	valsartan film (FV5)	128.6±9.55**

Values are presented as mean ± S.E.M. of 6 experiments. *P< 0.05; **P < 0.01, treatment versus control group.

CONCLUSION

The fast dissolving films of valsartan were prepared using the easily accessible component such as HPMC of different grades (E5, E50 and K4M) by solvent casting technique. The method of formulation was found to be modest and economic. Valsartan, a poorly water soluble drug could be magnificently assimilated in the fast dissolving films with the help of natural polymer guar gum which serves as carrier in increasing the solubility of valsartan and HPMC as film forming polymer. Amongst the all formulations, FV5 was found as best formulation which contains HPMC E5 and valsartan solid dispersion with guar gum at weight ratio of 1:4 and showed excellent film forming characteristics such as disintegration time of 57 sec and percentage drug release 94.95% within 10 minutes. A further pharmacodynamic study in spontaneous hypertensive rats (SHR) substantiated that the fast dissolving films of valsartan produced a quick therapeutic efficacy as equated to the conventional tablets. Thus, *in vitro* and pharmacodynamic evaluation of the FDF established their prospective as a pioneering dosage form to improve the delivery of valsartan.

REFERENCES

- Dixit RP, Puthli SP, Oral strip technology: Overview and future potential, J Cont Rel 139, 94-107, 2009.
- Vollmer U, Galfetti P, Rapid film: Oral thin films as an innovative drug delivery system and dosage form, Drug Dev Report 64-67, 2006.
- Kunte S, Tandale P, Fast dissolving strips: a novel approach for the delivery of verapamil, J Pharm Bioallied Sci 2(4), 325-328, 2010.
- Sushma M, Prasanna YR, Sundaresan C, Vandana K, Kumar NV, Chowdary VH, Transmucosal delivery of metformin- A comprehensive study, Curr Drug Deliv July, 2013. PMID: 23848354.
- Shimoda H, Taniguchi K, Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Hirano K, Yamamoto M, Kinosada Y, Itoh Y, Preparation of a fast dissolving oral thin film containing dexamethasone: a possible application to anti-emesis during cancer chemotherapy, Eur J Pharm Biopharm 73(3), 361-365, 2009.
- Prabhu P, Malli R, Koland M, Vijayarayana K, D'Souza U, Harish N, Shastry C, Charyulu R, Formulation and evaluation of fast dissolving films of levocetirizine dihydrochloride, Int J Pharm Inv 1(2), 99-104, 2011.
- Beg S, Swain S, Singh HP, Patra CN, Rao MB, Development, optimization and characterization of solid self-nanoemulsifying drug delivery systems of valsartan using porous carriers, AAPS Pharm Sci Tech 2(3), 112-114, 2012.
- Markham A, Goa KL, Valsartan: a review of its pharmacology and therapeutic use in essential hypertension, Drugs 54(2), 299-311, 1997.
- Flesch G, Lloyd P, Muller PH, Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man, Eur J Clin Pharmacol 52, 115-120, 1997.
- Rajesh K, Prasanna Raju Y, Nagaraju R, Dissolution enhancement of valsartan using natural polymers by solid dispersion technique, Der Pharmacia Lettre 5(2), 126-134, 2013.
- Cilurzo F, Irma E, Cupone PM, Selmin F, Montanari L, Fast dissolving films made of

- maltodextrins, *Eur J Pharm Biopharm* 70(3), 895-900, 2008.
12. Yoshifumi M, Takashi I, Kyoko KNN, Ryosei K, Preparation of fast dissolving films for oral dosage from natural polysaccharides, *Materials* 3, 4291-4299, 2010.
 13. Marina K, Charyulu RN, Prabhakara P, Mucoadhesive films of losartan potassium for buccal delivery: Design and characterization, *Ind J Pharm Educ Res* 44(4), 315-323, 2010.
 14. Shinde AJ, Garala KC, More HN, Development and characterization of transdermal therapeutics system of tramadol hydrochloride, *Asian J Pharm* 2(4), 265 - 269, 2008.
 15. Kumar GV, Krishna RV, William GJ, Konde A, Formulation and evaluation of buccal films of salbutamol sulphate, *Ind J Pharm Sci* 67(2), 160-164, 2005.
 16. Mashru RC, Sutariya, VB, Sankalia MG, Parikh PP, Development and evaluation of fast-dissolving film of salbutamol sulphate, *Drug Dev Ind Pharm* 31(1), 25-34, 2005.
 17. Renuka M, Avani A, Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film forming agent, *Ind J Pharm Edu Res* 45(1), 71-77, 2011.
 18. Badyal DK, Lata H, Dadhich AP, Animal models of hypertension and effect of drugs, *Ind J Pharmacol* 35, 349-362, 2003.
 19. Raghava NS, Prasanna RY, Rahul N, Omar Z, Ameer I, Salman M, Amirin S, Mohd ZA, Chronic effects of *Andrographis paniculata* chloroform extract in spontaneously hypertensive rats, *J Pharm Sci Res* 4(8), 1924-1928, 2012.

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