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Original Article

Formulation and evaluation of fast dissolving tablets containing a combination of valsartan and amlodipine for the treatment of hypertension

Ujjwal Sidgel, Sheeba FR*, Santosh Kumar

Mallige College of Pharmacy, Silvepura, Chikkabanavara, Bangalore-90, India

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ABSTRACT

The aim of this work was to formulate and evaluate fast dissolving tablets of amlodipine in combination with valsartan for rapid dissolution and absorption of drug to produce rapid onset of action in the management of hypertension. The tablets were prepared using superdisintegrants like crospovidone, croscarmellose, gellan gum, and banana powder. Twelve different groups of formulations (**F1**–**F12**) were prepared using natural and synthetic superdisintegrants by direct compression method. Tablet weight variation, hardness, friability, drug content, disintegration time and dissolution time were evaluated for each formulation and found satisfactory. From the result, it was concluded that **F3** was the best formulation among all other groups.

Keywords: amlodipine, crospovidone, croscarmellose, fast dissolving tablets, gellan gum, valsartan

INTRODUCTION

American guidelines for the treatment of most hypertension indicate that most hypertension patients will require at least two antihypertensive drugs to achieve the recommended goals [1]. Polypharmacy may decrease patient compliance and persistence. Valsartan [2] in combination with Amlodipine [3] are used in the treatment of hypertension. Valsartan is a specific angiotensin II receptor antagonist and Amlodipine is a calcium channel blocker. There have been various applications present in relation for the combinations of valsartan and amlodipine. Calcium channel blockers and angiotensin receptor blockers are being increasingly used in fixed dose combinations. The combination of amlodipine with valsartan achieved lower the incidence of peripheral oedema, enhance patient adherence, convenience, and BP control while reducing adverse effects than valsartan or amlodipine monotherapy [4].

The uncomplicated and easiest approach of administration of drugs is by oral route. It is the preferred route of administration which has a wide acceptance up to 50-60% of total dosage forms as it offers good patient compliance. Fast dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people [5]. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach [6]. The present work deals with easily-administrable fast dissolving tablets of valsartan and amlodipine in combination with various superdisintegrants for use in the treatment of hypertension.

MATERIALS AND METHODS:

Materials: Valsartan and Amlodipine were obtained from Yarrow Chem Products, Mumbai. Crospovidone, croscarmellose, gellan gum, lactose, stevia, magnesium stearate, talc, micro crystalline cellulose (MCC) were procured from Bangalore Fine Chemicals. Banana powder was purchased from local market. All the chemicals and solvents used were of analytical grade.

Preparation of fast dissolving tablets: Valsartan/ Amlodipine fast dissolving tablets were prepared by the direct compression method using different excipients [7]. The synthetic superdisintegrants such as crospovidone and croscarmellose or natural superdisintegrants such as gallen gum and banana powder were used for the study. Stevia, lactose, talc, magnesium stearate and microcrystalline cellulose were used as excipients.

***Corresponding Author Address:** Dr. Sheeba FR, Mallige College of Pharmacy, Silvepura, Chikkabanavara, Bangalore-9, India: Email: sheebafrs@yahoo.co.in*

Excipients in different concentrations were used to prepare different group of fast dissolving tablets. Compositions of various formulations are shown in **Table -1**. All the above ingredients were properly mixed together in an air tight plastic container, then finally 2 g of magnesium stearate and 2 g of talc were added for lubrication with initial mixture in a plastic container followed by direct compression of the blend. The total weight of the tablet formulation was maintained at 200 g.

Evaluations of prepared granules

Angle of repose: The angle of repose of blend granules was determined by funnel method. The accurately weighed granules were taken in funnel and allowed to flow through the funnel freely on to the surface. The height of the pile of the granules and the diameter of the granules were measured and angle of repose was calculated using the following equation. Tan θ = h/r. Where h and r are the height and radius of the powder concentration [8].

Bulk density and tapped density: Bulk density and tapped density of prepared granules were determined by using bulk density apparatus (Bulk density apparatus, Electro lab, Mumbai). The bulk density and tapped density were calculated using the following formula [7].

Bulk density =W/Vo

Tapped density = W/ Vf

Where Vo and Vf are the initial volume and final volume of the granules. W is the weight of granules.

Compressibility index: Compressibility index of the granules was determined by Carr's compressibility index [10].

Carr's compressibility index (%) = (Tapped density – Bulk density) x 100/ Tapped density

Evaluations of compressed fast dissolving tablets: All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution.

Weight variation: 20 tablets of each formulation were weighed using electronic balance (Electro lab, Mumbai) and the weight variation test was preformed according to the Indian pharmacopeia [10].

Friability test: Six tablets from each batch were examined for its friability [11] using Roche friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India) for 4 min at 25 revolutions per minute. The tablets were taken out, de-dusted and reweighed.

Hardness test: The hardness of the tablet [12] was determined using a Monsanto hardness tester (Campbell Electronics, Mumbai, India).

Disintegration time: The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus (scientific Engineering Corporation, Delhi, India). Distilled water was used as a disintegrating media at 37±0.5°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded [13].

Drug content: Five tablets from each batch were finely powdered and the powder equivalent to 40 mg of Valsartan and 5mg of amlodipine were dissolve in 10 ml of methanol and made upto volume 100 ml with pH 6.8 buffer. The sample was further diluted to get a concentration of 10 µg/ml. The sample was scanned over the two absorption maxima of valsartan and amlodipine respectively. The absorptivity of both the standards and a sample was substituted in the formula to get the drug content. Since sample contains two absorbing drugs [X (Valsartan) and Y(Amlodipine)] each of which absorbs at the λ max different from the other, it may be possible to determine both drugs by the technique of simultaneous equations [14]. The drug content of valsartan and amlodipine were analysed spectrophotometrically (Shimadzu, UV-1601) at 250 nm and 238 nm receptivity.

In-vitro drug release study: Dissolution study was conducted for all the formulation using USP dissolution rate test apparatus type –II (Electro lab, Mumbai, India). The dissolution medium, 900 ml of pH 6.8 buffer solution, was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and of 50 rpm. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 5 ml were withdrawn after every 2, 4, 6, 8, and 10 min and filtered. The fresh dissolution medium was replaced every time of interval to maintain sink condition. The collected samples were filtered through 0.45 µm Whatman filter paper. After suitable dilution samples were scanned in the absorption maxima for both drugs that is amlodipine and valsartan. The cumulative percentage drug release was calculated using simultaneous UV spectrophotometric method [15].

Stability studies: The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.

Formulations were selected for stability on the basis of the *in-vitro* drug release profile. According that formulation F3 was subjected to a accelerated stability studies as per ICH guidelines i.e. room temperature ,30±2°C/ 65±5%RH and 40±2°C/75±5%RH in air tight high density poly ethylene bottle for 6 months in thermos stated ovens. The samples were taken out at 0, 2 months, 4 months and 6 months [16].

RESULTS AND DISCUSSION

Valsartan/amlodipine fast dissolving tablet were prepared by direct compression method. Twelve formulations were prepared by using different ratio of natural and synthetic polymers. The result of angle of repose and compressibility index (%) ranged from 22.03±0.1 to 29.10±0.02 and 6.09 to 15.73 respectively (Table 2). The result of angle of repose (<30) indicate good flow properties of the granules. Generally, compressibility index values up to 15% results in good to excellent flow properties. All the batches of tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, thickness, weight variation test, disintegration time and *in-vitro* dissolution which was reported in table 3. Friability and weight variation values with in the I.P limit. All the tablets maintained hardness in the range of 2.9 to 4.2kg/cm^2. The drug content in different formulations was highly uniform and the range of 96.5 to 99.3%. Crosspovidone containing formulation were quickly disintegrate compared to other formulation. From the in-*vitro* dissolution studies, it was observed that formulation F3 showed valsartan 99.1% and amlodipine 92.6% dissolution efficacy in 10 min. The drug release patterns for different formulations were shown in Fig. 1 and 2. The tablet formulation F3 showed a lesser T 50% compared to the studied fast dissolving tablet. Hence the group contain crosspovidone is superdisintegrant selected as an optimized fast dissolving tablet. Stability studies for the promising formulation F3 were carried out (Table 4) and report showed that there is no significance change in all the parameters. Hence, formulation F3 proved to be useful for the treatment of most hypertension which require at least two antihypertensive drugs.

CONCLUSION

Valsartan/amlodipine fast dissolving tablet were successfully formulated using various supedisintegrants in different concentration by direct compression method. The formulation (F3) containing crospovidone superdisintegrant was found the best formulation among the series with a disintegration rate of 23.1 second. The dissolution study showed 99.1% valsartan and 92.6% amilodipine release. Hence F3 could be an acceptable formulation, which is a prerequisite for the rapid management of hypertension diseases.

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Figure 1: Drug release profiles of valsartan formulation **F1-F12**

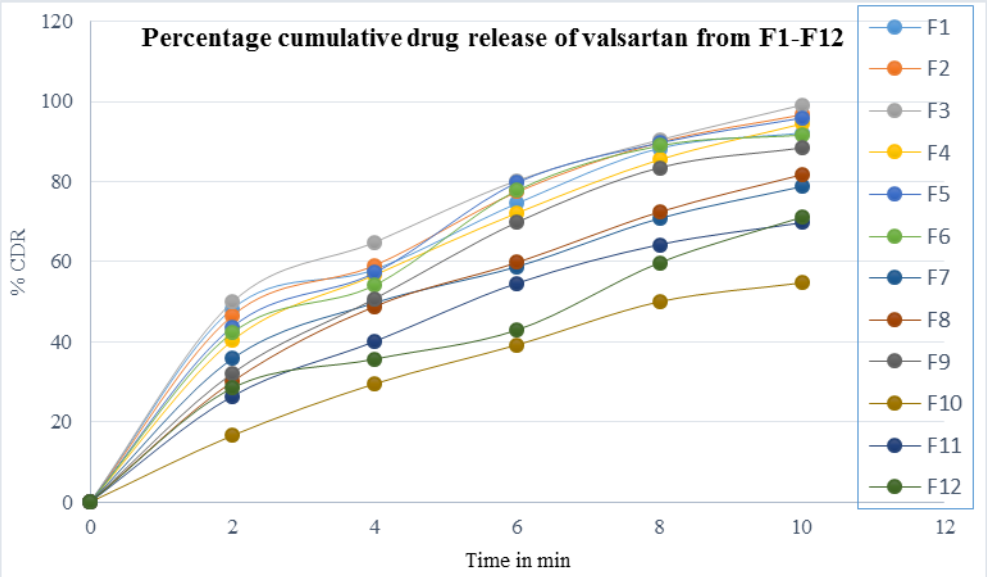

Figure 2: Drug release profiles of Amilodipine formulation **F1-F12**

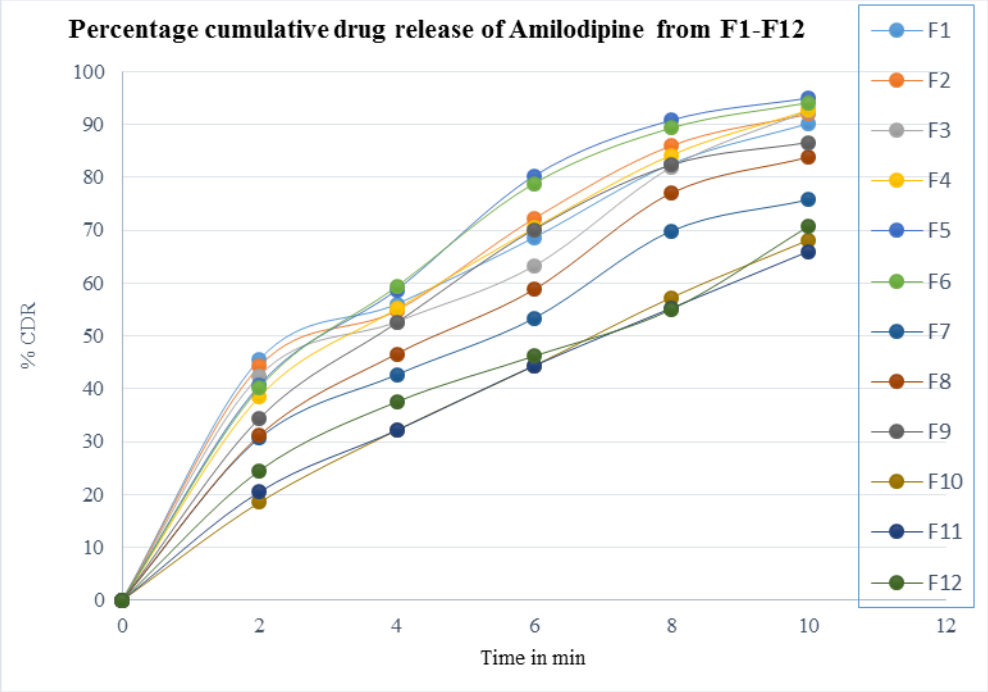

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Table 1: Different formulation of valsartan/amlodipine fast dissolving tablet.

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Valsartan	40	40	40	40	40	40	40	40	40	40	40	40
Amlodipine	5	5	5	5	5	5	5	5	5	5	5	5
Crosspovidone	45	90	135	_	_	_	_	_	_	_	_	_
Croscarmellose	_	_	_	45	90	135	_	_	_	_	_	_
Gellan gum	_	_	_	_	_	_	45	90	135	_	_	_
Banana powder	_	_	_	_	_	_	_	_	_	45	90	135
Lactose	12	12	12	12	12	12	12	12	12	12	12	12
Stevia	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesiun stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	91	46	1	91	46	1	91	46	1	91	46	1

Table 2: Evaluation data of prepared granules.

Formula	**Angle of repose**	**Bulk density**	**Tapped density**	**Carr's index**
F1	28.05 ± 1.20	0.50 ± 0.02	0.59 ± 0.02	14.23
F2	26.22 ± 0.79	0.40 ± 0.01	0.46 ± 0.03	12.60
F3	28.07 ± 1.14	0.33 ± 0.05	0.36 ± 0.24	8.33
F4	27.16 ± 0.50	0.56 ± 0.02	0.61 ± 0.02	8.19
F5	29.10 ± 0.02	0.60 ± 0.10	0.64 ± 0.04	6.19
F6	24.15 ± 0.83	0.52 ± 0.03	0.58 ± 0.06	11.20
F7	22.46 ± 1.90	0.51 ± 0.03	0.61 ± 0.02	15.73
F8	27.05 ± 1.06	0.49 ± 0.02	0.52 ± 0.03	6.09
F9	27.20 ± 1.20	0.60 ± 0.04	0.66 ± 0.03	8.40
F10	22.03 ± 0.10	0.41 ± 0.03	0.46 ± 0.02	10.79
F11	24.05 ± 0.90	0.52 ± 0.08	0.58 ± 0.01	9.10
F12	28.20 ± 1.20	0.51 ± 0.02	0.56 ± 0.04	8.89

Table 3: Evaluation data of valsartan/amlodipine fast dissolving tablet.

Formulation	Hardness Kg/cm^2	Thickness mm	Drug content (%)	Disintegration time	Dissolution efficacy (%) after 10 min		T 50% drug release in min
					Valsartan	Amlodipine	
F1	3.0 ± 0.31	3.6 ± 0.01	98.07 ± 1.2	50 ± 1.8	92.1± 0.4	90.1 ± 0.2	4
F2	3.2 ± 0.15	3.5 ± 0.04	98.07 ± 1.8	38.73 ± 1.1	96.6± 0.2	91.9 ± 0.1	4
F3	2.9 ± 0.23	3.6 ± 0.01	96.5 ± 2.7	23.1 ± 1.2	99.1± 0.4	92.6± 0.2	2
F4	3.4 ± 0.43	3.4 ± 0.02	96.47 ± 1.3	385 ± 2.3	94.4± 0.4	92.6 ± 0.2	4
F5	3.3 ± 0.36	3.6 ± 0.02	97.6 ± 2.24	215 ± 2.8	95.8 ± 0.2	95.0 ± 0.1	4
F6	3.1 ± 0.51	3.5 ± 0.01	97.6 ± 1.4	132 ± 2.6	91.6 ± 0.4	94.1 ± 0.2	4
F7	2.9 ± 0.69	3.8 ± 0.06	99.45 ± 0.9	270 ± 1.5	78.7 ± 0.4	75.7 ± 0.2	6
F8	3.5 ± 0.18	3.6 ± 0.02	97.6 ± 1.04	153 ± 1.8	81.7 ± 0.2	83.8 ± 0.1	6
F9	3.0 ± 0.26	3.5 ± 0.01	98.01 ± 1.9	96 ± 1.9	88.4 ± 0.4	86.6 ± 0.2	4
F10	3.8 ± 0.50	3.6 ± 0.06	96.45 ± 2.7	400 ± 2.8	54.7 ± 0.4	68.1 ± 0.2	8
F11	4.2 ± 0.22	3.7 ± 0.03	99.3 ± 1.51	280 ± 3.6	69.7 ± 0.2	65.9 ± 0.1	6
F12	4.1 ± 0.48	3.4 ± 0.03	98.12±1.99	169 ± 2.2	71.1 ± 0.4	70.68 ± 0.2	8

Table 4: Stability studies of F3 formulation.

Parameters	Duration of stability study						
	Initial 30±2°C/ 65±5% RH	2 months		4 months		6 months	
		30±2 °C/ 65±5%RH	40±2 °C/ 75±5%RH	30±2 °C/ 65±5%RH	40±2 °C/ 75±5%RH	30±2 °C/ 65±5%RH	40±2 °C/ 75±5%RH
% Drug release	96.45	96.38	96.35	96.27	96.24	96.19	96.12
% Friability	passes	passes	passes	passes	passes	passes	passes
Hardness (Kg/cm^2)	2.9	2.7	2.8	3.0	2.9	2.7	2.7
Disintegration time (s)	23.0	23.2	23.0	23.1	23.4	23.3	23.4