Research Article

Design, Development, and Optimization of Valsartan and Amlodipine Micro Tablets

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ABSTRACT

In the present study combination product of Amlodipine, 10 mg, and Valsartan 160 mg in the Capsule dosage form is developed through micro tablets technology. The effect of various excipients was studied through the Design of Experiments and optimization of the formulation was conducted to achieve the most suitable formulation. The manufacturing process was a simple direct compression process and can be scaled up to various manufacturing scale. The same formulation can be extended to various combinations of Valsartan and Amlodipine. The developed capsule dosage form had a similar drug release profile as that of the marketed formulations. The formulation with sufficient operational range was selected for comparison of drug release in various dissolution media with various pH along with the marketed formulation. The developed micro tablets with the larger surface area were found to have better results in dissolution studies.

Keywords: Micro tablet, Valsartan, Amlodipine, Capsules, DoE.

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INTRODUCTION

Micro-tablets are smaller tablets with a breadth normally equivalent to or less than 2,000 µm that are regularly filled into a capsule. It is conceivable to join various micro-tablets, everyone detailed separately to release to achieve a combinational drug release in the gastrointestinal tract, from one capsule. This approach can incorporate quick release, delayed release, as well as controlled release. It is additionally conceivable to fuse Micro-tablets of various drugs to treat simultaneous diseases or a combination of drugs to improve by and large helpful results while conveying particular release rates of each as indicated by disease necessities.

Depends upon the dose requirement the number of micro tablets can be increased or decreased for filling into the capsule. Dose titration is easily possible especially in treatments like hypertension where long term therapy is required and to be adjusted as per the therapeutically need. The manufacturing process flow is depicted as shown in **FIG.1**[1–4]

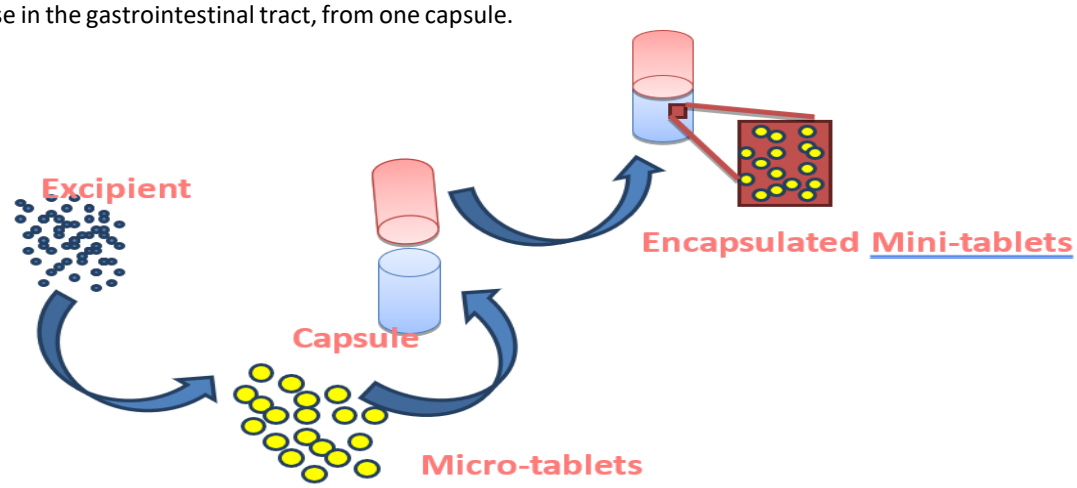

Figure 1: Micro Tablets Delivered as A Capsule

This study (Combination therapy vs. Monotherapy in Doubled-dose in hypertensive patients with inadequate Response to monotherapy, COMMODORE) was designed to answer the commonly encountered, specific clinical

question of whether the combination of a calcium channel blocker and an angiotensin receptor blocker (Amlodipine/Valsartan 10/160 mg) is superior to monotherapy with a double dose of a calcium channel blocker (Amlodipine 10 mg) when the initial conventional dose of the calcium channel blocker (Amlodipine 5 mg) has been inadequate in blood pressure (BP) control. There was a study that showed that Amlodipine 5 mg and Valsartan 160 mg showed comparable BP reduction, this comparison seems to be reasonable.[5]

It is difficult for small children and older men to take two tablets a day. Both drugs (Valsartan and Amlodipine) can be given in the same capsule as an encapsulated micro tablet.

MATERIALS AND METHODS

Table 1: Valsartan Micro Tablets Composition

	B. No: FV1		B. No: FV2		B. No: FV3		B. No: FV4		B. No: FV5	
Ingredients	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**
Valsartan	50.00	4.00	50.00	4.00	50.00	4.00	50.00	4.00	50.00	4.00
Avicel PH 102	45.50	3.64	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Avicel PH 302	0.00	0.00	45.50	3.64	0.00	0.00	22.50	1.80	21.50	1.72
Avicel PH 200	0.00	0.00	0.00	0.00	45.50	3.64	23.00	1.84	21.50	1.72
Crospovidone XL	2.50	0.20	2.50	0.20	2.50	0.20	2.50	0.20	5.00	0.40
Colloidal Silicon Dioxide(Aerosil)	1.00	0.08	1.00	0.08	1.00	0.08	1.00	0.08	1.00	0.08
Magnesium stearate	1.00	0.08	1.00	0.08	1.00	0.08	1.00	0.08	1.00	0.08
Total	100.00	8.00	100.00	8.00	100.00	8.00	100.00	8.00	100.00	8.00

Table 2: Amlodipine Micro Tablets Composition

	B. No: FA 1		B. No: FA 2		B. No: FA 3		B. No: FA 4		B. No: FA 5	
Ingredients	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**	**Qty per tab in %w/w**	**Quantity in mg/tab**
Amlodipine Besylate	8.675	0.694	8.675	0.694	8.675	0.694	8.675	0.694	8.675	0.694
Avicel PH 102	59.325	4.746	0.000	0.000	0.000	0.000	0.000	0.000	24.325	1.946
Avicel PH 302	0.000	0.000	59.325	4.746	26.000	2.080	36.000	2.880	42.000	3.360
Di Basic Calcium Phosphate	26.000	2.080	26.000	2.080	59.325	4.746	49.325	3.946	19.000	1.520
Sodium Starch Glycollate	5.000	0.400	5.000	0.400	5.000	0.400	5.000	0.400	5.000	0.400
Magnesium stearate	1.000	0.080	1.000	0.080	1.000	0.080	1.000	0.080	1.000	0.080
Total	100.000	8.000	100.000	8.000	100.000	8.000	100.000	8.000	100.000	8.000

40 micro tablets of B.NoFV5 and 20 micro tablets of B.NoFA5 are filled into Size #0 hard gelatin capsules to achieve Valsartan 160 mg and Amlodipine Besylate 10 mg in the capsule dosage form. New B. No FVA 01 was assigned for the combined capsule dosage form.

HPLC method development

Standard stock solutions

Standard stock solutions of amlodipine and valsartan were prepared separately by dissolving 50 µg of amlodipine besylate and 50 mg of valsartan in 50 mL acetonitrile and water (1:1). These solutions were prepared freshly every time, during method development and application period. Phosphate buffer solution 1.74 g of K_2HPO_4 was dissolved in 1 L of deionized water and pH was adjusted to 3.6 with orthophosphoric acid.[6–8]

Calibration standards

Calibration standards for amlodipine (as besylate salt) and valsartan (1.25, 2.0, 3.0, 4.0, 10.0, 20.0, 30.0, 40, and 50.0 µg/mL) were daily prepared from standard stock solutions by appropriate dilution processes using mobile phase.[11,12]

Instrumentation

The HPLC system consisted of Agilent 1200. A C18 column (Zorbax Eclipse XDB-C18, 5 µm, 2.1 mm × 150 mm) was used for separation and quantification. The mobile phase consisted of water: acetonitrile: trifluoroacetic acid (55:45:0.1 v/v/v) and was filtered through a 0.45 µm filter and degassed before use. The injection volume was 5 µL and the ultraviolet detector was set at 265 nm. Analyses were run at a flow rate of 0.4 mL/min at ambient temperature (25°C). The peak areas were integrated automatically using Empower ®software. Under these conditions, amlodipine and valsartan were eluted at 1.64 min and 4.08 min, respectively. Total run time was shorter than 7 min.[11,12]

Dissolution Study of selected formulation

Dissolution of 6 capsules was performed in pH 6.8 phosphate buffer, Volume: 900ml, Apparatus: USP type II (paddle type), Speed: 50rpm, Temperature: 37 ± 0.5°C, Sampling intervals, Five ml of sample was withdrawn and was replaced with an equal volume of fresh medium. Collected samples were analyzed at 209nm.[13–15]The concentrations of AMD and VAL in samples were determined by the proposed HPLC method. A dissolution study was conducted for B.No FVA 01 capsules. Cumulative percentage of drug releases of amlodipine and valsartan mentioned in **TABLE 3.**

Table 3: Dissolution profile of Valsartan and Amlodipine Capsules

Time (Min)	Valsartan B. No FVA 01	Amlodipine B. No FVA 01
5	36	28
10	58	62
15	72	77
20	82	86
30	96	96
45	98	98

Formulation Optimization

Various formulations were evaluated for the physical parameters. The breakage of tablets was the biggest challenge observed during the development. The grade of Avicel was playing a major role in controlling the breakage of micro tablets. Formulation B. No FV5 and B. No FA5 were selected respectively for Valsartan and Amlodipine for further formulation optimization as these formulations were promising in terms of physical parameters and later dissolution studies. The ranges selected were based on prior knowledge. The Design of Experiments study was conducted with Design expert software. [16–18]

The Mixture design was selected to study the effect of various excipients and optimization of concentration to achieve the desired responses. The optimization of response was conducted based on the physical properties of tablets. The Batch size studied for each trial was 20,000 tablets.

In both the micro tablets, Magnesium Stearate was not studied as part of formulation optimization. 17 runs were the number of trials suggested by the software. Micro tablet of valsartan and amlodipine DOE.

All the runs were executed in the same manufacturing process and the same equipment trial and the runs were followed exactly as per the order.

Dissolution Study

Valsartan and Amlodipine Capsules 160/10 mg were manufactured with 40 micro tablets of FV23 and 20 micro tablets of FA23 were manually counted and filled into Size #0 hard gelatin capsules. New B.No assigned was FVA02. To evaluate the drug release of the formulation, a dissolution study was conducted in various dissolution media. The media details are as follows.[6,19]

Table 4: Dissolution Media

S. No	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)
1	Type II (Paddle)	50	phosphate Buffer pH of 6.8	900
2	Type II (Paddle)	50	pH 1.2 Buffer	900
3	Type II (Paddle)	50	pH 4.5 Buffer	900

Temperature: 37 ± 0.5°C, Sampling intervals, 5,10,15,20,30,45,60,120,minutes. Five ml of sample was withdrawn and was replaced with an equal volume of fresh medium.

To compare the Dissolution profile of the developed formulation, the reference product Exforge Tablets 160/10 mg was also studied for drug release.

Dissolution Testing (Valsartan / Amlodipine)

Dissolution of 6 capsules was performed in pH 6.8 phosphate buffer, Volume: 900ml, Apparatus: USP type II (paddle type), Speed: 50rpm, Temperature: 37 ± 0.5°C, Sampling intervals, Five ml of sample was withdrawn and was replaced with an equal volume of fresh medium. Collected samples were analyzed at 209nm using the same as blank on the HPLC. Dissolution study was conducted for all formulations of Valsartan and Amlodipine.[20–24]

RESULTS AND DISCUSSION

Table 5: Valsartan Micro Tablet Results

Run No	B. No	Response 1: Individual weight % RSD	Response 2: Mean hardness (N)	Response 3: Friability (%)	Response 4: % Breakage (%)	Response 5: Disintegration Time (Seconds ')
1	FV6	2.68	35.8	0.24	1	169
2	FV7	6.9	26.8	0.49	9	130
3	FV8	2.9	35.3	0.23	1	160
4	FV9	4.4	31.8	0.27	4	140
5	FV10	4.6	31.6	0.29	4	148
6	FV11	7.5	28.4	0.62	10	88
7	FV12	2.8	33.5	0.22	1	236
8	FV13	4.62	30.8	0.49	3	142
9	FV14	5.2	33.5	0.41	3	222
10	FV15	5.4	32.1	0.43	3	78
11	FV16	4.2	31.8	0.27	1	81
12	FV17	4.7	32.1	0.42	3	141
13	FV18	7.2	27.6	0.68	10	244
14	FV19	2.52	34.6	0.2	0	212
15	FV20	2.82	35.6	0.19	0	82
16	FV21	3.1	33.4	0.29	2	170
17	FV22	4.2	31.8	0.51	3	145

Table 6: Amlodipine Micro Tablet Results

Run No	B. No	Individual weight (%RSD)	Average hardness (N)	% Friability	% Breakage	DT (Seconds)
1	FA6	2.500	38.900	0.190	3.000	88
2	FA7	3.900	36.200	0.380	7.000	95
3	FA8	4.200	36.900	0.360	6.000	91
4	FA9	2.600	41.300	0.250	4.000	106
5	FA10	2.800	35.800	0.220	3.000	132
6	FA11	3.500	38.200	0.360	5.000	94
7	FA12	4.900	38.600	0.480	10.000	116
8	FA13	3.300	41.200	0.350	5.000	87
9	FA14	2.700	42.900	0.320	4.000	88
10	FA15	4.600	40.100	0.620	9.000	83
11	FA16	3.600	33.800	0.350	7.000	87
12	FA17	3.600	43.700	0.440	8.000	168
13	FA18	4.100	42.900	0.540	8.000	174
14	FA19	3.300	38.200	0.380	6.000	101
15	FA20	2.600	34.500	0.190	4.000	128
16	FA21	2.400	36.900	0.160	2.000	83
17	FA22	2.500	40.300	0.180	2.000	89

Characterization of responses by design expert

ANOVA summary Response data were analyzed by ANOVA (Analysis of Variance) for the quadratic model. The results of Valsartan micro tablets are as below mentioned in **Table 7**: [25–27]

Table 7: ANOVA Summary For Valsartan Micro Tablets

Response	Model p-Value	Lack of fit (p-Value)	R^2 values	Predicted R^2 values	Adjusted R^2 values	Adequate Precision
Individual weight (% RSD)	<0.0001 (significant)	0.1100 (Not significant)	0.9711	0.9284	0.9615	27.8877
Mean Hardness (N)	<0.0001 (significant)	0.1729 (not significant)	0.9535	0.8972	0.938	25.6952
%Friability	0.0005 (significant)	0.9389 (not significant)	0.7917	0.6421	0.7223	10.0514
% Breakage	<0.0001 (significant)	0.1170(not significant)	0.9516	0.8982	0.9354	22.7962
Disintegration Time	<0.0001 (significant)	0.1105 (not significant)	0.9902	0.9659	0.9825	34.7510

Table 8: ANOVA Summary For Amlodipine Micro Tablets

Response	Model p-Value	Lack of fit (p-Value)	R^2 values	Predicted R^2 values	Adjusted R^2 values	Adequate Precision
Individual weight (% RSD)	<0.0001(significant)	0.2344 (not significant)	0.9697	0.9229	0.9516	21.9505
Mean Hardness (N)	<0.0001(significant)	0.7618 (not significant)	0.9569	0.8369	0.8369	20.5048
% Friability	<0.0001(significant)	0.297 (not significant)	0.9739	0.923	0.9583	26.2602
% Breakage	<0.0001(significant)	0.2069 (not significant)	0.9264	0.7106	0.8822	14.7759
Disintegration Time	<0.0001(significant)	0.4638 (not significant)	0.9623	0.9104	0.9396	20.126

The 'p' values indicate the variance, the low 'p' values of all the responses show the model is significant. Lack of fit 'p' value for all the responses were not significant. Thus, Design expert recommends the studied model is fit. "Adequate precision" measures the signal to noise ration. A ratio greater than 4 is desirable and indicates a strong signal to be used for optimization. Thus, the adequate precision for all responses indicates adequate signal and can be used to navigate the design space. The difference between predicted 'R^2' to the adjusted 'R^2' for all responses were less than 0.2 indicates the model is fitted and can reliably be used to interpolate. ANOVA summary for valsartan and amlodipine mentioned in Table 8.

Final Equation in Terms of Actual Components

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor.

Based on the model equation for Individual weight, the %RSD is mainly dependent on fillers in both Valsartan and Amlodipine micro tablet. As it is a direct compression process the flow is mainly dependent upon the fillers. Although the coefficient of Crospovidone also shows its effect on %RSD, the total of fillers coefficient is higher than the coefficient of Crospovidone in Valsartan micro tablets. There were 3 fillers used in Amlodipine micro tablets, the DoE study evaluated the significance of each filler with its presence and absence through various experiments. Based on the study outcome and model equation the presence of all three fillers is required to achieve a satisfactory formulation of the Amlodipine micro tablet.

In valsartan micro tablets, in all the responses the presence of both Avicel PH 302 and Avicel PH 200 was shown an important role. Thus, both the grades of Avicel are necessary for a satisfactory formulation. The flow of blend is an important criterion in achieving satisfactory weight. Colloidal Silicon dioxide was shown to be important in achieving all the responses in the Valsartan micro tablet. In the disintegration time of the Valsartan micro tablet, Crospovidone plays a significant role in comparison to fillers. Similarly, in the Amlodipine micro tablet also the coefficient of disintegrant Sodium Starch Glycollate was proven to have a significant role in the disintegration of the

formulation. However, in Valsartan micro tablet Crospovidone and Sodium Starch Glycollate in Amlodipine Micro tablet had an inverse relation in controlling the breakage. As the disintegrants have a major role in controlling the disintegration time in both the micro tablet the concentration cannot be significantly reduced. So during the optimization, this needs to be studied further. The various grades of Avicel were important in achieving satisfactory breakage in both Amlodipine and Valsartan micro tablet.

Trace plots are advantageous in evaluating the effect of all the factors on one response plot. The effect of changing each component along an imaginary line from the reference blend to the vertex. This also provides the broadest coverage of the experimental space. Thus, the component which affects the most in any particular response can be studied. The length of each line depends upon the concentration of the factor used.

Among the Trace plot, the Disintegration time graph of both valsartan and Amlodipine clearly shows the significance of Disintegrate in the formulation. A slight change in the concentration shows the biggest shift in the graph.

All the fillers used in the formulation indicates significant in achieving the satisfactory responses in both Valsartan and Amlodipine micro tablets. The relative effects coming up from all the factors can be understood using Trace plots.

The Dibasic Calcium Phosphate in Amlodipine Micro tablets indicates a significant role in the breakage of micro tablets which is the case in friability also. Thus, breakage and friability are inter-related responses and significantly dependent upon Di Basic Calcium Phosphate in the formulation.

Optimization of Formulation

Based on the factors and responses studied Design Expert system proposed Solutions for the composition of both the formulation to get a satisfactory formulation.

Four compositions were suggested by Design expert software. It was decided to evaluate the composition with the highest desirability. So thus Trial 1 was selected for further studies.

Solutions: Amlodipine.

A total of seven solutions were suggested by the software. Sodium starch Glycollate was a similar quantity in all the proposed solutions. Although much difference was not seen in the number of other components based on the highest desirability trial number 1 was selected for further studies.

Optimization batch

Optimized batch B.NO FV23, valsartan micro tablets, and B.NO FA 23 amlodipine micro tablets mentioned in **Table 9** and **Table 10.**

Table 9: B. No FV23, Valsartan Micro Tablets.

S. No	Number	mg/ micro tablet	%w/w
1	Valsartan	4.00	50.00
2	Avicel PH 302	1.41	17.63
3	Avicel PH 200	2.06	25.75
4	Crospovidone XL	0.41	5.13
5	Colloidal Silicon dioxide	0.04	0.50
6	Magnesium stearate	0.08	1.00
	Total	8.00	100.00

Table 10: B. No FA 23 Amlodipine Micro Tablets.

S. No	Number	mg/ micro tablet	%w/w
1	Amlodipine Besylate	0.69	8.68
2	Avicel PH 102	2.841	35.51
3	Avicel PH 302	2.716	33.95
4	Dibasic Calcium Phosphate	1.069	13.36
5	Sodium Starch Glycollate	0.600	7.50
6	Magnesium stearate	0.080	1.00
	Total	8.00	100.00

The %RSD was less than the predicted values in both Valsartan and Amlodipine micro tablets. This indicates the weight variation was well controlled. The average hardness achieved in Valsartan was higher than the predicted hardness range. However, in Amlodipine the observed values were less than the average predicted hardness. The friability of both formulations was very close to the predicted ranges. Breakage was not observed in both Valsartan and Amlodipine micro tablets. The disintegration time was lower in the Valsartan micro tablet whereas in the Amlodipine micro tablet it was slightly more. Overall, all the physical parameters were satisfactory and thus this composition was preferred for further evaluation in Dissolution.

The Dissolution study of optimized formulation

In vitro dissolution of six tablets containing AMD and VAL was performed using phosphate buffer (pH 6.8) as the dissolution media at 50 rpm using a USP Apparatus II. The dissolution study was carried out in a 900 mL volume of phosphate buffer at 37 °C (± 0.5) using the paddle method. Five mL of sample was withdrawn and replaced with fresh dissolution medium at the time intervals of 5, 10, 15, 20, 30, 45, 60, and 120 minutes.[6,28]Amlodipine cumulative drug release (%) and valsartan cumulative drug release (%) are mentioned in **Table 11.**

Dissolution study performed in Exforge tablets B.No: BCY17 and Test product B.NoFVA02

Table 11: Amlodipine Cumulative Drug Release (%)

Time in minutes	Amlodipine Cumulative drug release (%)					
	pH 6.8 Phosphate Buffer,		pH 1.2 Buffer		pH 4.5 Buffer	
	Exforge	Test product	Exforge	Test product	Exforge	Test product
5	69.3	54.5	65.8	52.4	14.8	12.4
10	80.6	82.8	73.1	75.6	25	26.3
15	87.7	88.9	74.7	78.6	34.9	38.6
20	92.4	93.6	82.3	86.4	43.8	46.7
30	96.8	98.6	92.3	94.6	56.3	62.3
45	98.9	99.2	94.9	96.6	69.9	76.3
60	100	100.5	98.2	98.9	80.1	88.2
120	100.8	100.8	100.7	100.2	89	96.4
F2	61.7		61.9		64.8	

The developed Valsartan/ Amlodipine Capsules 160/10 mg were studied in multimedia dissolution and compared against the reference product Exforge Tablets 160/10 mg. All the Dissolution profiles of both Amlodipine and Valsartan were comparable with the reference product dissolution profile. The similarity factor F2 was above 50 in all the comparative dissolution profile. The first time point of 5 minutes drug release was slightly slow in most of the dissolution profile. This may be because of the capsule shell opening time.

CONCLUSION

The present study demonstrated the successful micro tablet encapsulated formulation and evaluation of two antihypertensive agents in a single dosage form as a capsule. The formulation development was carried out through the Design of experiment studies with mixture design for optimization of the composition. The developed formulation demonstrated a comparable drug release profile in multimedia dissolution in comparison with Exforge tablets.

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