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Formulation development and evaluation of immediate release tablets containing antihypertensive agent amlodipine besylate and valsartan

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Abstract
The main aim of this study was to formulate the immediate release tablet containing Amlodipine besylate as calcium channel blocker and Valsartan as angiotensin II receptor blocker. The advantage of this combination therapy for hypertension include better blood pressure control by synergistic combination of angiotensin II receptor blocker with calcium channel blocker. The objective of the present study was to formulate and evaluate an oral administrable tablet containing Amlodipine besylate and Valsartan by different granulation technique. The tablets were prepared using different excipients and crospovidone is used as a disintegrant.

The prepared tablets were evaluated for various pre-compression characteristics like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and post-compression characteristics like appearance, weight variation, hardness, thickness, disintegration, friability, In vitro dissolution study etc. The stability studies were carried out for the optimized batch for three months and it showed no significant changes in the physicochemical parameters and in vitro release pattern. The present study concludes that combined pill has the potential to improve the management of hypertensive patients with additional cardiovascular risk factors and reducing prescription costs.

Keywords: Formulation development, immediate release, antihypertensive agent

Introduction

The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes: First- the disintegration of tablet into granules and second- dissolution of these granules through the GIT into the blood. Disintegration is the rate-limiting step in case of highly soluble drugs whereas dissolution is the rate limiting step in case of drugs with low solubility.

The release of drug from an immediate release dosage form can be achieved by placing the drug in a layer or coating that is sufficiently thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a rapid rate.

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption.

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Super disintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants.

Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrant [1, 2].

Hypertension, commonly referred to as "high blood pressure", is a medical condition where the pressure is chronically elevated, is one of the commonly found diseases, affecting most of the populations in the world. So, for treating hypertension effectively is main criterion of this study. For treating hypertension, commonly used drugs include angiotensin receptor blockers, ACE inhibitors, α blockers, β blockers, calcium channel blocker, diuretics and combination of any of these categories in immediate action required. The advantage of this combination therapy for hypertension include better blood pressure control by synergistic combination of

angiotensin II receptor blocker with calcium channel blocker.

Materials and Methods

Materials

Amlodipine besylate, Valsartan, microcrystalline Cellulose dicalcium phosphate and sodium starch glycolate were received as gift sample from Glochem Pharma, and Roguette Pharma, Mumbai respectively. All other chemicals and reagents used were of analytical reagent grade.

Methods

1. **Solubility studies:** Buffers of different pH were prepared according to the procedure in IP 2012. 1 g drug was weighed and transferred to 200 ml volumetric flask. 100 ml of each buffer was added to the respective flasks and flasks were placed on mechanical shaker adjusted at 150 rpm for 24 hours. After 24 hours, each solution was filtered using 0.45µm nylon filter. The solubility of the drug in different buffers was determined initially and at the end of 24 hours after shaking [4].
2. **UV spectroscopy:** Accurately weighed about 100 mg of Amlodipine besylate and Valsartan and dissolved in phosphate buffer (pH 6.8). Diluted the solution to 100ml with phosphate buffer (pH 6.8). Further 10 ml of this solution was diluted to 100ml with phosphate buffer (pH 6.8). The resultant solution was scanned for absorption maxima (λ_{max}) spectro photo metrically between 200nm and 400nm [5].
3. **Infrared spectroscopy:** IR spectrum of drug was measured in the solid state as potassium bromide (KBr) mixture. The pure Amlodipine besylate and Valsartan was previously ground and mixed thoroughly with KBr, an infrared transparent matrix at 1:100 (sample: KBr) ratio, respectively. The KBr pellets were prepared by applying 10-12 metric ton of pressure in a motorized pellet press (Kimaya engineers, India). The pellets were then scanned over a wave range of 4000 – 400 cm^{-1} and spectra was obtained by using a Shimadzu –IR Prestige-21 spectrophotometer [5].

Formulation of tablets

Table 1: Formulation of tablets by different methods

Sr. no.	Ingredients	Quantity (mg/tab)			
		By Direct compression (F1)	By slugging approach (F2)	By wet granulation (F3)	
Dry mix				Dry mix I	Dry mix II
1	Amlodipine besylate	10.00	10.00	10.00	-
2	Valsartan	160.00	160.00	-	160.00
3	Microcrystalline cellulose	75.25	71.00	87.00	85.50
4	Crospovidone	30.00	30.00	-	30
5	Colloidal silicon dioxide	-	1.50	-	-
6	Magnesium stearate	-	3.00	-	-
7	Pregelatinised Starch	-	-	15.00	-
8	Dicalcium phosphate	-	-	79.50	-
				Granulation make by water	
Prelubrication					
9	Crospovidone	10.00	12.00	19.00	
10	Colloidal silicon dioxide	0.75	10.00		
Lubrication					
11	Magnesium stearate	3.00	3.00	3.00	
Total weight		300	300	490	
Coating					
12	Opa. dry yellow	9.00	9.00	14.70	
13	Water	qs	qs	qs	
Targeted weight		309	309	504	

Evaluation

A) Physical evaluation of tablet blend

Angle of repose [8]

Angle of repose was determined by measuring the height of the cone of the powder and calculating the angle of repose from following formula.

$\tan\theta = h/r$

Where,
h = height of cone
r = radius of powder cone

Bulk density [8]

Bulk density was determined by pouring gently 20 gm of sample through a glass funnel into a 100 ml graduated cylinder. The powder was carefully leveled without compacting it and the apparent volume was measured (V_o). Bulk density was calculated by following formula,

Bulk density = M/Vo

Where,
M = mass of powder
V_o = apparent unstirred volume

$$\text{Bulk Density (g/ml)} = \frac{\text{Mass of powder ( )}}{\text{bulk volume of the powder (Vo)}}$$

Tapped density [8]

The tapped density was determined by pouring 20 gm sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated by following formula,

$$\text{Tapped Density (g/ml)} = \frac{\text{Weight of powder}}{\text{Tapped volume of the powder}}$$

Carr's index [8]

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. Carr's index is also known compressibility index and which was calculate as,

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio [8]

It provides an indication of the degree of densification that could result from vibration of feed hopper. Lower the Hausner's ratio better is the Flow ability.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

B) Evaluation of tablets

Weight variation test [9]

Twenty tablets of each formulation were weighed individually using an electronic balance. The average weight was calculated and individual tablet was compared with the average value and the deviation was recovered.

Dimension

Compressed tablets were selected randomly from each batch and thickness, length was measured by using digital vernier caliper. Thickness was measured in mm for all batches.

Hardness [9]

Hardness of the tablets was measured using Pfizer hardness tester. The hardness was measured in Newton (N) for tablets of each batch.

Friability test [9]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. (according to USP monograph 1216 - tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 gm.) Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions/min. Tablets were dusted and reweighed. The percentage friability was calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

Percentage weight loss was calculated. A loss of less than 0.5 to 1 % in weight was generally acceptable.

Disintegration study [9]

The process of breakdown of a tablet into smaller particles is called as disintegration. The disintegration time of a tablet was determined using disintegration test apparatus. The disintegration test was carried out using USP disintegration test apparatus-II. Tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water (900 ml) was used as the medium which is maintained at 37 ± 2°C and the time taken for each tablet to disintegrate completely was recorded.

Dissolution study [10]

In-vitro release profile studies of immediate release Tablets were carried out using USP type II dissolution apparatus. Tablet was kept in a flask having paddle rotated at 75 rpm. The medium used for release rate study was 900 ml 6.8 pH phosphate buffer. During the course of study whole assembly was maintained at 37˚C ± 0.5ºC and 5 ml sample was withdrawn at time interval 5, 10, 15, 30 and 45 min. The samples were analyzed by HPLC for calculating the amount of drug released.

Stability study [18, 19]

The formulation for stability testing was selected on the basis of optimization results. The batch with optimum dissolution results (Batch F3) was selected for stability purposes. According to ICH guidelines Accelerated stability studies are testing at $40^0C \pm 2^0C/75 \pm 5\%RH$ for a specific period up to 3 months. The tablets were checked before stability studies for parameters like physical appearance, hardness, assay, weight variation, and % drug release of the drug.

Results and Discussion

Solubility studies

The solubility of amlodipine besylate in water, 0.01N HCl, pH 1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer was reported as 757.75, 1823.77, 1724.38, 1055.97 and 1949.42 respectively. From the above discussion, it is concluded that the amlodipine besylate is sparingly soluble in pH 6.8 phosphate buffer solution.

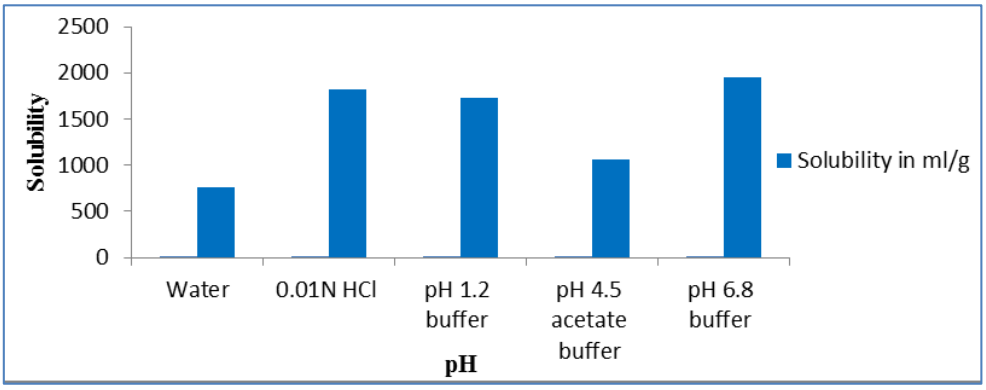

Fig 1: Solubility in ml/g of amlodipine besylate

The solubility of Valsartan in water, 0.01N HCl, pH 1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer was reported as 649.61, 741.07, 568.65, 613.96 and 1302.8 respectively. From the above discussion, it is concluded that the Valsartan is sparingly soluble in pH 6.8 phosphate buffer solution.

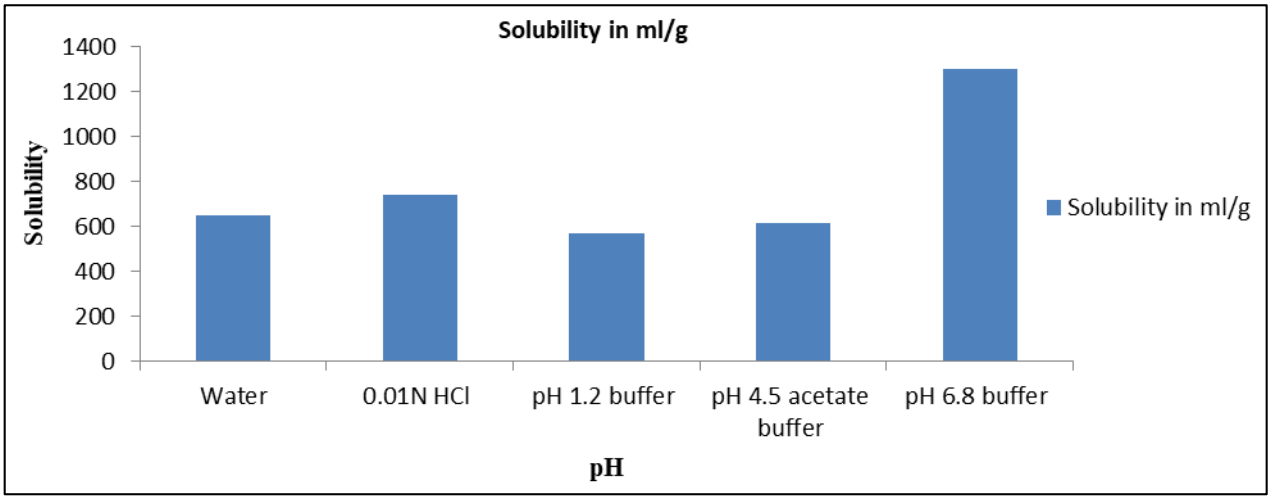

Fig 2: Solubility in ml/g of Valsartan

UV spectroscopy

Table 2: Preparation of standard calibration curve of amlodipine besylate (λ_{max}364)

Sr. No	Conc. ppm	Absorbance
1	0	0
2	5	0.153
3	10	0.234
4	15	0.356
5	20	0.542
6	25	0.648

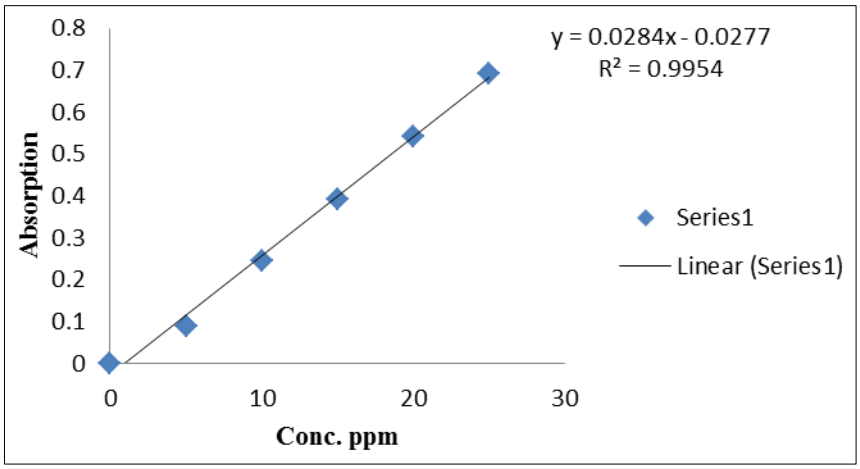

Fig 3: Calibration curve of Amlodipine besylate in pH 6.8 phosphate buffer

Table 3: Preparation of standard calibration the curve of valsartan (λ_{max}249)

Sr. No	Conc. ppm	Absorbance
1	0	0
2	5	0.216
3	10	0.324
4	15	0.433
5	20	0.541
6	25	0.649

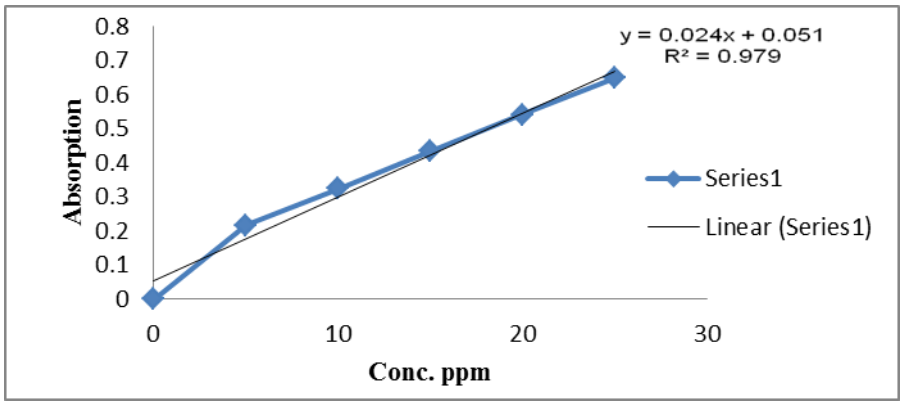

Fig 4: Calibration curve of Valsartan in pH 6.8 phosphate buffer

Infrared spectroscopy

Amlodipine besylate: IR spectra are shown in fig.6. The pure amlodipine besylate showed various characteristic peaks at 721.30, 2852.72, 1303.88, 2920.23 and 1269.16 cm^{-1}. The peak at 721.30 shows C-Cl bending, 2852.72 shows –C-H stretching, 2920.23 shows C-H stretching and 1269.16 shows C-O stretching.

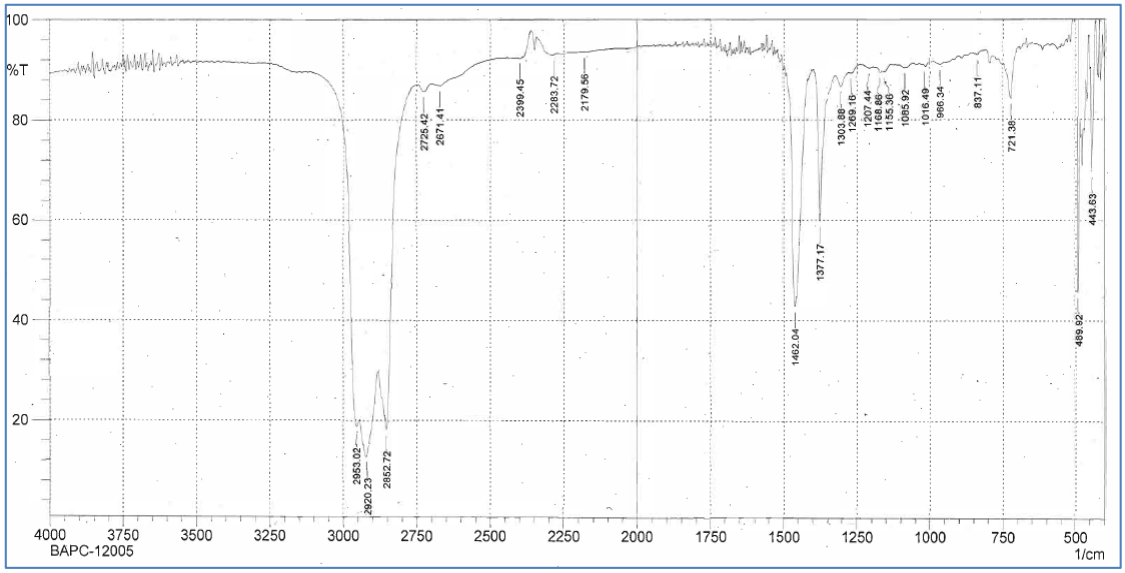

Fig 5: IR spectra of amlodipine besylate

Valsartan: IR spectra are shown in fig.7. The pure drug Valsartan showed various characteristic peaks at 2982.88, 1730.15, 1479.40 and 759.92 cm^{-1}. The peak at 759.92 shows an aromatic compound may be present, 2982.88 shows C-H stretching, 1479.40 shows CH_2bending and 1730.15 shows CO stretching.

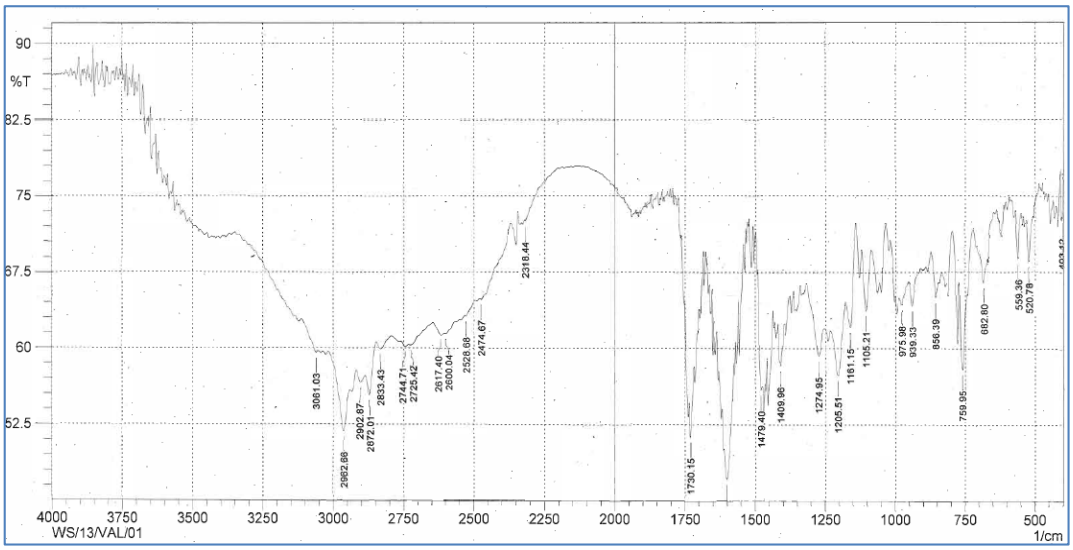

Fig 6: IR spectra of Valsartan

Table 4: Physical evaluation of Tablet blend

Sr. No.	Parameters	F1	F2	F3
	Angle of Repose	44	47	39
	Tapped density(g/ml)	0.521	0.646	0.785
	Bulk density (g/ml)	0.373	0.466	0.67
	Compressibility Index (%)	26.8	27.9	17
	Hausner's ratio	1.32	1.36	1.18

Table 5: Evaluation parameters of Tablets

Trial	F1	F2	F3
Targeted wt per tablet (mg)	309	309	504
Thickness (mm)	5.17	5.19	5.6
Length (mm)	12.97	12.92	16.06
width (mm)	6.97	6.92	8.06
Hardness(N)	168	120	170
Disintegration time	2min 20sec	1min 59sec	1min 32sec
Assay (%) Amlodipine besylate valsartan	99.2% 101.2%	98.5% 100.1%	99.5% 101.9%

Evaluation of tablets

Dissolution profile

The influence of different granulation method on the dissolution of amlodipine besylate and valsartan from tablets is shown in fig.8 and fig.9 respectively. From the dissolution profile, the better drug release observed for amlodipine besylate and Valsartan by wet granulation method. Immediate release tablets prepared by using wet granulation showed the drug release 88.2% for amlodipine besylate and 98.8% for valsartan.

Table 6: Dissolution profile for amlodipine besylate

Time	F1	F2	F3
0	0	0	0
5	38.2	37.8	49.8
10	47.7	51.6	58.6
15	59.2	56.6	69.4
20	64.9	59.1	79.8
30	72.4	63.2	85.6
45	78.1	65.5	87.9
60	84	70.9	88.2

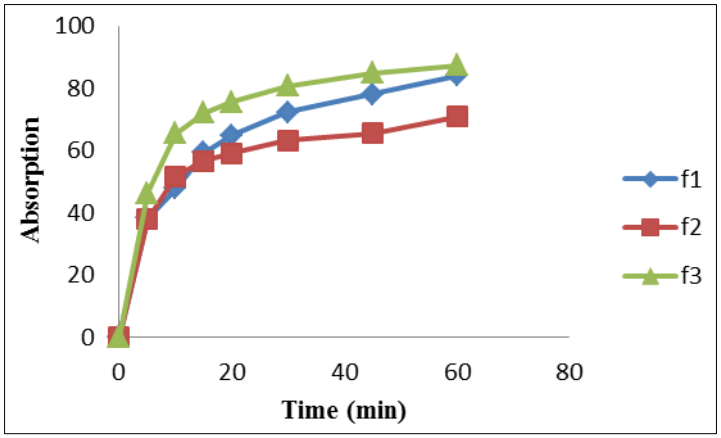

Fig 7: Dissolution profile of development trials. (For amlodipine besylate)

Table 7: Dissolution profile for valsartan

Time	F1	F2	F3
0	0	0	0
5	90.5	91.3	94.3
10	91.7	93.9	97.6
15	92.3	95.1	97.7
20	92.8	95.5	97.9
30	95.02	97.8	98.4
45	95.3	98.1	98.6
60	97.5	98.3	98.8

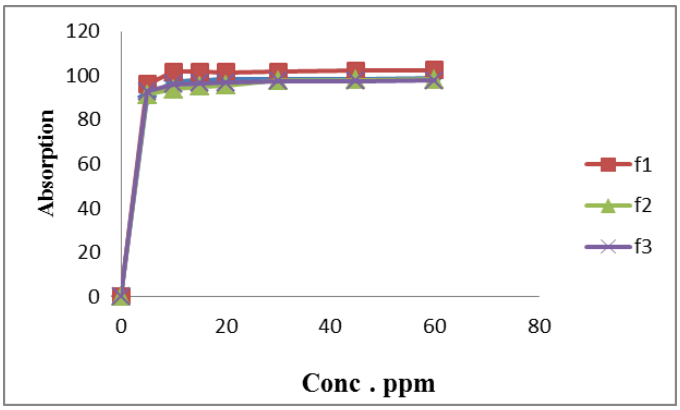

Fig 8: Dissolution profile of development trials. (For Valsartan)

Stability study

Table 8: Stability batch observation

Storage condition	Room Temperature	40 ^{0}C/75%RH
	Initial	3 Months
Formulation Batch	F3	F3
Parameters	-	-
Appearance	Light Yellow Colored	Light Yellow Colored
Hardness(N)	130	130
Width(mm)	8.05	8.05
Thickness(mm)	5.51	5.53
Length(mm)	16.05	16.05
Assay of Amlodipine besylate Assay of Valsartan	98.23% 99.45%	98.76% 99.41%

Table 9: Stability Dissolution Profile of Batch F3

Sr. no.	Time	Initial		3 months (F3 Batch)	
		Amlodipine besylate	Valsartan	Amlodipine besylate	Valsartan
1.	0	0	0	0	0
2.	5	49.8	94.3	50.1	93.2
3.	10	58.6	97.6	57.2	97.4
4.	15	69.4	97.7	71.9	97.6
5.	20	79.8	97.9	77.4	97.9
6.	30	85.6	98.4	84.3	98.5
7.	45	87.9	98.6	86.4	98.6
8.	60	88.2	98.8	87.9	98.8

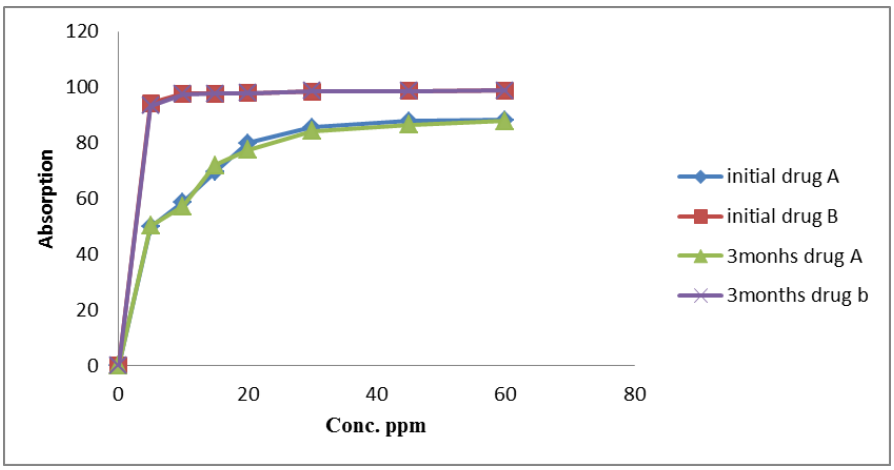

Fig 9: Stability Dissolution Profile of Batch F3
Footnotes: drug A- Amlodipine besylate drug B- Valsartan

Conclusion

In this work, successfully developed immediate release tablet of Amlodipine besylate and Valsartan in combination. In this study, the tablet prepared by the wet granulation method and granulation is the key process in the production. Granules of different formulations were evaluated for pre-compression parameters which indicate good flow properties of the granules. The prepared tablets of different formulation were

evaluated for post-compression parameters. The in vitro drug release characteristics were studied using USP dissolution apparatus type II for both the Amlodipine besylate and Valsartan indicated that the formulation F3 was the optimized formulation.

The optimized tablet formulation F3 showed satisfactory results in several in vitro tests also optimize batch tablets were stable and retain their pharmaceutical properties over a period of 3 months at 40^0C /75% RH.

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