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Design and Evaluation of Bilayered Tablets of Amlodipine Besilate with Enalapril Maleate

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ABSTRACT

Bilayer tablets of Amlodipine Besilate (Immediate Release) Enalapril Maleate (Sustained Release) were formulated for treatment of hypertension. The main objective of this combination is to encourage the low doses of drug to reduce patients BP, to reduce the dose dependent side effects. Twelve different formulations are prepared with amlodipine as immediate release layer and Enalapril maleate as sustained release layer .In the formulation of immediate release sodium starch glycolate were used as a superdisintegrant and was directly compressed .In sustained release portion cross povidone polymer were used in granulation stage and also extra granularly. Pre-compression studies were performed before compression. All the evaluated parameters of the optimized formula showed the Enalapril Maleate drug release over a period of 12 hours and the amlodipine Besilate shows at 1hour. IR studies revealed that there is no disturbance peaks of pure drugs Amlodipine Besilate and Enalapril Maleate. The stability studies were carried out for the optimized formulation for acceptable results. The kinetic studies for the formulation were formulated .The optimized formulation of bilayer tablet showed good release profile and are within pharmacopoeial limits .The optimized formulation shows Non-Fickian diffusion mechanism and this formulation is subjected to stability studies. It showed acceptable results.

1. INTRODUCTION

In the recent times, multi-layer matrix tablets are giving importance in the design of oral Controlled drug delivery systems. Bi-layer tablets are novel drug delivery systems where Combination of two or more drugs in a single unit. To co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing.[1] In the present study a combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure, minimize dose dependent side effects and adverse reactions. Amlodipine Besilate is second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a half-life of 20-30 hours and the initial effects are cumulative over many days & more over for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose.[2] Enalapril maleate is a prodrug, it is angiotennsin inhibitor enzyme .This ACE inhibitor used to treat high blood pressure, diabetic kidney disease, heart failure. It has half-life of 11 hours. Inhibition of ACE decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure.[3]

2. MATERIALS AND METHODS

Formulation of bilayer tablets: Amlodipine Besilate, Enalapril Maleate, Sodium starch glycolate, Crosscaremellose sodium, Sodium bicarbonate, Crosspovidone, Mint flavour, Microcrystalline cellulose, Sodium saccharin, Magnesium stereate, Talc. These chemicals was obtained as a gift sample from the active pharma Pvt. Ltd.

Preparation of bilayer tablets: The bilayer tablets was prepared by using Amlodipine immediate release powder and Enalapril Maleate sustained release powder in a concave shape punch compression machine. During the formulation the sustained released layered powder were introduced first into the die followed by slight pre-compression for uniform distribution of powder of immediate released layer was added then final compression was made to form bilayered tablet.[4]

The Bilayer tablets were prepared by direct compression method. The tablets were evaluated for their hardness, friability, and weight variation, thickness, disintegration and in-vitro drug release. The optimized formula was f11.The tablet hardness of different formulation was measured by using Monsanto Hardness tester. The thickness is measured by using screwguage. Randomly 10 tablets were taken from each formulation and their thickness was measured. Friability test is performed by using a laboratory friability tester Roche friabilator. 10 tablets at a speed of 25 rpm, dropping the tablets from a distance of 6 inch with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process the tablets were deducted and weighed. Percentage loss of tablet weight was calculated .The limit for friability is NMT 1%

Weight variation test for 20 tablets which were randomly selected from each formulation and their weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight .The mean ± S.D were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit & if no tablet differs by more than 2 times the percentage limit. For measuring drug content uniformity 5 tablets are taken and weighed .The tablets are then triturated into a fine powder from that 100mg of the powder is taken and in 100ml volumetric flask and is diluted with distilled water . The powder is allowed to dissolve in solvent, the solution was filtered & 1ml of filtrate was taken in 10ml of volumetric flask and diluted up to the mark with distilled water & analyzed spectrophotometrically at 235nm. Drug content studies were carried out in triplicate for each batch of formulation.

In-vitro dissolution study:

For Amlodipine Besilate (IR): Dissolution parameters: Dissolution studies for amlodipine were performed by using pH 1.2 buffer: 900ml using dissolution apparatus type 2 (paddle) with rotating speed of 75 rpm & temperature of 37±0.5℃. Samples are withdrawn at the time intervals 5, 10, 15, 20 until 60mins and the dissolution samples were analyzed spectrophotometrically at 237 nm using UV Visible spectrophotometer.[6]

For Enalapril maleate (SR): Dissolution studies were performed by using pH 6.8 buffer 900ml volume using dissolution apparatus type 2 with rotating speed of 75 rpm & temperature 37±0.5℃.Samples are withdrawn at the time the time intervals 1, 2, 4, 6, 8, 10, 12 hours .The dissolution fluids were analyzed spectrophotometrically at 230 nm using UV-visible spectrophotometer.[6]

3. RESULTS AND DISCUSSION

Bilayered tablets of amloipine with enalapril were prepared by using different polymers like crospovidone, sodium starch glycolate used as a super disintegrants. The tablets were fabricated using direct compression. The pre blend powders of sustained release layer and immediate release layer were characterized. The pre-compresssion and post-compression parameters of tablet hardness 4.66kg/cm^2,friability0.4389, thickness 4.10 mm, weight variation 701.0mg, and drug content 95.546 mg were optimized. We can conclude that all formulations were prepared with good quality.

In-vitro dissolution study of Amlodipine (IR): The in-vitro dissolution profile of amlodipine were obtained. This shows the satisfactory release of amlodipine from immediate release layer showed 98.2% release in 60 min .

In vitro dissolution study for Enalapril (SR): The in-vitro dissolution profile of enalapril were obtained .This shows the satisfactory release of enalapril from sustained release layer showed 98.65% release in 12hours.

Table.1.Formulation of amlodipine besilate immediate release layer (in mg)

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Amlodipine besilate	4	4	4	4	4	4	4	4	4	4	4	4
Sodium starch glycolate	25	23	21	19	17	25	23	21	19	17	25	23
Sodium bicarbonate	18	20	22	24	26	18	20	22	24	26	18	20
Lactose	2	2	2	2	2	2	2	2	2	2	2	2
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight	50	50	50	50	50	50	50	50	50	50	50	50

Table.2.Formulation of Enalapril maleate as sustained release layer (in mg)

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Enalapril maleate	10	10	10	10	10	10	10	10	10	10	10	10
Hpmc	1	0	2	4	6	1	0	2	4	6	1	0
Croscarmellose sodium	0	1	2	2	2	0	1	2	2	2	0	1
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
Avicel PH-102	106.5	106.5	103.5	101.5	99.5	106.5	106.5	103.5	101.5	99.5	106.5	106.5
Sodium saccharin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mint flavor	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Table.3.Evaluation of pre-compression parameters for Amlodipine Besilate

Formulation code	Angle of repose	Bulk Density	Tapped Density	Hausner's ratio	% Compressibility
FI 1	27.64	0.6	0.68	1.13	12.09
FI 2	29	0.59	0.68	1.14	12.1
FI 3	28.77	0.6	0.71	1.17	12.01
FI 4	26.11	0.63	0.70	1.12	11.46
FI 5	26.65	0.61	0.7	1.13	12.56
FI 6	27.15	0.65	0.69	1.15	12.68
FI 7	26.55	0.61	0.67	1.14	12.95
FI 8	27.59	0.62	0.68	1.16	12.34
FI 9	28.03	0.6	0.69	1.14	12.26
FI 10	29.35	0.62	0.7	1.15	12.32
FI 11	27.22	0.63	0.71	1.16	12.65
FI 12	26.58	0.59	0.68	1.17	12.49

Table.4.Evaluation of pre-compression parameter for Enalapril maleate

Formulation Code	Angle of Repose (ɵ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's ratio	% Compressibility
FS1	25.46	0.61	0.74	1.21	16.71
FS2	27.76	0.59	0.6	1.13	13.69
FS3	23.3	0.63	0.72	1.14	14.60
FS4	30.86	0.60	0.68	1.12	13.91
FS5	26.00	0.62	0.70	1.13	14.25
FS6	24.03	0.63	0.70	1.12	12.81
FS7	24.33	0.60	0.71	1.17	14.11
FS 8	27.33	0.59	0.70	1.18	13.23
FS 9	30.46	0.57	0.66	1.14	13.79
FS10	23.33	0.60	0.73	1.20	19.22
FS11	22.23	0.57	0.64	1.12	12.52
FS12	24.66	0.65	0.73	1.12	13.03

Table.5.Evaluation of post compression parameters

Formulation Code	Uniformity of Thickness (n=3) (mm)*	Hardness (n=3) (kg/cm^2)*	Friability % (n=10)	Uniformity of Weight (n=20) (mg)*	Drug Content (n=3) (mg)*
FT1	4.1	4.76	0.3972	698.9	93.63
FT2	4.20	4.36	0.2388	701.3	94.84
FT3	4.08	4.53	0.2807	700.4	91.45
FT4	3.98	4.9	0.2794	699.3	92.53
FT5	3.96	4.26	0.3180	699.5	95.54
FT6	4.36	4.73	0.3604	698.3	94.50
FT7	3.94	4.76	0.2401	699.9	93.25
FT8	3.85	4.56	0.4801	700.2	91.49
FT9	3.84	4.46	0.4769	701.8	96.94
FT10	3.94	4.46	0.3607	700.5	91.52
FT11	4.10	4.66	0.4389	701.0	97.54
FT12	4.07	4.7	0.4401	697.4	91.55

Evaluation of Dissolution Studies:

Table.6.In-Vitro Dissolution profile of the formulations of FI1, FI2, FI3 & FI4

pH 1.2 buffer, 900 mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}c				
Time (min)	Cumulative percent drug release			
	FI1	FI2	FI3	FI4
0	0	0	0	0
5	35.49	37.85	43.04	65.76
10	37.38	39.34	50.91	71.37
15	43.08	48.89	56.89	73.50
20	45.25	51.51	60.84	86.82
25	51.84	57.61	63.38	86.93
30	56.23	70.44	66.59	88.82
40	60.34	72.29	70.25	92.58
50	68.53	74.30	71.91	95.43
60	71.84	79.60	74.04	97.36

Table.7.In-Vitro Dissolution profile of the formulations of FI5, FI6, FI7&FI8

pH 1.2 buffer, 900mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}c				
TIME (min)	Cumulative percent drug release			
	FI 5	FI 6	FI 7	FI 8
0	0	0	0	0
5	59.06	39.42	32.03	46.42
10	67.23	39.89	38.48	52.19
15	72.45	42.43	44.26	58.04
20	76.38	46.74	50.22	62.82
25	82.35	52.12	55.04	64.32
30	87.12	57. 42	62.28	67.28
40	92.58	62.32	72.14	73.14
50	96.43	71.84	75.29	76.32
60	98.25	72.24	79.80	76.89

Table.8.In-Vitro Dissolution profile of the formulations of FI 9, FI10, FI11 & FI12

pH 1.2 buffer, 900mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}c				
TIME (min)	Cumulative percent drug release			
	FI 9	FI 10	FI 11	FI 12
0	0	0	0	0
5	62.36	62.73	38.33	34.28
10	72.84	68.41	40.41	39.38
15	75.05	74.54	43.28	48.02
20	85.23	78.23	48.58	52.12
25	87.82	84.44	55.65	58.24
30	89.93	87.35	59.01	66.32
40	93.43	88.65	64.20	73.40
50	96.22	96.59	72.20	77.33
60	98.39	97.89	72.84	80.38

Table.9.In-Vitro Dissolution profile of the formulations of FT1, FT 2, FT3

pH 6.8 Phosphate buffer, 900mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}c			
Time (hrs)	Cumulative percent drug release		
	FT 1	FT 2	FT3
0	0	0	0
1	30.19	43.47	33.11
2	49.46	71.79	39.67
3	58.53	83.33	46.49
4	68.29	87.72	53.55
5	79.17	97.49	76.15
6	87.54	-	84.56
7	98.19	-	97.27

Table.10.In-Vitro Dissolution profile of the formulations of FT4, FT5, FT6

pH 6.8 Phosphate buffer, 900 mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}C			
Time (hrs)	Cumulative percent drug release		
	FT4	FT5	FT6
0	0	0	0
1	39.36	17.11	21.29
2	53.15	33.33	29.21
3	56.13	38.63	44.92
4	57.64	49.13	62.54
5	64.67	59.15	69.24
6	71.16	64.46	85.20
7	77.15	72.14	91.29
8	80.1	91.13	96.59
9	96.16	99.16	-

Table.11.In-Vitro Dissolution profile of the formulation FT7, FT8, FT9

pH 6.8 Phosphate buffer, 900 mL, USP-II (paddle) Apparatus, 75 rpm, 37± 0.5^{0}C			
Time (hrs)	Cumulative percent drug release		
	FT7	FT8	FT9
0	0	0	0
1	11.62	14.68	07.17
2	20.16	21.47	19.73
3	22.67	28.50	23.36
4	23.57	33.34	34.62
5	29.23	39.52	49.69
6	39.04	47.27	54.77
7	57.65	53.41	58.75
8	71.67	60.78	61.47
9	87.16	79.52	69.37
10	98.13	99.23	83.21
11	--	--	97.36

Table.12.In-Vitro Dissolution profile of the formulations FT10, FT11& FT12

pH 6.8 Phosphate buffer, 900 mL ,USP-II (paddle) Apparatus,75 rpm, 37± 0.5^{0}C			
Time (hrs)	Cumulative percent drug release		
	FT 10	FT 11	FT 12
0	0	0	0
1	18.7	12.54	6.19
2	30.19	20.56	12.65
3	32.23	22.53	21.47
4	41.24	26.64	28.33
5	60.72	30.49	39.21
6	69.7	41.28	48.33
7	74.70	48.56	54.33
8	86.22	60.22	61.41
9	89.74	71.24	76.43
10	98.2	78.38	80.42
11	--	86.21	95.49
12	--	98.65	--

Table.13.Released kinetics for all formulations

Formulation code	Zero order	First order	Higuchi	Korse – mayer's	
	R^2	R^2	R^2	R^2	N
FT 1	0.9458	0.8365	0.9935	0.9945	0.585
FT 2	0.8592	0.9466	0.9842	0.9510	0.487
FT3	0.9580	0.8030	0.9437	0.9065	0.560
FT4	0.8492	0.7829	0.9616	0.9369	0.356
FT5	0.9842	0.6971	0.9428	0.9873	0.765
FT6	0.9768	0.9288	0.9518	0.9804	0.787

FT7	0.9362	0.6567	0.7905	0.8964	0.919
FT8	0.9540	0.5390	0.8530	0.9531	0.788
FT9	0.9815	0.7181	0.9135	0.9815	1.017
FT10	0.9809	0.8361	0.9461	0.9725	0.755
FT11	0.9807	0.7407	0.8740	0.9443	0.841
FT12	0.9932	0.7877	0.8859	0.9981	1.153

Table.14.Selected Formulation for stability studiesFT11 stored at 40ºC/ 75% RH

Formulation code	**Tested after time (in days)**	**Hardness (kg/cm2) *Mean± SD (n=3)***	**Drug content *Mean ± SD (n=3)***	**Friability %**
FT 11	10	4.66 ± 0.18	97.54±0.11	0.4386
	20	4.66 ± 0.23	97.54±0.17	0.4381
	30	4.66 ± 0.29	97.54±0.22	0.4378

4. CONCLUSION

Bilayer tablets of Amlodipine and Enalapril were prepared by direct compression method .And found to be good without sticking, chipping & capping. FTIR studies of drug & polymer are compatible .The drug content was same in all the formulations of prepared tablets. Stability studies were carried out optimized formulation for 3months and it showed acceptable results .kinetic studies of the formulation shows zero order and it follows Fickian mechanism of drug release.

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