Original Article

Formulation And Evaluation Of Immediate Release And Modified Release Bilayer Tables Of Telmisartan And Metoprolol

K. BALAMURUGAN *

Assistant Professor, Department of Pharmacy, FEAT, Annamalai University, Annamalai Nagar, Chidambaram - 608002, Tamil Nadu, India. E-mail: placementbala@yahoo.co.in

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Abstract

In the present investigation, efforts were made to develop immediate release and modified release bilayer tables of Telmisartan (TL) and Metoprolol (ML) for the treatment of hypertension, to meet the release pattern of Telmisartan tablets (IP) and Metoprolol succinate extended release tablets (USP). Formulation of Telmisartan part and formulation of Metoprolol part was carried out by wet granulation technique individually. Evaluation of granules such as angle of repose, loose bulk density and tapped bulk density, Carr's compressibility index, Hausner's ratio was carried out and the results were satisfactory. Evaluation of tablets like weight variation, thickness of tablets, hardness, friability, drug content, disintegration time, In-vitro dissolution studies, water content and moisture content was carried out. The results proved that the combination of this formulation immediate release and modified release bilayer tables of TL and ML will enhance the bioavailability of dosage regimen reduction and attenuation of drug administration for the effective antihypertensive therapy.

Keywords: Telmisartan, Metoprolol, immediate release, modified release bilayer tables.

1.0 Introduction:

Choice of antihypertensive drugs for individual patients may be complex; there are many sources of influence that modify therapeutic decisions. Two drug combinations will control blood pressure in a higher proportion of patients and may be necessary in most patients to achieve optimal levels.(1) Beta Adrenergic receptor antagonists (Metoprolol) are highly preferred drugs for angina pectoris, cardiac arrhythmias, myocardial infarction, ischemic heart disease, congestive heart failure(2). Similarly ACE inhibitors/Angiotensin receptor antagonists (Telmisartan) are first-line drugs in the treatment of diabetics with hypertension (3). Metoprolol is a cardio selective bets blocker has hall life of about 3-7 h. Telmisartan is an angiotensin II receptor antagonist has half-life of 24h. Clinical study explains that combination of these drugs results of less toxic and safe to the patients. The combination of this formulation will enhance the bioavailability of Metoprolol, dosage regimen reduction and attenuation of drug administration for the effective antihypertensive therapy (4). In view of the above fact, the aim of the current work was designed to develop the bilayer sustained release dosage form of Metoprolol and Telmisartan as immediate release for the treatment of hypertension, to meet the release pattern of Telmisartan tablets IP and Metoprolol succinate extended release tablets in USP.

2.0 Formulation Development - Part –I (Wet Granulation)

S.NO	INGREDIENTS	QTY / (In mg)
1	Telmisartan	40.000
2	Mannitol	150.000
3	Microcrystalline cellulose 102	48.000
4	Sodium hydroxide	3.200
	LUBRICATION PART	
5	Talc	4.400
6	Magnesium stearate	3.000
7	Colloidal silicon dioxide	1.000
8	Povidone XL	5.000

2.1 Formulation Development - Part-II (Wet Granulation)

S.NO	INGREDIENTS	QTY / (In mg)
1	Metoprolol Succinate	52.450
2	Dicalcium Phosphate	27.950
3	HPMC K 100 M	40.000
4	Carbomer 940	60.000
5	Ethyl cellulose 15 cps	26.400
6	Methylene dichloride	
	LUBRICATION PART	
7	Talc	4.800
8	Magnesium Stearate	2.400
9	HPMC K 100 M	20.000
10	Carbomer 940	16.000

2.2 Formulation of Telmisartan part:

Telmisartan, mannitol, microcrystalline cellulose was weighed accurately and sieved individually and transfer to the mass mixer and mixed; to this Sodium hydroxide solution was added and mixed to get uniform granules. The wet granules was dried in the tray drier and dry at 40°C to 50°C for 30 min, after it was sifted in 20 mesh. Talc, Colloidal silicon dioxide and Povidone XL were weighed accurately and sieved individually and mixed in the Mass Mixer to the above Magnesium Stearate was added and mixed.

2.3 Formulation of Metoprolol part:

Metoprolol Succinate, Dicalcium phosphate, HPMC K100M and Carbomer 940 are weighed accurately, sieved individually transferred to the mass mixer and mixed. Ethyl cellulose 15cps was mixed required quantity of methylene dichloride and subjected in the above mixer to get uniform granules. The wet granules are dried in the tray drier and dry at 40°C to 50°C and sieved through 20 mesh. The Compression machine is set with 11.50 mm punches and dies and subjected for compression.

3.0 Evaluation of granules

3.1 Angle of repose (5)

20 gm of the granules was taken in a funnel, the height of the funnel was adjusted and the tip just touched the apex of the heap of the granules blend (a distance of 10 cm from the flat surface). The granules was allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice, the height of the heap (h) formed as well as the radius of the heap (r) and the diameter of the granules heap was noted. Further, the angle of repose was calculated using the following equation:

$\theta = \tan (h/r)$

θ = Angle of repose, h = height and r = radius of granules heap.

3.2 Loose bulk density and tapped bulk density (6)

The loose bulk density (LBD) and tapped bulk density (TBD) was evaluated for the granules by standard procedure, 20 gm of granules was weighed on a chemical balance and transferred into a 100 ml measuring cylinder. The cylinder was dropped on a wooden platform from a height of 2.5 cm three times at 2 sec intervals. The volume occupied by the granules was recorded as the bulk volume. The cylinder was then tapped on the wooden platform up to the volume occupied by the blend remains constant. The tapping was then extended until no further change in volume was noted. LBD and TBD were calculated using the following:

$$\text{LBD} = \frac{\text{Weight of the blend}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the blend}}{\text{tapped volume of the packing}}$$

The data obtained was used for calculating the Carr's compressibility index and Hausner's ratio as below.

3.3 Carr's compressibility index (7)

Carr's compressibility index determinations are an indirect measure of bulk density, cohesiveness, moisture content, size / shape and surface area of granules can influence the observed compressibility index. The granules was evaluated for the influences the flow properties of Compressibility Index (Carr's Index) was determined by using the following,

$$\text{Carr's compressibility Index (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

3.4 Hausner's ratio (8)

Hausner's ratio is an indirect index of measure of ease of powder flow characters and was calculated by the following,

Hausner's Ratio= TD / BD

TD=Tapped Density, BD = Tapped density.

3.5 Evaluation of tablets:

3.5.1 Weight Variation: (9)

In weight variation of tablet studies, twenty tablets from each batch were selected randomly and individually weighed, and the average weight and standard deviation of twenty tablets were calculated.

3.5.2 Thickness of tablets (10)

The thickness of the tablet is the only dimensional variable related to the tablet compression process. The thickness of the tablet was measured by a Vernier calliper, three measurements were taken.

3.5.3 Hardness: (11)

Tablets' hardness is a vital parameter that prevents the breakage of the tablet during transportation, handling, and storage. The hardness of tablets was determined using the Monsanto hardness tester, and it was recorded in kg/cm^2.

3.5.4 Friability: (11)

Friability was measured to find the strength of the tablet by Roche Friabilator. Ten undusted tablets were weighed and placed in a friabilator for 100 cycles, undusted, and weighed again. The percentage friability was then calculated using the following equation. A percentage of friability less than 1% is considered acceptable.

Percentage friability = Initial weight-Final weight / Initial weight ×100

3.5.5 Drug Content: (12)

Randomly 20 tablets were taken, weighed and powdered. The powder equivalent to 100 mg of drug was weighed accurately and dissolved in 100ml of phosphate buffer 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman filter paper 41. The dilutions were made and the absorbance of the diluted solutions was measured at 223nm. The concentration of the drug was computed from the standard curve of the Telmisartan and Metoprolol

3.5.6 Disintegration Time: (11)

Tablet disintegration apparatus was used to determine the disintegration time of all the formulations. One tablet was placed in each of the six tubes having distilled water. The temperature was kept constant at 37± 2°C and the time taken for the entire tablet to disintegrate completely was recorded 16

3.5.7 In-vitro Dissolution Studies: (13)

In-vitro drug release performed using USP apparatus-II (paddle) using 900 ml of 6.8 pH phosphate buffer with paddle rotation of 50 rpm at 37± 0.5°C. 1ml of the sample was withdrawn at predetermined time intervals and replaced with the fresh medium of 6.8 pH phosphate buffer. The samples were filtered through Whatman filter paper, suitably diluted, and analyzed at 223 nm

3.5.8 Water content (14)

Evaluation of the water content 10 tablets of each formulation are dried in a desiccators containing of activated silica gel for 4 hours. Water content of 0.5% or less is acceptable

3.5.9 Moisture content of the tablets (15)

The moisture content of the tablets was determined using a Karl Fischer titrator. One tablet was weighed and its moisture content determined as previously described for the filling formulae. All titrations were done in duplicate.

4.0 RESULT AND DISCUSSION

4.1 Results of flow properties of Telmisartan and Metoprolol blend

Formulation Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio (HR)	Carr's compressibility index
Telmisartan	30.96	0.544	0.634	1.09	11.11%
Metoprolol	28.25	0.435	0.501	1.17	13.0%

4.2 Results of water Content and Moisture Content of tablet

Formulation Code	Water Content	Moisture Content
Telmisartan	2.52%	2.10%
Metoprolol	4.38%	4.90%

4.3 Results of evaluation of bi-layer tablets

Sample	Average thickness	Average diameter	Average hardness	Friability	Average Weight(mg)
1	4.87	11.53mm	4.0 kg/ cm^2	0.701%	0.5077mg
2	4.94	11.60 mm	4.5 kg/ cm^2	0.787%	0.5085mg
3	4.46	11.60 mm	4.6 kg/ cm^2	0.742 %	0.5057mg

The colour of the tablets was orange/white colour circular shaped slightly biconvex uncoated and the bilayer sustained release tablets, both sides are plain.

4.4 Results of In vitro dissolution studies

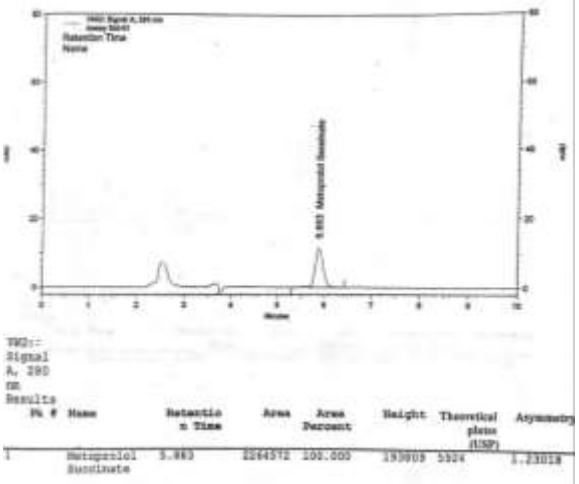
Medium-:500ml; 6.8 phosphate Buffer; Apparatus - : Paddle; Speed- : 50RPM (**Metoprolol)**

Time in interval (min)	(Tt)	$(Rt-Tt)^2$
0	0.00	0.00
1	13.51	1.04
4	31.78	5.02
8	59.61	1.23
20	98.62	0.81
		8.10

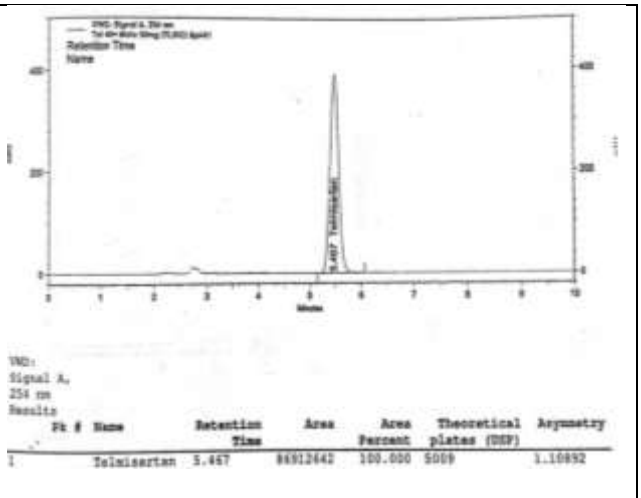
Medium-: 900ml; 0.1 M HCl; Apparatus -: Paddle; Speed- : 75RPM **(Telmisartan)**

Time in interval (min)	(Tt)	$(Rt-Tt)^2$
0	0.00	0.00
1	23.65	41.99
2	48.23	8.53
3	73.24	3.42
4	95.80	8.07
		62.00

4.5 Results of HPLC graph Metoprolol and Telmisartan



HPLC graph of assay of Metoprolol



HPLC graph of assay of Telmisartan

SUMMARY AND CONCLUSION

In view of above fact, the aim of the current design is to develop the bilayer sustained release dosage forms of Metoprolol as Sustained release and Telmisartan as immediate release. This combination will enhance the bioavailability of Metoprolol, dosage regimen reduction and attenuation of drug administration for the effective antihypertensive therapy. Three batches of trials have been taken for the formulation. The batches taken for formulation pass all the evaluation tests. In the evaluation results, the formulation showed the results were found to be within the limits of the specifications.

CONCLUSION

The present study aimed to formulate Metoprolol succinate SR and Telmisartan IR bilayer matrix tablet. Combination of this formulation will enhance the bioavailability of Metoprolol, dosage regimen reduction and attenuation of drug administration for the effective antihypertensive therapy.

Conflicts of interest: None declared.

Ethical approval: None.

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Reference:

1. Waeber B. Treatment strategy to control blood pressure optimally in hypertensive patients. Blood pressure. 2001 Jan 1;10(2):62-73.
2. Ellison KE, Gandhi G. Optimising the use of β-adrenoceptor antagonists in coronary artery disease. Drugs. 2005 Apr;65:787-97.
3. Francischetti EA, Celoria BM, Francischetti A, Genelhu VA. Treatment of hypertension in individuals with the cardiometabolic syndrome: role of an angiotensin II receptor blocker, telmisartan. Expert review of cardiovascular therapy. 2008 Mar 1;6(3):289-303.
4. Sica DA. Fixed-dose combination antihypertensive drugs: do they have a role in rational therapy?. Drugs. 1994 Jul;48:16-24.
5. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. Aaps Pharmscitech. 2008 Mar;9:250-8.

6. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. Aaps Pharmscitech. 2008 Mar;9:250-8.
7. Gupta R, Sharma P, Garg A, Soni A, Sahu A, Rai S, Rai S, Shukla A. Formulation and evaluation of herbal effervescent granules incorporated with Calliandra haematocephala leaves extract. Indo American Journal of Pharmaceutical Research. 2013;3(6):4366-71.
8. Bhattacharyya S, Swetha G. Formulation and evaluation of effervescent granules of Fexofenadine hydrochloride. The Pharma Innovation. 2014 May 1;3(3, Part A):1.
9. Kimura SI, Uchida S, Kanada K, Namiki N. Effect of granule properties on rough mouth feel and palatability of orally disintegrating tablets. International Journal of pharmaceutics. 2015 Apr 30;484(1-2):156-62.
10. Vercruysse J, Delaet U, Van Assche I, Cappuyns P, Arata F, Caporicci G, De Beer T, Remon JP, Vervaet C. Stability and repeatability of a continuous twin screw granulation and drying system. European journal of pharmaceutics and biopharmaceutics. 2013 Nov 1;85(3):1031-8.
11. Otsuka M, Mouri Y, Matsuda Y. Chemometric evaluation of pharmaceutical properties of antipyrine granules by near-infrared spectroscopy. AAPS PharmSciTech. 2003 Sep;4:142-8.
12. Mahaparale SP, Gonjari ID, Jayaveera KN. Stability indicating HPLC method for simultaneous estimation of Metoprolol succinate and telmisartan. Journal of Liquid Chromatography & Related Technologies. 2013 Nov 8;36(18):2601-11.
13. Nandi U, Dastidar SG, Pal TK. Development and in-vitro evaluation of a bilayer matrix tablet containing sustained Release Metoprolol succinate and immediate release telmisartan. Journal of Pharmacy Research. 2012 Feb;5(2):1136-9.
14. Aslani A, Jahangiri H. Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets. Advanced pharmaceutical bulletin. 2013 Dec;3(2):315.
15. Gabbott IP, Al Husban F, Reynolds GK. The combined effect of wet granulation process parameters and dried granule moisture content on tablet quality attributes. European Journal of Pharmaceutics and Biopharmaceutics. 2016 Sep 1;106:70-8.