ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Research Paper

Formulation and Evaluation of Bilayer Tablet Containing Metoprolol Layer as A Sustain Release Part & Ramipril Layer as an Immediate Release Part

Patel Vijay [*1], Patel Dipika[2], Patel Indravadan[3]

[1]Brooklyn Campus, Long Island University, New York-11201, USA

[2]B. N.Girls' College of Pharmacy, Udaipur (Raj.)313001 India

[3]Shree Swaminarayan Sanskar Pharmacy College, Zundal (Guj.)382421 India

The present study was to establish Bi-layer tablets containing as metoprolol layer as sustained release and ramipril layer as immediate release layer. Sustained layer were prepared by wet granulation method using HPMC K15 and immediate release layer were prepared by wet granulation method using Pregelatinized Starch and MCC PH 102. The tablets were evaluated for physicochemical properties. All the values were found to be within limit. In vitro release studies were carried out by USP type-2 paddle apparatus. The result showed that polymer HPMC K4 in sustained layer can control the release of drug. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R^2 =0.9992) and diffusion was the dominant mechanism of drug release. The formulation (F10) is comparable with innovator. The present study concluded that Bilayer tablets of metoprolol and ramipril as an alternative to the conventional dosage form.

Keywords: Bilayer tablets, Metoprolol, Ramipril, Sustained Release, Higuchi equation.

INTRODUCTION:

Hypertension is a major cardiovascular risk factor but most patients remain asymptomatic for many years. Hypertension is a major contributor to cardiovascular disease and a leading cause of stroke, myocardial infarction, heart failure and kidney disease. The prevalence of hypertension increases with age and older patients are more likely to suffer from cardiovascular complications of hypertension.

Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet.

A single drug act mainly on a single pathophysiological mechanism, whereas it is widely known that hypertension is a multifactorial pathology, in which many mechanisms interact, it is also known that

***Address for correspondence**
vijaykarnavat@gmail.com

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

when a particular system is blocked, other systems are activated that reduce the initial therapeutic effect. Hence, two classes of medications, which can act on different physiological systems and could be combined into a single dosage unit, would have an additive effect.

Metoprolol reduce BP by competitive antagonism of catecholamine peripherally and through suppression of rennin activity. Ramipril reduce BP by inhibition of the angiotensin converting enzyme. Because the two active ingredients act on two different physiological systems, additive effects and enhanced BP reduction would result. The Metoprolol component and Ramipril both have duration about 24 hours so that once daily dosing with this combination rational and appropriate for each of the ingredients. Also this combination does not have any pharmacokinetic reaction.

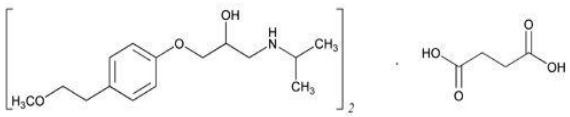

Fig: 1 Structure of Metoprolol

Metoprolol is a beta-adrenergic blocking agent that is used for treating high blood pressure, heart pain, abnormal rhythms of the heart, and some neurologic conditions. It is Class I drug, freely soluble in water, having Half Life 3-4 hrs. Metoprolol tartrate is rapidly and almost completely absorbed from the GI tract. After an oral dose (as conventional tablets), about 50% of the drug undergoes first-pass metabolism in the liver. Peak plasma concentrations are reached in about 7 hours following administration as extended-release tablets.

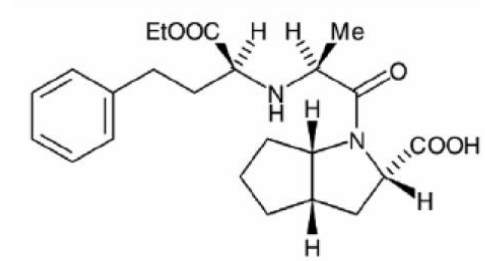

Fig:2 Structure of Ramipril

Ramipril is antihypertensive agent. Ramipril causes a marked reduction in peripheral arterial resistance. Generally there are no major changes in renal plasma flow and glomerular filtration rate. Administration of Ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate. Ramipril is rapidly absorbed from the GI tract (50% to 60%). Peak plasma concentrations are reached in about 1 hours following administration as Immediate-release tablets.

MATERIAL AND METHODS

Materials

Metoprolol, MCC, Xanthan gum 75 M, HPMC K 100, HPMC K 15, Isopropyl Alcohol, Klucel EXF, Aerosil, Sodium

stearyl fumarate were collected from Zydus Cadila Healthcare ltd, Ahmedabad, India. All others reagents and chemicals used were of analytical reagent grade.

Development of bilayer tablet of Metoprolol and Ramipril was carried in two different stages. Blends of Sustained release layer of Metoprolol and immediate release layer of Ramipril were separately prepared. After optimization of individual layer, the bilayer tablet was prepared using optimized formulas.

Methodology

Preparation of Bilayered tablets

Blends of immediate release layer of Ramipril

Immediate release layer of Ramipril (P1 to P6) were prepared by wet granulation technique as per the composition Table 1. Ramipril, MCC were passed through #40 mesh and ferric oxide red passed through 100#. Mix all geometrically and again pass through 40# mesh. Above sifted material were mixed in Rapid mixing granulator for 10min (Impeller 150). Weigh HPMC 6cps and prepare binder solution using water. Then above mixture with binder solution HPMC 6cps solution was granulated at Impeller 150 for 2min and kneading for 2min (Impeller 150 and chopper 1500) for 30sec. dry the granules in fluid bed dryer. Pass the dried granules from #20mesh in Oscillating granulator. Weigh required quantity of MCC PH 102 (omit in formula5) and pregelatinized starch and pass through 40 # mesh and mix in cage blender for 10 min @ 18 rpm. Weigh SSF, pass through # 60 mesh, lubricate the above blend with SSF in cage blender for 5 min @ 18 rpm.

Blends of sustain release layer of Metoprolol

Sustain release layer of Metoprolol (M1 to M11) were prepared by wet granulation technique as per the composition Table 2. Metoprolol, MCC, Xanthan gum, HPMC K 100 pass them through # 40 mesh. Mix all excipients in rapid mixing granulator and mix it for 10min (Impeller 150). Weigh the HPC and prepare binder solution by IPA. Then above mixture with binder solution HPC solution was granulated at Impeller 150 for 2min and kneading for 2min (Impeller 150 and chopper 1500) for 30sec. dry the granules in fluid bed dryer. Pass the dried granules from #20mesh in Oscillating granulator. Weigh HPMC K 100, & Aerosil pass them through # 40 mesh & mix it. Mix these blend with the dried granules in cage blender for 10 min @ 18 rpm. Weigh Sodium Stearyl Fumarate (SSF), pass it through # 60 mesh, lubricate above blend in cage blender for 3 min @ 18 rpm.

Characterization of granules

Prior to compression, blends of two layers were evaluated for their characteristic

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 1: Preparation of immediate release layer of Ramipril

Sr. No.	Ingradients Qty (mg/Tab)	P1	P2	P3	P4	P5	P6
1	Ramipril IP	5	5	5	5	5	5
2	MCC PH 102	-	-	-	-	-	-
3	MCC IP	94	92	89	88	72	74
4	HPMC 6cps	8	6	5	5	5	3
5	Ferric oxide red	0.06	0.06	0.06	0.06	0.06	0.06
6	D M Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s
7	MCC PH 102	-	5	8	2	2	20
8	Pregelatinized Starch	30.94	30.94	30.94	34.94	35.94	35.94
9	SSF	2	2	2	2	2	2
10	Total	140	140	140	140	140	140

parameters, such as density, bulk density, tapped density, compressibility index and Hausner Ratio. Carr's index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd. india).

Preparation of Bilayer formulation

Take the blend of two different layers and poured in the two hoppers according to table 3. Compression was done on 45 stations D- Tooling bi-layer machine using 13/32" FFBE (Flat Face Beveled Edge) punch set.

Physico chemical properties of bilayer tablets

Standard physical tests for the sustained release bilayer tablets were performed and average values were calculated. Mass variation was determined by weighing 20 tablets individually, the average mass was calculated and the percent variation of each tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a Mansanto hardness tester (Electrolab Pvt. Ltd, India) and the average of pressure (kg cm^{-2}) applied for crushing the tablet was determined. Friability was determined by first weighing 20 tablets after dusting and placing them in a Roche Friabilitor, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Thickness was determined by digital vernier caliper. It is expressed in mm.

Drug content

Twenty tablets were weighed and finely powdered. The powder equivalent to 47.71 mg of Metoprolol HCl and 5 mg of Ramipril were transferred to a 100 ml volumetric flask. Add about 50 ml of diluents and sonicate to dissolve. Make volume up to the mark with diluents and mix.

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 2: Preparation of sustain release(SR) layer of Metoprolol

Sr. No.	Ingredients Qty (mg/Tab)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
1	Metoprolol	47.71	47.71	47.71	47.71	47.71	47.71	47.71	47.71	47.71	47.71	47.71
2	MCC	86.3	86.3	86.3	69.3	60.8	50.8	40.8	40.8	65.8	36.8	36.8
3	Xanthan gum 75M	150	-	100	100	110	110	120	120	120	124	124
4	HPMC K100	-	100	50	50	50	60	60	-	-	-	-
5	HPMC K15	-	-	-	-	-	-	-	60	80	100	100
6	Klucel ELXF	8	8	8	10	8	8	8	8	8	8	8
7	IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	sq.s
8	HPMC K100	-	-	-	15	15	15	15	-	-	-	-
9	HPMC K15	-	-	-	-	-	-	-	15	20	25	25
10	Aerosil	4.49	4.49	4.49	4.49	4.49	4.49	4.49	4.49	4.49	4.49	4.49
11	sodium Stearyl Fumarate	3.50	3.50	3.50	3.50	4.00	4.00	4.00	4.00	4.00	4.00	4.00
12	Total	300	300	300	300	300	300	300	300	300	300	300

Dilute 1.0 ml of this solution to 100.0 ml with diluents and mix. Acetronitrile was used as diluents. The total amount of drug within the tablets was analyzed by modified HPLC method.

In vitro dissolution studies[1]

Chromatographic conditions for Ramipril

Column : Symmetry c 18(15cm×4.6 mm), 5 µm or equivalent

Detector : 210 nm

Apparatus : High Performance Liquid Chromatography

Medium : 500 ml, 0.01N HCl

Apparatus : USP II (paddle)

RPM : 75

Temp. : 37^{o} C ± 0.5^{o} C

Time : 45 minutes

Buffer preparation: Dissolve 14 g Sodium perchlorate in 1.0 liter milli Q water. Adjust pH 3 with orthophosphoric acid.

Mobile Phase: Prepare a filtered and degassed mixture of buffer preparation and acetonitrile in the ratio of 65:35

Diluent: Use 0.01 N hydrochloric acid as diluents.

Release of Ramipril was determined using a dissolution Apparatus type II at 75 rpm. The dissolution was studied using 500ml of 0.01N Hydrochloric acid. The temperature was maintained at 37 ± 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e, 45, minutes, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Ramipril content using chromatogram.

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 3: Comparative *In-Vitro* Drug Release Profile of Ramipril IR Layer at 0.01N HCl

Time in Min	Innovator	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0	0
45	99.43	74.23	88.45	67.74	75.98	95.69	97.89

The percentage of Ramipril release was calculated.

Chromatographic conditions for Metoprolol

Column : Symmetry c 18,(15 cm × 4.6 mm), 5 µm or equivalent

Detector : 210 nm

Apparatus : High Performance Liquid Chromatography

Medium : 500 ml, pH 6.8 phosphate buffer

Apparatus : (USP II) paddle (Use sinker)

RPM : 50

Temperature : 37^{o} C ± 0.5 ^{o} C

Time : 1, 8 and 24 hours

Release of Metoprolol was determined using a dissolution Apparatus type II at 50 rpm. The dissolution was studied using 500ml of Phosphate Buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1, 8 and 24 hours, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Metoprolol content using chromatogram.

Characterization of the Release Profile:

The experimental results of the release studies were fitted according to the exponential equation.

Zero order Release Equation:

$Q = K0t$

First Order Release Equation

$\text{Log } C = \log C0 – Kt / 2.303$

Higuchi's Square Root of Time Equation:

$Q = Kt1/2$

Table 4: Comparative In-Vitro Drug Release Profile of Metoprolol SR Layer (M1 to M7) at pH 6.8

Time in Hrs	Innovator	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
0	0	0	0	0	0	0	0	0	0	0	0	0
1	15.00	6.75	8.97	28.45	17.56	16.25	15.92	15.23	25.24	19.42	15.27	15.32
4	32.54	25.67	23.45	46.89	43.45	39.56	42.22	35.61	48.49	41.54	33.06	34.29
8	51.11	48.52	35.45	64.35	62.46	64.54	59.41	55.78	69.19	58.82	50.19	50.12
20	86.24	74.23	60.51	86.45	85.45	85.26	84.19	76.34	91.24	87.78	85.75	85.39
24	93.68	81.34	70.34	91.71	86.12	88.23	88.40	84.46	95.11	93.67	93.47	92.17

Korse-Meyer Peppas Equation:

$Mt / M\alpha = Kmtn$

Where, Q = Amount of drug release at time t, C = Amount of drug remained at time't', C0 = Initial amount of drug, K = First – order rate constant (hr^{-1}). Mt = drug release at time t, Mα = total amount of drug in dosage form, F = fraction of drug release at time t, K0 = zero order release rate constant, K = Higuchi square root of time release rate constant, Km = constant depend on geometry of dosage form, n = diffusion exponent indicating the mechanism of drug release where for cylinder value of n is <0.5 indicate Fickian diffusion, between 0.5 and 1.0 indicate Non-Fickian and > 1.0 indicate case-II transport.

FTIR study

Infrared spectrum was taken (FT-IR, spectrum RXI, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

RESULTS AND DISCUSSION:

The FTIR studies proved chemical and physical compatibility of drug with excipients.

Tablet characteristics

Tablets of all formulations were subjected to various physico–chemical evaluation parameters such as thickness, hardness, friability, and drug content. The results of these studies were also found to be within limits and were uniform given in Table 6.

Table 5: Preparation of Bi-layer Tablet of Ramipril and Metoprolol

Trial	Ramipril	Metoprolol
F1	P1	M1
F2	P2	M2
F3	P2	M3
F4	P3	M4
F5	P3	M5
F6	P4	M6
F7	P4	M7
F8	P5	M8
F9	P5	M9
F10	P6	M10
F11	P6	M11

Table 6: Post compression parameter of Bilayer tablets

Batch No	Friability (%)	Hardness(Kg/cm^2)	Thickness(Mm)	Disintegration time(For IR part)
I*	0.28	14-16	4.22-4.30	1-2 min
F1	0.97	11-13	3.88-3.91	30-60 sec
F2	1.37	11-13	3.88-3.91	30-60 sec
F3	1.04	11-13	3.88-3.91	30-60 sec
F4	0.15	14-16	4.08-4.12	5-6 min
F5	0.18	14-16	4.08-4.12	5-6 min
F6	0.33	14-16	4.08-4.12	4-5 min
F7	0.31	14-16	4.08-4.12	4-5 min
F8	0.29	14-16	4.08-4.12	4-5 min
F9	0.34	14-16	4.28-4.32	1-2 min
F10	0.38	14-16	4.28-4.32	1-2 min
F11	0.31	14-16	4.28-4.32	1-2 min

I = Innovator*

In vitro Drug Release Study

Figure 2 show cummulative percentage drug release of Ramipril formulations (P1

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 7: The Regression coefficient values for different formulations

Order of Kinetic	Zero order	First order	Higuchi	Korsmeyer peppas
R^2 Value	0.9422	0.9296	0.9992	0.9996

to P6). The percentage *in vitro* drug release from formulations P1 to P6 ranged from 74.23% to 97.89% is given in table 3. Complete Ramipril release occurred within 45 minutes, from the P5 formulation showed comparable drug release with innovator. Next batch P6 formulation is reproducible batch to prove the optimization of P5 batch. So, P5 is considered for IR layer.

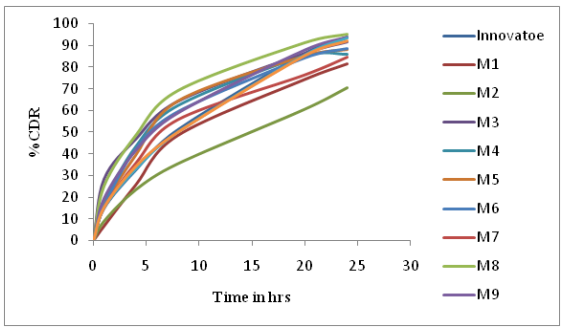

Figure 3: *In-vitro* dissolution of Metoprolol SR layer

Figure 3 show cumulative percentage drug release of Metoprolol formulations (M1 to M11). The *in vitro* drug release from formulations M1 to M11 is given in table 4. Complete release of Metoprolol occurred from the bilayer tablets within 24 hours. The drug release rate in sustained layer decrease as the viscosity of HPMC increases. Good dissolution profile of M11 might be due combination of HPMC K100 and HPMC K15 and it showed comparable drug release with innovator.

The result suggested that for highly water soluble drug like Metoprolol, it is desirable to use HPMC K15 for sustained release layer and incorporation of superdisintegrant such as SSF and MCC in immediate release layer. The release data further indicated that combination of HPMC K15 can give the sustained release effect followed by the initially burst release effect due to the superdisintegrant Pregelatinized Starch and MCC PH 102 in immediate release layer.

Kinetic modelling of drug release

The kinetics parameters for Metoprolol release are shown in table 7. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R^2 >0.988). Release of the drug from the sustained release tablets containing hydrophilic polymers generally involves factors of diffusion. To confirm the diffusion mechanism, the data was fitted into korsmeyer's equation, with slope (n) values ranging from 0.5 to 1. This result suggests that, the release of drug follows Non-Fickian transport and it indicates the delivery of drug from the

tablet through diffusion dominated mechanism.

CONCLUSION

The present research work was carried out to develop a Bi-layer tablet of Metoprolol as sustained release layer was prepared by HPMC K15 and Ramipril as immediate release layer was prepared by Pregelatinized Starch and MCC PH 102 in order to match release profile with the innovator product. The result demonstrated that initially burst release was due to Pregelatinized Starch and MCC PH 102 as superdisintegrant in immediate release formulation and followed by sustained release due to combination of polymers such as and HPMC K15 in sustained release formulation. Hence it concluded that Bi-layer tablets showed an immediate release effect to provide the loading dose of the drug, followed by sustained release for 24 hrs, indicating a promising potential of the Metoprolol and Ramipril Bi-layer tablet as an alternative to the conventional dosage form.

Acknowledgement

The authors are thankful to Cadila Health Care Ltd., Ahmedabad, India for their support and cooperation in carrying out the research work.

REFERENCE

1. Ramesh D. Sathis Kumar, Guruviah, Harani A., Formulation and evaluation of bilayered sustained release matrix tablets of Metformin HCl Sr and Pioglitazone., *American Eurasian journal of Scientific Research.* 2010; 5(3): 176-182.

2. Paramar J., Rane M., Tablet formulation design and manufacture: Oral immediate release application. Pharma times, 2009 :21-29

3. Margret C. R., Jayakar B., Pasupathi A., Chakrabarty B. L., Maurya P., Design Development and Evaluation of Immediate Release Atorvastatin and Sustained Release Gliclazide Tablets. J. of Pharm. Res. 2009; 2(6): 1039-1041.

4. Asgar A., Sharma S. N., Evaluation of oral sustained release formulation. The Eastern Pharmacist 1991: 69-74.

5. Baveja S. K., Ranga Rao K.V., Padmalatha-Devi K., "Zero-order release hydrophilic matrix tablets of beta-andrenergic blockers," Int. J. Pharm., 1987: 39-45.

6. Dixit Ritu B., Gupta Rajat R., Patel Harsha V., Patel Pradeep S., Dixit Bharat C., Formulation and Characterization of Sustained Release Matrix Tablet of Metformin Hydrochloride., International J. Pharma Recent Research. 2009; 1(1): 49-53.

7. Singhvi Gautam., Singh mahaveer, Review: in-vitro drug release Characterization models, Int. J. of Pharmaceutical Studies and Research, Jan.

March 2011; 2(1) :77-84.

8. Huang G., Wang R., Wang D., Zhang Z., Deng S. The factors influencing metoprolol succinate release from hydroxypropyl methylcellulose matrix tablet. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2006; 23 (3): 587-91.

9. Vijaya Rani K. R., Prakash S.E.L., Lathaeswari S.R. Rajeswari. Formulation and Development of ER Metoprolaol Succinate Tablets. Int. J. of Pharm. Tech. Research. 2009; 1 (3): 634-638.

10. Ramipril Consumer Information [Internet], [cited 2011 Jan 10]. Available from: http://www.drugs.com/ramipril.html

11.Metoprolol succinate extended release tablets, [cited 2011 Jan 10]. Available from:http://www.drugs.com/cdi/metoprolol-succinate-extended-release-tablets.html

12. Raymond C Rowe, Paul J Shesky and marian E Quinn C Owen, Handbook of pharmaceutical Excipients, Pharmaceutical press, Fifth edition, 2006, Pg 346, 188,364,705,821.336,731