IJPSR (2012), Vol. 3, Issue 07 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 March, 2012; received in revised form 18 April, 2012; accepted 22 June, 2012

INVESTIGATION ON THE IMPACT OF CORE AND BARRIER LAYER COMPOSITION ON THE DRUG RELEASE FROM A TRIPLE LAYER TABLET

Kanwarpreet Singh Bakshi*, K. Vivek, Rajan K. Verma, Murali Krishna B., Sreekanth Narravula, Romi Barat Singh and Ajay K. Singla

NDDS Department, Ranbaxy Laboratories Ltd., (R & D-2), Plot No 20; Sec 18, Sarhaul, Udyog-Vihar, Gurgaon-122015, Haryana, India

Keywords:
Metoprolol succinate,
Controlled Release,
Monolayer Matrix Tablet,
Triple Layer Matrix Tablet,
Zero Order Kinetics

Correspondence to Author:

Kanwarpreet Singh Bakshi

Senior Research Chemist, NDDS Department, Ranbaxy Laboratories Ltd., (R & D-2), Plot No 20; Sec 18, Sarhaul, Udyog-Vihar, Gurgaon- 122015, Haryana, India

ABSTRACT

In this study, Monolayer matrix (MLM) tablet and triple layer matrix (TLM) tablet formulation of metoprolol succinate were fabricated by using Hydroxypropyl-methylcellulose and Polymethacrylates (Eudragit) as the matrix forming agent in both the tablet core layer and barrier layers. The prepared tablets were analyzed for their drug content and *in-vitro* drug release studies. *In-vitro* evaluation and comparison of the MLM dosage form and TLM dosage form was done. The role of impermeable barrier layer in controlling the drug release from the core was studied. The *in-vitro* dissolution studies were carried out and showed a significant difference statistically (P value > 0.05 by ANOVA tool). Mean dissolution time (MDT) increased, while dissolution efficiency (DE %) decreased, indicating that the release of metoprolol succinate is slower from triple layer matrix tablets. The thermal analysis studies (DSC) performed on the initial TLM formulation and three month old accelerated stability sample of the same showed no variation in the thermograph, indicating TLM as stable formulation. The finding of the study indicated that the MLM tablets may prolonged the drug release, but a non linear drug release profile was observed with an initial burst release. In TLM tablets, layering with Hydroxypropyl-methylcellulose and Polymethacrylates (Eudragit) as impermeable barrier on the matrix core, resulted in linear/zero order drug release kinetics. The initial burst release was not observed in TLM tablets.TLM tablets showed significant and marked controlled release of a freely water soluble drug as compared to MLM tablets.

INTRODUCTION: It is well known fact that oral dosage form is the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. Multi layered matrix tablet formulation is one of the many available different techniques to design modified release dosage forms for oral administration.

Geomatrix [1] technology or multilayered matrix tablet formulation, having one to three (multi) layer matrix tablets is a drug delivery system, which consists of a matrix core containing the active pharmaceutical ingredient and one or more barriers (modulating layers) incorporated during process of tablet compression.

The drug release from the MLM [2] is usually of first order, when this type of formulation comes in contact with dissolution medium; initially the surface area exposed is high, resulting in initial faster drug release, but as the time progresses the rate of drug release decreases. In case of erodible matrix tablet, as the time progress, the actual surface area available for drug absorption decreases because tablet erodes by dissolution. In case of matrix gel tablet, swelling takes place which causes increase in the diffusion path length.

In both of the above cases rate of drug release depends on the concentration of the drug at that time and therefore follow a nonlinear/ first order release rate. On the other hand, the Triple layer/Geomatrix technology is applied to achieve customized levels of controlled release of specific drugs from the formulation. Zero order or linear release profile [3, 4] can be obtained by multilayered matrix tablet formulation.

The controlled release is achieved by constructing a multilayered tablet made up of two basic key components

(1) Core layer containing the active pharmaceutical ingredient and;

(2) Surface area controlling barrier layers [5].

Active pharmaceutical ingredient containing in the core layer is available for drug release on exposure to the dissolution medium, is controlled by barrier layers. The combination of layers, each with different rates of swelling, gelling and erosion, is responsible for the controlled rate of drug release within the body.

The barrier layers [6, 7] delay the interaction of active pharmaceutical ingredient with dissolution medium by two ways, first by limiting the surface available for the active pharmaceutical ingredient release and secondly at the same time controlling solvent penetration rate.

In this drug delivery system, the barrier layers prevent the dissolution medium penetration to the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erodes or slowly become permeable to the dissolution medium resulting in the increase in the surface area available for drug release.

In this way the decrease of delivery rate due to the increase in diffusion path length (saturation effect) is counter balanced by the simultaneous increase of the area available for drug release. Thus, by combining a time-dependent control of the hydration rate of the device and by controlling the tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile(Zero order profile) [8, 9].

One of the major benefits of the Geomatrix/triple layer technology is its ability to be easily incorporated into the production line. The Geomatrix tablets can be manufactured by readily available equipment that can be integrated into widely-used pharmaceutical processes, thus giving firms more control over their own production activities.

Metoprolol succinate is selective β-adrenoreceptor blocking agent used in the treatment of various cardiovascular disorders and prophylaxis of migraine. It has been classified as a class I substance according to the bio pharmaceutics classification system (BCS), that it is freely soluble and highly permeable having pKa value of 9.68.

The drug is readily and completely absorbed throughout the intestinal tract but is subject to extensive first pass metabolism resulting incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentrations occur after 1-2 hours [10].

The drug is eliminated within 3 to 4 hours, which depending on therapeutic intention, makes it necessary to administer simple formulation of Metoprolol succinate up to four times daily. Based on these properties and the well defined relationship between the beta blocking effect and plasma drug concentration, Metoprolol succinate which is freely water soluble drug, lends itself to a controlled-release (CR) formulation smooth out peaks and valleys in the plasma levels and enable less frequent dosing intervals are typically reduced to once or twice a day.

Though work has been reported [11- 15] on the triple layer tablet and the role of thickness of barrier layers in controlling the drug release from the core, not much information is available on the effect of core layer and barrier layer composition on the drug release from a triple layer matrix tablet.

In this present study, monolayer and triple layer tablets of a freely water soluble drug were prepared using different core and barrier layer compositions (Hypromellose [16] and Polymethacrylates (Eudragit) [17]), the *in-vitro* dissolution studies were performed and compared by calculating the drug release kinetics [18] of both the drug delivery systems. There comparison with the available marketed formulation of the Metoprolol succinate ER tablet-50 mg was also done.

The role of impermeable barrier layers in obtaining a linear drug release profile was studied and compared with drug release profile from monolayer tablet formulation. The effect of the barrier layers composition in controlling or modulating the drug release from the core component was also evaluated.

MATERIALS AND METHODS: Metoprolol Succinate and the excipients for this project were kindly provided by Ranbaxy Research Laboratories, Gurgaon, India. The vendors of the various excipients used are as follows: Hypromellose - (HPMC K4MCR, HPMC K15MCR, HPMC K100MCR, HPMC E15, HPMC E50, HPMC K100LVCR) of M/s; Dow Chemicals, USA, Lactose monohydrate of M/s; DMV international Netherlands, Poly-methacrylates (Eudragit) (L100, S100) and Aerosil of M/s Evonik industries, Magnesium stearate and Stearic acid of M/s Mallinckrodt USA, Povidone; M/s BASF,; industries were used. All other materials were of analytical or reagents grade.

Preparation and Characterization of TLM and MLM tablets of Metoprolol succinate:

1. **Preparation of Metoprolol succinate Core Layer Granules:** The drug and polymers for the MLM tablets TLM tablets were passed through 180µm sieve before their use in the formulation. The matrix formulations were prepared and coded as M1, M2 and M3 respectively presented in **Table 1**.

   Matrix core granules were prepared by wet granulation procedure using polymers Hypromellose and Polymethacrylates (Eudragit) S-100, lactose as filler, Povidone as binding agent. The wet mass obtained was dried at 50° C for 1hr in a fluid bed dryer to moisture content of not more than 3.0%w/w. The dried granules were then milled through Quadro co-mill fitted with 40G screen (1mm screen) at 25Hz. Then, the milled granules were lubricated in a V-blender for 10 minutes with magnesium stearate and aerosil in 1:1 ratio.

2. **Preparation of Barrier Layer Granules:** The barrier layer containing hydrophilic polymer Hypromellose and Eudragit L-100, were prepared by wet granulation technique. The polymers Hypromellose and Eudragit L-100 and Povidone and Stearic acid were mixed well and the resulting blend was granulated with Isopropyl alcohol.

   The wet mass obtained was dried at 50° C for 1hr in a fluid bed dryer to moisture content of not more than 3.0%w/w. The dried granules were then milled through Quadro co-mill fitted with 40G screen (1mm screen) at 25Hz. Then the milled granules were lubricated in a V-blender for 10 minutes with magnesium stearate and aerosil in 1:1 ratio.

3. **Preparation of MLM tablets and TLM tablets:** The composition of formulation used in the study containing 50 mg of Metoprolol succinate in each case is shown in Table 1. TLM tablets were prepared by using different combinations of drug loaded matrix core granules and release retardant layer granules. Initially the volume of die cavity was adjusted equivalent to 520mg i.e. total weight of triple layer matrix tablets.

   Then pre weighed amount of polymer granules of Hypromellose and Eudragit L-100 equivalent to bottom layer 185mg were taken and placed in the die cavity and uniformly spread.

   The upper punch was lifted up and 150mg of matrix core granules were placed over the bottom layer of polymer granules in the die cavity and slightly compressed. The remaining volume of die cavity was filled with pre weighed amount of polymer granules Hypromellose and Eudragit L-100 equivalent to bottom layer 185mg and finally compressed on a rotary compression machine (Cadmach, Ahmadabad, India).

   The Hardness of matrix tablet and triple layer matrix tablets was adjusted to 12-15 Kp.

TABLE 1: COMPOSITION OF TLM FORMULATION AND MLM TABLET FORMULATION

	TLM tablet formulations					MLM tablet formulation		
	GM1	**GM2**	**GM3**	**GM4**	**GM5**	**M1**	**M2**	**M3**
Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
CORE	**C1**	**C2**	**C3**	**C4**	**C5**			
Metoprolol Succinate	50	50	50	50	50	50	50	50
HPMC K 4 MCR	0	0	0	0	0	**200**	**75**	0
HPMC K15	**48**	**48**	**48**	**18**	**30**	0	**125**	**75**
HPMC K 100MCR	0	0	0	**30**	**18**	0	0	**125**
Lactose	20	20	20	20	20	90	90	90
Eudragit S 100	21	21	21	21	21	125	125	125
Povidone	8	8	8	8	8	25	25	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	5	5	5
Aerosil	1.5	1.5	1.5	1.5	1.5	5	5	5
TOTAL	**150**	**150**	**150**	**150**	**150**	**500**	**500**	**500**
BARRIER LAYER 1	**(B1)1**	**(B1)2**	**(B1)3**	**(B1)4**	**(B1)5**			
HPMC E15	0	0	0	0	0			
HPMC E 50	**70**	**70**	0	0	0			
HPMC -K100 LV	0	0	**70**	**70**	**70**			
Lactose	42	42	42	42	42			
Eudragit L100	27	27	27	27	27			
Povidone	8	8	8	8	8			
Stearic acid	35	35	35	35	35			
Magnesium stearate	1.5	1.5	1.5	1.5	1.5			
Aerosil	1.5	1.5	1.5	1.5	1.5			
TOTAL	**185**	**185**	**185**	**185**	**185**			
BARRIER LAYER 2	**(B2)1**	**(B2)2**	**(B2)3**	**(B2)4**	**(B2)5**			
HPMC E15	**70**	0	0	0	0			
HPMC E 50	0	0	0	0	0			
HPMC -K100 LV	0	**70**	**70**	**70**	**70**			
Lactose	42	42	42	42	42			
Eudragit L100	27	27	27	27	27			
Povidone	8	8	8	8	8			
Stearic acid	35	35	35	35	35			
Magnesium stearate	1.5	1.5	1.5	1.5	1.5			
Aerosil	1.5	1.5	1.5	1.5	1.5			
TOTAL	185	185	185	185	185			
Total tablet wt.	**520**	**520**	**520**	**520**	**520**	**500**	**500**	**500**

TABLE 2: PHYSICOCHEMICAL CHARACTERIZATION OF DIFFERENT FORMULATIONS. (MEAN ± SD)

	Formulation	Weight (mg) N=20	Hardness (kp).N=6	Thickness (mm).N=10	Drug Content (%).N=3
Core	**C1**	150(±1.1)	10(±0.6)	2.25(±0.5)	101±1.1
(Core+barrier-1)	**C1+(B1)1**	335(±1.2)	12(±0.8)	4.52(±0.7)	99.5±1.2
(Core+barrier-2)	**C1+(B2)1**	335(±1.0)	13(±0.5)	4.42(±0.6)	99.7±1.5
	C1+(B1+B2)1 [GM-1]	520(±1.3)	13±(0.6)	6.76(±0.4)	98.2±1.0
	GM-2	520(±1.1)	14±(0.9)	6.59(±0.5)	97.5±1.8
TLM tablet	**GM-3**	520(±1.12)	13±(1.6)	6.56(±0.8)	100.5±1.3
	GM-4	520(±1.10)	15±(1.1)	6.55(±0.4)	96.2±1.0
	GM-5	520(±1.5)	12±(1.4)	6.65(±0.4)	97.2±1.6
	M1	501(±1.1)	13±(1.7)	6.25(±0.7)	99.2±1.3
MLM Tab	**M2**	500(±1.0)	14±(1.2)	6.23(±0.5)	96.9±1.5
	M3	502(±1.5)	14±(1.3)	6.24(±0.3)	101.1±1.3

Physical tests for the Prepared Matrix Tablets: Ten tablets from each formulation were taken for measurement of diameter and crown thickness with Vernier calipers and an average of ten determinations was carried out. Hardness of the matrix tablets and triple layer matrix tablets was evaluated by using hardness tester (Dr. Schleuniger Pharmatron) .Weight variation test (Afcoset, India) was performed for twenty tablets from each batch and average values were calculated.

Friability of MLM and TLM tablets was determined by first weighing 10 tablets after de dusting and placing in a friability tester (Roche friabilator, Pharma labs, Ahmadabad, India),which was rotated for 4min at 25rpm. After dedusting, the total remaining weight of the tablets was recorded and the percent friability was calculated. The drug content of the prepared tablets of each batch was determined in triplicate.

In vitro dissolution studies for the prepared MLM and TLM tablets were conducted for a period of 24h using a six station USP 34,NF 25-type II apparatus (DISTEK . dissolution system) at 37±0.5°C and 50 rpm speed. The dissolution studies were carried out (n=3) and dissolution medium used was 0.1N HCl (pH 1.2), volume of dissolution medium used was 500ml at 37±0.5°C for 24 hr.

Dissolution was carried out in these conditions as Metoprolol succinate was reported to have pH dependence and drug was having comparatively more solubility in 0.1N HCl. Samples were analyzed [19] for UV absorbance by U.V spectrophotometer (UV 2450-Shimadzu) at a wavelength of 274 nm.

The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from reference standards. During the drug release studies, the formulations were observed for physical integrity at different time intervals.

Characterization of Release Data: The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

RELEASE KINETICS MODEL	EQUATION
ZERO ORDER	$M = M_o - K_0 t$
FIRST ORDER	$\ln M = \ln M_0 - K_1 t$
HIGUCHI MODEL	$Q = K_s \sqrt{t}$
KORSEMEYER'S EQUATION	$M_t / M_\infty = K_k . t^n$
HIXSON CROWELL CUBE ROOT LAW	$\sqrt[3]{M} = \sqrt[3]{M_o} - K_{HC}.t$

Where, M_t is the amount of drug dissolved in time t, Mo the initial amount of drug, K_1 is the first order release constant, K_0 the zero order release constant, K_s the Higuchi rate constant, K_k the release constant and n is the diffusion release exponent indicative of the operating release mechanism. The correlation coefficient (R^2) was used as an indicator of the best fitting, for each of the models considered. The dissolution parameters used for comparing the different formulations were R^2, MDT and DE% (calculation done by using DD solver Software) [20].

1. **Mean dissolution time (MDT):** The following equation was used to calculate the **mean dissolution time (MDT)** from the mean dissolution data.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where (i) is the dissolution sample number, n is the number of dissolution sample time, t mid is the time at the midpoint between i and i-1 and ΔM is the additional amount of drug dissolved between i and i-1. MDT, which is calculated from the amount of drug released to the total cumulative drug. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate.

2. **Dissolution efficiency (DE %)** after 16hr of release test was used to compare the results of dissolution tests of different formulations:

$$DE\ \% = \frac{\int_0^t y\, dt}{y_{100}\, t} \times 100$$

3. **Thermal analysis:** DSC scan was performed by accurately weighing the sample of pure drug Metoprolol succinate and the triple-layer matrix tablets (DSC- 827e, Mettler, Toledo- Inc., 1900, U.S.A) aluminum pans were used in the experiment and the empty pan were also sealed which are used as references.

The temperature was calibrated with indium as standard. The scanning rate of samples was from 50°C -300°C at 10°C/min, nitrogen gas was allowed at 10ml/min.

4. **Stability studies:** Stability studies were conducted for the optimized formulations .To assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing at 40°C/75% RH for 3 months in Heavy weight High Density Polyethylene bottles (40cc capacity) with screw cap was evaluated.

5. **Similarity factor (f2):** FDA's [Food and Drug Administration] guidance on scale up and post approval changes for immediate release oral solid dosage forms [SUPAC-IR] [21] recommends a metric that can be used to compare dissolution profiles of different formulations. This metric, f2, is called the similarity factor and is defined by the following equation:

$$f_2 = 50\log\{[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}x100\}$$

Where Rt is the percentage dissolved at each time point for the reference formulation and Tt is the percentage dissolved at each time point for the test formulation. This method of comparing dissolution profiles was introduced by Moore and Flanner [22]. The similarity factor is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f2 value between 50 and 100 suggests that 2 dissolution profiles are similar and indicates a point-to-point difference of 10% or less. This f2 value comparison was also performed for the TLM tablet and MLM tablet by taking marketed formulation of metoprolol succinate ER tablet-50mg strength, as reference.

RESULTS AND DISCUSSION:

Comparison of Drug Release from Core tablet, Core with single barrier, and Core tablet with barrier layer on both sides (Table 5, figure 1): The time taken for 25%,50%75%,80% fraction of the drug to be released from the dosage form (T25%, T50%, T75%, and T80%) respectively was studied (**Table 3**). For Core (C) the values for above parameter were (0.4hrs, 1.47hrs, 3.09hrsand 3.59hrs) respectively. The fast release might be attributed to the maximum surface area available for dissolution of the drug from the dosage form. For the core + barrier layer 1 (CB1) containing HPMC E50 the values were increased (0.76hrs, 1.92hrs, 5.11hrs and 6.41hrs) respectively. This might be attributed to relatively less surface area available for the dissolution as compared to only core tablet.

Whereas, for Core + barrier layer 2(CB2) having HPMC-E15 the values were (0.53hrs, 1.92hrs, 4.15hrs and 4.67 hrs) respectively. The release profile of CB2 was appeared to be faster than the CB1, this might be attributed to the lower viscosity of the polymer used in case of CB2. On the other hand in case of (B1CB2), Core layer with barrier layers on both sides, the values were increased (1.48hrs, 6.44hrs, 11.41hrs and 12.02 hrs) respectively, a better controlled release might be attributed to the less surface area available for the dissolution at the initial stages of the dissolution process resulting in the better control of a freely water soluble drug release from the core layer. The drug release profile in (B1CB2) was much linear as compared to other formulation by comparing the R^2 of all formulations (**Table 4 and Figure 1**).

TABLE 3:COMPARISON OF DRUG RELEASE AT DIFFERENT TIME PERIODS FOR DIFFERENT FORMULATION (CALCULATION DONE USING DD-SOLVER SOFTWARE)

		Drug fraction release as function of Time Parameter			
Formulations	**Code**	**T25%**	**T50%**	**T75%**	**T80%**
Core tablet	**C**	0.40	1.47	3.09	3.59
(Core+barrier-1)tablet	**C+(B1)1**	0.76	1.92	5.11	6.41
(Core+barrier-2)tablet	**C+(B2)1**	0.53	1.92	4.15	4.67
TLM tablet	**(B1CB2)/ GM-1**	1.48	6.44	11.41	12.62
	GM-2	1.69	5.38	9.16	10.09
	GM-3	3.66	7.90	14.58	16.64
	GM-4	3.90	8.03	13.58	15.16
	GM-5	2.60	5.97	10.69	12.07
MLM Tab	**M1**	0.46	2.76	6.07	7.04
	M2	1.13	2.59	6.26	7.15
	M3	0.26	3.03	6.73	7.78

TABLE 4:COMPARISON OF PARAMETERS OF GOODNESS OF FIT OF DIFFERENT FORMULATION, WHERE R^2 IS RESIDUAL MEAN SQUARE, MSE- MEAN SQUARE ERROR, WSS- SUM OF SQUARE; AIC-AKAIKE INFORMATION CRITERION; MSC- MODEL SELECTION CRITERION.

		Goodness of fit						
Formulations	**Code**	**R**	**R^2**	**R^2_adj**	**MSE root**	**WSS**	**AIC**	**MSC**
Core tablet	**C**	0.820	0.672	0.607	15.020	1128.02	53.198	0.544
(core+barrier-1) Tablet	**C+(B1)1**	0.885	0.783	0.740	11.588	671.414	49.566	0.957
(core+barrier-2) Tablet	**C+(B2)1**	0.841	0.707	0.648	16.022	1283.5	54.102	0.656
TLM tablet	**(B1CB2)/ GM-1**	0.996	0.992	0.991	2.427	29.457	27.680	4.311
	G M-2	0.991	0.982	0.978	4.483	100.48	36.270	3.447
	GM-3	0.989	0.978	0.973	4.448	98.938	36.162	3.238
	GM-4	0.995	0.989	0.987	3.220	51.827	31.635	3.964
	GM-5	0.984	0.969	0.963	5.735	164.45	39.718	2.904
MLM Tab	**M1**	0.951	0.904	0.885	9.018	406.650	46.056	1.770
	M2	0.976	0.952	0.943	6.126	187.608	40.641	2.471
	M3	0.958	0.918	0.902	7.957	316.537	44.302	1.931

TABLE 5:DRUG RELEASE FROM CORE TABLET (C), CORE TABLET WITH BARRIER LAYER 1(CB1, CORE TABLET WITH BARRIER LAYER2 (CB2)) AND CORE TABLET WITH BARRIER ON BOTH SIDES (B1CB2):

	% Drug release in Dissolution Media- 0.1N HCl-500ml-USP2-50RPM			
Time (hr)	**(C)**	**(CB1)**	**(CB2)**	**(B1CB2)**
	Core	**Core(C) + barrier 1 having HPMC-E50**	**Core(C) + barrier 2 having HPMC-E15**	**Core(C) +both Barrier (B1)1&(B2)1**
0	0	0	0	0
1	39.6	32.3	40.9	21.2
2	60.6	51.7	55.2	29.8
4	82.8	68.6	62.3	36.5
6	92.9	79.2	96.6	47.5
8	98.9	82.3	104.5	58.2
12	101.9	93.5	102.4	77.6
16	101.7	93.8	103.4	90.6
20		95.6	99.8	96.3
24		96.0	100.8	95.8

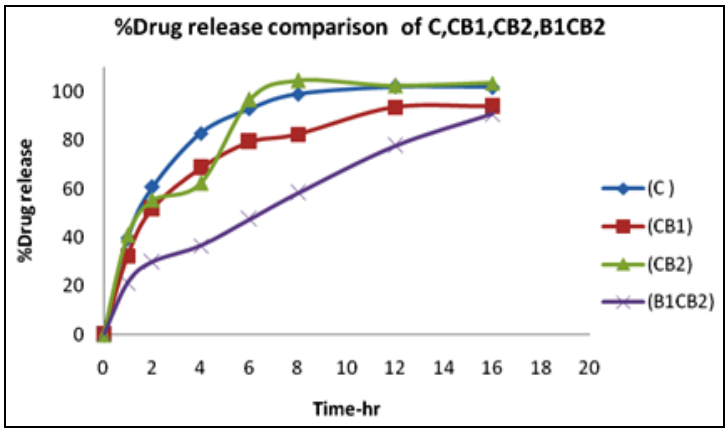

FIGURE 1: %DRUG RELEASE COMPARISON FROM CORE TABLET (C), CORE TABLET WITH BARRIER LAYER 1(CB1, CORE TABLET WITH BARRIER LAYER2 (CB2)) AND CORE TABLET WITH BARRIER ON BOTH SIDES (B1CB2)

It can be concluded from the above data that core alone was not able to control the release of a freely soluble drug from a matrix unit dosage form .With application of barrier layer on one side of the core, the drug release rate was controlled to some extent but with application of barrier layers on both the sides a significant control of drug release was observed. This can be attributed to the reduction in effective surface area available for dissolution because of presence of the barrier layers to the core layer. Secondly, by changing the viscosity of the polymer of the barrier layer the drug release can be modulated, the high viscosity polymers were able to control the drug release for extended period of time.

Comparison of drug release from TLM tablet having same core but with different barrier layer composition (table 6, figure 2): Formulation GM-2 and GM-3 both had same core but the barrier layers were

different. The parameters T25%, T50%, T75%, and T80% for GM -2 having HPMC-E-50 in one barrier layer and HPMC K100LV in second barrier layer was 1.69hrs, 5.38 hr, 9.16hrs and 10.09hrs respectively, whereas for the GM-3, which has HPMC-K100 LV in both of the barrier layer, the values were 3.66 hrs, 7.90hrs, 14.48hrs and 16.04 hrs respectively (Table 3).

TABLE 6: COMPARISON OF DRUG RELEASE FROM TABLET HAVING SAME CORE BUT WITH DIFFERENT VISCOSITY OF POLYMER IN THE BARRIER LAYERS

	GM2	GM3
Time-hr	**HPMC-E50 in Barrier one and HPMC-K100LV in second barrier)**	**(HPMC-K100LV in both barrier layers)**
0	0	0
1	16.9	4.4
2	29.1	14.4
4	44.1	29.1
6	54.6	40.1
8	64.6	49.1
12	87.1	63.6
16	102.4	82.2
20		95.7
24		96

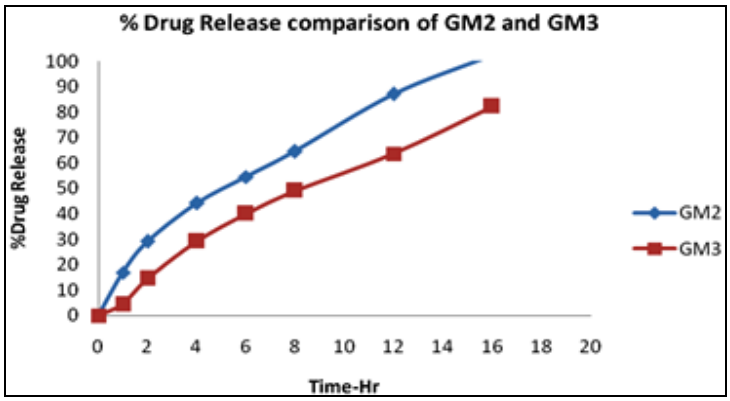

FIGURE 2: % DRUG RELEASE COMPARISON OF GM2 AND GM3

The GM2 with barrier layer of lower viscosity was showing faster release as it might had lost its integrity comparatively faster than the GM3 ,which was having polymer of comparatively high viscosity and caused early exposure of the core layer to the external environment. By using polymer of higher viscosity in GM3, a better and stronger gel formation occurred which might have retarded the drug release more effectively. Hence, with use of polymer with higher viscosity the barrier layer remained intact for longer time and able to control the drug release for longer duration of time. From this, we can conclude that barrier layer composition was significantly modulating the release of water soluble drug from the core matrix.

Effect of changing polymers in core tablet keeping the barrier layer of high viscosity polymer on both sides (table 7, figure 3.): In this we compared formulation GM3 and GM4.The GM3 and GM4 had both of the barriers layer same but difference was in the core .The core of GM4 had HPMC-K-15: HPMC-K100MCR in ratio of 18:30 but core of GM-3 had only HPMC-K15MCR, i.e. the core of GM-4 had more ratio of high viscosity polymers. For the formulation GM-3, the parameters T25%, T50%, T75%, and T80% were 3.66 hrs, 7.90hrs, 14.48hrs and 16.04 hrs respectively. For the formulation GM-4 the values were 3.90hrs, 8.03hrs, 13.58hrs and 15.16 respectively (Table 3).

TABLE 7: EFFECT OF CHANGING POLYMERS IN CORE TABLET KEEPING THE BARRIER LAYER OF HIGH VISCOSITY POLYMER ON BOTH SIDES

% Drug release in Dissolution Media 0.1N HCl-500ml-USP2-50RPM		
	GM3	GM4
Time(hr)	**Core with HPMC- K15MCR**	**Core with HPMC-K15: HPMCK100MCR(18:30)**
0	0	0
1	4.4	4.4
2	14.4	15.8
4	29.1	28.0
6	40.1	38.5
8	49.1	47.9
12	63.6	66.3
16	82.2	85.6
20	95.7	94.6
24	96.0	94.9

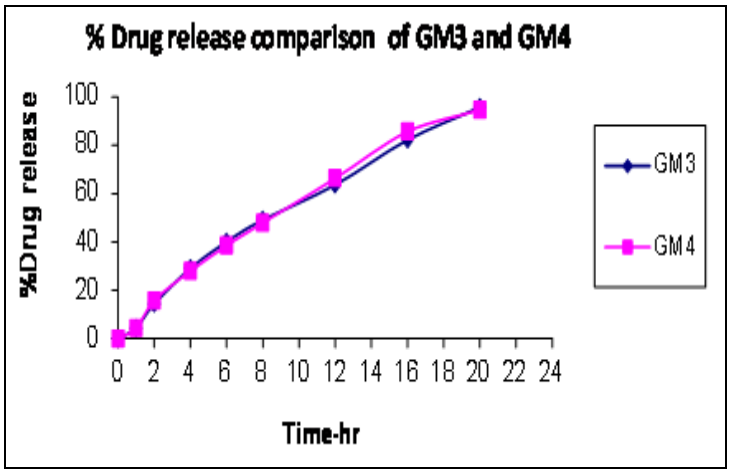

FIGURE 3: %DRUG RELEASE COMPARISON OF GM3 AND GM4

From the above result, it was evident that there was not any significant effect of changing polymer viscosity in the core and keeping the same barrier layer composition. The formulation GM-4 with core layer of higher viscosity was showing similar release when compared to GM-3 having core layer of comparatively lower viscosity. It can be concluded that the core layer composition has very less effect in modulating the release of a freely water soluble drug from a matrix tablet.

Comparison of Drug release from TLM tablets with MLM tablet dosage form (table 8, figure 4): The GM-4 (a TLM formulation) was compared with the MLM tablets M1, M2 and M3. Same types of excipients were used as in triple layered tablet.

Where M1 had HPMC K 4 MCR: (200)

Where M2 had HPMC K 4 MCR: HPMC K15 in ratio:

(75: 125)

Where M3 had HPMC K15: HPMC K 100MCR in ratio: (75: 125)

The parameters T25%, T50%, T75%, and T80% for M-1 the value were 0.46hrs, 2.76hrs, 6.07hrs and 7.04hrs respectively. For M-2 the values were 1.13hrs, 2.59h, 6.26hrs and 7.16 hrs respectively. For M-3 the values were 0.26hrs, 3.03hrs, 6.73 hrs and 7.78 hrs respectively.

On the other hand for TLM tablet GM-4 (Core +barrier layer on both sides) the values were 3.90hrs, 8.03hrs, 13.58hrs and 15.16 respectively (Table 3).

By comparison of the R^2 value of all formulations it can be concluded that GM4, the TLM tablet was following zero order drug release profile (Table 4). Metoprolol succinate in TLM formulation with two barrier layers resulted in better drug retardation from tablet dosage form when compared to the monolayer tablets.

This can be attributed to the reduction in effective surface area for the drug containing core layer to the dissolution media after the introduction of the barrier layers. The barrier layers inhibit the dissolution medium ingress into the drug core from all directions.

The barrier layers after sufficient swelling themselves allowed more dissolution medium to enter the tablet and result in further dissolution. That helped in controlling the release of a freely soluble drug and a linear release profile (**Figure 4**). In the MLM tablets, dissolution media penetrated the tablet from all sides resulting in more dissolution medium ingress, polymer swells, resulting in faster drug dissolution and a non-linear drug release profile (Figure 4).

TABLE 8: COMPARISON OF DRUG RELEASE FROM TLM DOSAGE FORM (GM4) WITH MLM FORMULATIONS (M1, M2, M3)

% Drug release in Dissolution Media 0.1N HCl-500ml-USP2-50RPM				
Time(hr)	**GM4**	**M1**	**M2**	**M3**
0	0.0	0.0	0.0	0.0
1	4.4	28.3	35.7	30.9
2	15.8	46.7	49.0	42.2
4	28.0	61.1	61.2	58.4
6	38.5	72.9	73.0	70.7
8	47.9	82.0	81.6	79.5
12	66.3	95.0	97.5	92.7
16	85.6	103.1	107.0	99.4
20	94.6	107.6	108.5	103.9
24	94.9	109.6	109.3	104.4

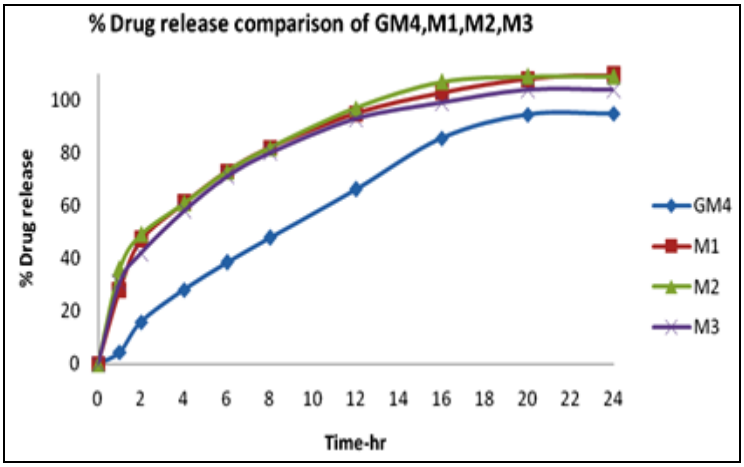

FIGURE 4: % DRUG RELEASE COMPARISON OF GM4, M1, M2, M3

M1, M2, M3 were fabricated as a MLM tablet formulation by using different polymers. It was found that there was no difference in the drug release from all formulations This indicates the inability of the monolayer tablet system to control the initial burst release even after increasing the polymer viscosity (HPMC K4MCR in M1; Combination of HPMC K4MCR + HPMC K15MCR in M2 and HPMC K15MCR in M3)

Comparison of Dissolution efficiency (DE %) and Mean Dissolution time (MDT) of different formulation (Table 9): By comparing the DE% and MDT of the different formulation (Table-9), it was clear that drug release was effectively controlled by application of barriers layer as the DE % for Triple layer tablet formulation was showing remarkably less value than core or MLM formulation. The DE% value of reference and GM-5 were also comparable.

TABLE 9:COMPARISON OF MEAN DISSOLUTION TIME-[MDT], DISSOLUTION EFFICIENCY-DE %, SIMILARITY FACTOR (F2 VALUE) OF DIFFERENT FORMULATION

Formulations	Formulation Codes	MDT	DE (%)	F2 value
Marketed tablet - Metoprolol Succinate ER tab-50 mg	**Reference tablet-(R)**	7.19	53.5	-
Core	**C**	4.01	86.2	23
Triple layer tablet	**GM1**	6.37	56.3	61
	GM2	6.65	62.5	52
	GM3	7.46	45.4	54
	GM4	7.58	46.1	56
	GM5	6.98	55.6	70
Monolayer tablet	**M1**	5.32	74.5	33
	M2	5.18	76.7	33
	M3	5.3	72.2	35

This was also demonstrated by the MDT parameter comparison, the value increased by application of barrier layer on core. The MDT value of reference and GM-5 were also comparable. This further supports that barrier layer had a role in modulating the drug release from core tablet.

DSC Studies: The Thermogram obtained by these studies for the pure drug Metoprolol succinate showed a sharp peak at 141.9°C.The reported value for the metoprolol succinate is 138^{o}C [23] . Thermogram of the formulation GM-5(initial) showed the peak at 149.1°C. As melting point of Metoprolol succinate and peak showed by formulation GM-5(initial) were nearer it revealed that there was no much interaction between the drug and excipients used in study. More over the Thermogram GM-5 (3 months at 40±2°C/75±5% RH (ACC)) was 150.1°C which was very close to GM-5 (initial). The formulation was not showing any interaction even after 3 months of accelerated stability conditions (**Figure 5**). So it can be concluded that there was not any interaction in the excipients of Triple layer tablet even after storing at 40°C/75% RH for 3 months in Heavy weight High Density Polyethylene bottles (40cc capacity) with screw cap.

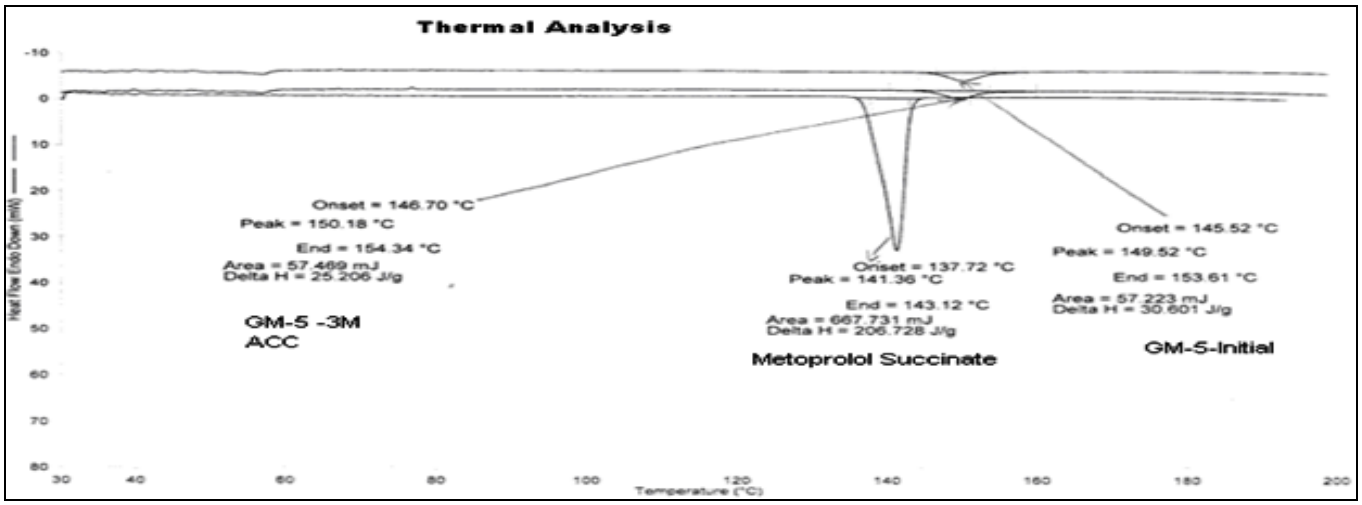

FIGURE 5: THERMOGRAM SHOWING PEAKS FOR GM-5-3M-ACC (3M-40±2°C/75±5% RH), METOPROLOL SUCCINATE AND GM-5-INITIAL FORMULATION

Stability Studies: The TLM tablets GM-5 after storing at 40±2°C /75±5% RH for 3 months showed no changes in physical appearance and the dissolution profile as shown in **Fig. 6**. So we can conclude that triple layer formulation was stable as clear from the *in-vitro* evaluation after the accelerated stability studies for 3 month time period.

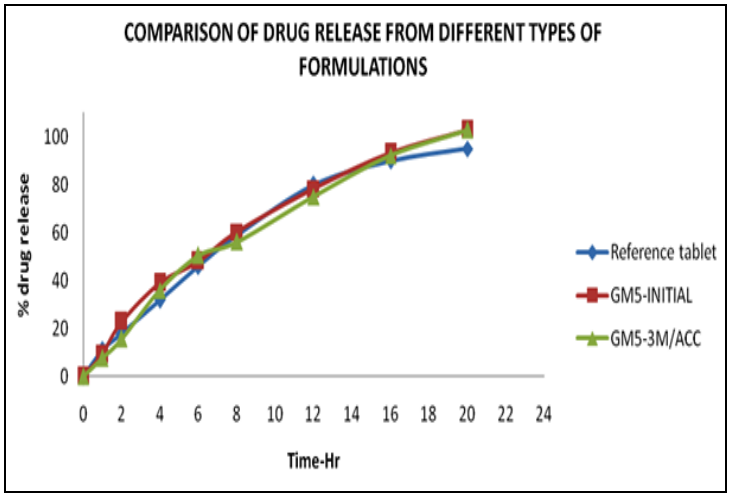

FIGURE 6: COMPARISON OF DRUG RELEASE FROM REFERENCE TABLET (MARKETED TABLET OF METOPROLOL ER TABLET-50 MG), GM5-INITIAL, GM5-3M/ACC (3 MONTH STABILITY AT 40^0 C/75%RH) FORMULATION.

Similarity factor: The F2 value comparison (Table 9) of TLM formulation and reference (marketed formulation of Metoprolol succinate ER tablets was comparable, where as MLM formulation was not similar to reference marketed formulation of Metoprolol succinate ER tablets as clear from Table 9. This result clearly indicates that the TLM formulation is better in controlling the drug release of a freely water soluble drug as compared to the MLM formulation.

CONCLUSION: From the present study, it was found that change in the polymer viscosity did not alter the drug release profile (in M1, M2 and M3 tablet formulation) in the MLM tablet system. Also by changing the polymer viscosity in the core layer of a TLM tablet systems, it did not alter the drug release from the TLM tablet (as seen in GM3 and GM4). On the other hand by changing the polymer viscosity in the barrier layer composition altered the drug release from the final TLM tablet system (as seen in GM4 and GM5). This confirmed the role of barrier layer in controlling the release of a freely water soluble drug from a TLM tablets.

It can be concluded from the study that the control of freely water soluble drug release was effectively achieved by only TLM tablet formulation, with drug core layer entrapped in two polymeric barrier layers. With application of the barrier layers, the initial burst release of the drug was also controlled, as effective surface area exposed for dissolution was reduced significantly and a linear drug release order profile achieved, which was not observed in case of MLM tablet.

ACKNOWLEDGEMENT: Kanwarpreet Singh Bakshi is thankful to the Ranbaxy Laboratories Limited, for providing the resources required for the research and also acknowledges the guidance and kind support of K. Vivek, Senior Research Scientist, Murali Krishna B, Senior Research Scientist, Sreekanth Naravulla, Senior Research Scientist and Romi Singh, Associate Director, Ajay K. Singla, Director in Ranbaxy Research Laboratories, Gurgaon and Rajan K. Verma, Associate Director, Ferring Pharmaceutical, Mumbai, India.

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How to cite this article:
Bakshi KS, Vivek K, Verma RK, Krishna B M, Narravula S, Singh RB and Singla AK.: Investigation on the impact of Core snd Barrier Layer Composition on the Drug Release from a Triple Layer Tablet. *Int J Pharm Sci Res*, 2012; Vol. 3(7): 2168-2179.