Singaporean Journal of Scientific Research(SJSR)
An International Journal (AMIJ)
Vol.9.No.1 2017,Pp.65-76
available at :www.sjsronline.com
Paper Received : 02-01-2017
Paper Accepted: 05-03-2017
Paper Reviewed by: 1.Prof. Cheng Yu 2. Dr.M. Akshay Kumar
Editor : Dr. R. Akilesh Mathur

Design and Development of Metoprolol Tartrate and Hydrochlorothiazide Bi-Layer Tablets By Using Carbopol 971 and HPMC K-100 Polymers

Jayanthi Bangaru
Department of Pharmacy
Annamalai University
Annamalai Nagar, Tamilnadu, India.

Abstract

The present investigation relates to the development of Bilayer dosage form containing combination of Extended and immediate release layer by using Metoprolol Tartrate and Hydrochlorothiazide respectively for the treatment of Hypertension. Metoprolol (ER) is a beta-1 cardio-selective adrenoreceptor blocking agent, for oral administration in the treatment of hypertension through controlled and predictable release of metoprolol, angina pectoris and heart failure. Metoprolol reduces the force of contraction of heart muscle and thereby lowers blood pressure. By reducing the heart rate and the force of muscle contraction. Hydrochlorothiazide is a first line diuretic drug of the thiazide class that acts by inhibiting the kidney's ability to retain water; it is also a well-established diuretic and antihypertensive agent, which promotes natriuresis by acting on the distal renal tubule. This reduces the volume of the blood, decreasing lower peripheral vascular resistance. The combination product is more effective than mono therapy with the individual components because the combination product allows a low-dose multidrug regimen as an alternative to high-dose monotherapy, thereby, minimizing the likelihood of dose-related side-effects. The purpose of this study is to improve the efficacy of the polymer controlling the drug release, therefore increasing the bioavailability of bilayered tablets of Metoprolol Tartrate Extended release and Hydrochlorothiazide immediate release by inducing a synergistic interaction after introduction of CARBOPOL 971 hydrophilic polymer in a previously used polymer matrix of HPMC K-100 (Hydroxypropyl methyl cellulose).

Keywords: Bilayer dosage, Metoprolol Tartrate, Hydrochlorothiazide, Hypertension, Carbopol 971, HPMC K-100.

1. INTRODUCTION

1.1 EXTENDED RELEASE CONCEPT [6, 42]

Over the past 30 years as the expenses and complications involved in marketing new drug entities have increased. With concomitant recognition if the therapeutic advantages of extended drug delivery, greater attention has been focused on development of extended or controlled release drug delivery systems[1-3]. The attractiveness of these dosage forms is due to awareness to toxicity and other properties of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments, etc. Usually conventional dosage forms produce wide range fluctuation in drug concentration in the blood stream

and tissues with consequent undesirable toxicity and poor efficiency. The factors such as repetitive dosing and unpredictable absorption led to the concept of extended drug delivery systems.

MATRIX TABLETS: [7,45]

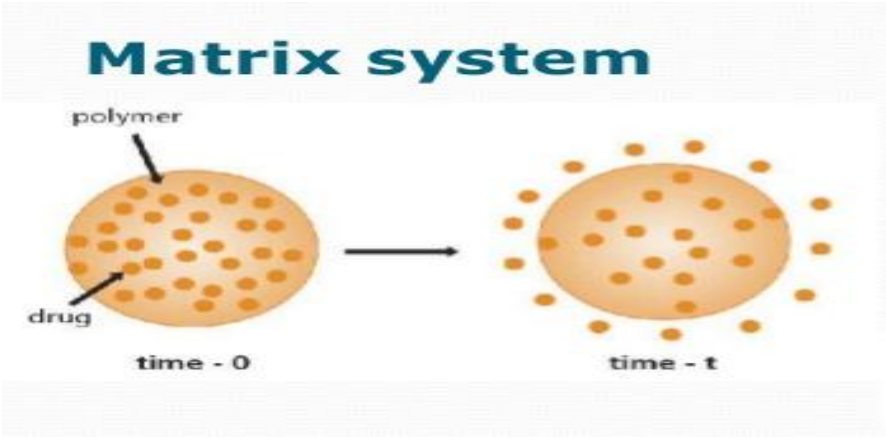

Figure-1- Drug release from a matrix

Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix[4,5].

This system involves the following assumptions:

- A pseudo steady state is maintained during drug release.
- The diameter of the drug particles is less than the average pores of drug diffusion throughout the matrix.
- The diffusion coefficient of drug in the matrix remains constant i.e., no change occurs in the characteristics of the polymer matrix.
- The mechanism of release from these systems can be considered in two ways:
  a) Extraction of the medicament by a simple diffusion process through enveloping homogenous matrix.
  b) Leaching of the medicament by the bathing fluid, which is able to enter the drug-matrix through pores, cracks and inter granular spaces.

Table-1-: Materials used as retardants in Matrix tablet formulations:

Sl. No	Matrix characteristics	Materials
1.	Insoluble, Inert	Polyeythylene, polyvinyl chloride, Methylacrylate Co-polymer, Ethyl cellulose[8,9,10]
2.	Insoluble, Erodible	Carnauba wax, stearyl Alcohol, Stearic acid, PEG[11-16]
3.	Hydrophilic	Methyl cellulose, HPMC, sodium CMC, Carbomers[17,18]

Drug release from Carbopol 971 polymer matrix tablets is controlled more by the polymer structure (crosslink density) than by viscosity. Lightly cross linked polymers have fewer crosslink sites to constrain the polymer, and a homogeneous gel structure forms at lower concentrations compared to highly cross linked polymers. As a result, the active ingredient is less subjected to diffusion through the gel layer. In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers (eg: Carbopol 974P NF, Carbopol 980NF, etc.). Lightly cross linked carbomers such as Carbopol 971 polymer are generally more efficient in controlling drug release than highly cross linked carbomers such as Carbopol 974 polymer (higher viscosity)

Potential Benefits of a Combination Matrix (Carbopol 971 Polymer and Hydroxypropyl Methyl Cellulose) vs. use of a single Polymer Matrix[20-24]

Data demonstrates a synergistic interaction may occur when Carbopol polymers are used in combination with Hydroxypropyl methyl cellulose. Specifically, a lower total polymer level could be used in a formulation, thus enabling smaller tablet sizes and overall formulation cost savings.

Additionally, more consistent drug release can be achieved. By varying the total polymer levels and ratio of the two polymers, it is possible to modulate the drug release profile.

Synergistic use of Carbopol polymers with other extended release excipients such as (hydroxypropyl cellulose, sodium carboxymethyl cellulose, sodium alginate, polyethylene oxide and methacrylic polymers) can also be achieved[25,26].

Key recommendations to Facilitate wet granulation processes with carbopol 971 [21]

- In order to avoid fast and extensive swelling of the polymer, use a low amount of granulation liquid added at a slow rate in fine droplets (uniform distribution of the solvent in the wet mass). In general, a lower quantity of granulation liquid is used with Carbopol polymers compared to hypromellose[27,28].
- Incorporation of microcrystalline cellulose improves the processability of the formulation. Generally less than 10% of microcrystalline cellulose should be used to prevent disintegration of the tablets.
- Granulation should be controlled in order to prevent over wetting (sticky, rubbery mass[29-31]).
- It is very important to control the drying process and residual moisture in the granules (typical values 1 - 3%), however these parameters are formulation specific. If over dried, Carbopol polymers form hard granules. High residual moisture may lead to tablets sticking in to the punches and may cause stability problems[32-35].

3. MATERIALS AND METHODS

Metoprolol Tartrate, Hydrochlorothiazide, Micro Crystalline Cellulose, Lactose, Hydroxy Propyl Methyl Cellulose K-100, Carbopol 971, Poly vinyl PyrrolidoneK-30, Aerosil were Purchased Analytical grade.

3.1 PRE-FORMULATION STUDIES

A.1 Compatibility studies:

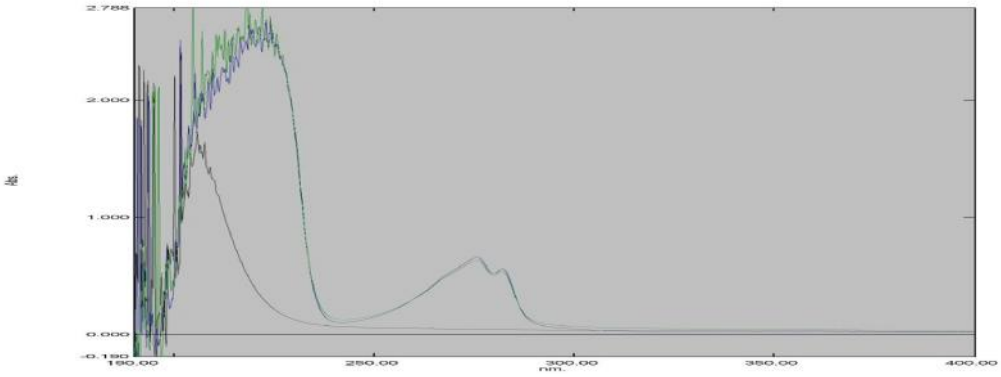

Figure-2-: UV spectrum of the standard Metoprolol Tartrate and the prepared Metoprolol granules compared to its placebo granules.

The previous figure represents UV spectrum of Metoprolol standard (purple line/highest peak), Metoprolol granules (Green line/2nd peak), and its Placebo granules (off Black line/no peak) obtained from assay of Metoprolol as mentioned earlier in the experimental work chapter.

The absorbance of standard Metoprolol was 0.630, as the one of Metoprolol granules was 0.658 which resulted in drug content of 104.59%. But clearly the off-black line representing the placebo granules does not have any

peak at 273nm in the UV range of (200nm – 400nm), which means that no excipients from the placebo granules interact with the drug Metoprolol.

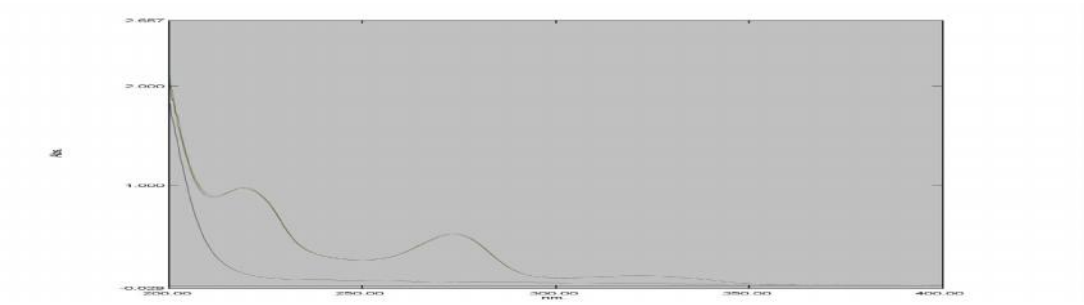

Figure-3-: UV spectrum of the standard Hydrochlorothiazide and the prepared Hydrochlorothiazide granules compared to its placebo granules

The above figure represents UV spectrum of Hydrochlorothiazide standard (Red line/highest peak), Hydrochlorothiazide granules (Green line/2nd peak), and its Placebo granules (off-Black line/no peak) obtained from assay of Hydrochlorothiazide as mentioned earlier in the experimental work chapter.

The absorbance of standard Hydrochlorothiazide was 0.520, as the one of Hydrochlorothiazide granules was 0.521 which resulted in drug content of 99.8%. But clearly the off-Black line representing the placebo granules does not have any peak at 273nm in the UV range of (200nm – 400nm), which means that no excipients from the placebo granules interact with the drug Hydrochlorothiazide.

Physical observation

After 14 days, the samples kept in stability chamber at 40°C ± 2°C / 75 ± 5% RH and 25°C ± 2°C /60± 5% RH both manifested no physical change, the same after 28days. Based on the above results, the compatible excipients were used for formulation and development using suitable processes. Development trials of about 5000 tablets were made and evaluated.

4. EVALUATION OF GRANULES

4.1 Physical Evaluation

4.1.1 Flow Properties of Metoprolol Tartrate Granules

Bulk density and tapped density of Metoprolol Tartrate Extended release granules were found to be 0.373(T1), 0.479(T2) and 0.430(T1), 0.541(T2) respectively which insures good flow properties in addition of an excellent Angle of repose which was 27°55' for (T1), and 28°39'for (T2). Therefore good compressibility of the granules was assured through Carr's index found to be 11.46 for (T1), and 13.26 for (T2) and Hausner's ratio for frictional resistance were found to be excellent (0.870 and 0.885) respectively to T1 and T2. Moisture content was found to be 0.2% and 0.25% for T1 and T2 respectively against the IP claim of NMT 0.5%. Results proving all properties are tabulated table 2.

Table-2: Flow properties of Metoprolol Tartrate (ER) Granules

S.No	Parameters	T1	T2	Inference
1.	Angle of repose(ɵ)*	27°55'	28°39'	Excellent
2.	Bulk density (g/cm3) Untapped*	0.373	0.479	Good
	Tapped*	0.430	0.541	Good
3.	Compressibility index	13.26%	11.46%	Good
4.	Hausner's ratio	0.870	0.885	Excellent
5.	Moisture content* (%)	0.20	0.25	Within limit

All the values are mean, n=3

4.2 Flow properties of hydrochlorothiazide (IR) Granules

Good flow properties were observed through Bulk density, Tapped density and angle of repose of Hydrochlorothiazide IR granules which were found to be (0.36 for T1, 0.38 for T2) and (0.44 for T1, 0.43 for T2) and (33°70´.for T1, 32°71' for T2) respectively. Carr's compressibility index was found good (11.63 for T1, 18.18 for T2) and an excellent frictional resistance was obtained from Hausner ratio (0.88 for T1, 0.82 for T2). Results are tabulated table 3.

Table-3: Flow Properties of Hydrochlorothiazide (IR) Granules

S.no	Parameter	T1	T2	Inference
1.	Angle of repose(ɵ)*	33°70'	32°71'	Good
2.	Bulk density (g/cm3) Untapped*	0.36	0.38	Good
	Tapped*	0.44	0.43	Good
3.	Compressibility Index (%)	18.18	11.63	Good
4.	Hausner's Ratio	0.82	0.88	Excellent
5.	Moisture Content* (%)	0.29	0.32	Within limits

*all the values are mean, n=3

4.3 Assay of Granules

It was done as per the procedure given in experimental work chapter. The test was done for T1 and T2 formulations as per IP 2018 and all the granules passed the test within limits. The results are illustrated in the following table 4.

Table-4: Assay Results of granules:

S.No	**Assay**	**IP specification**	**Results**
T1	Metoprolol (ER)	90.0% - 110.0% of LA	97.540%
	Hydrochlorothiazide	92.5% - 107.5% of LA	98.200%
T2	Metoprolol (ER)	90.0% - 110.0% of LA	105.120%
	Hydrochlorothiazide	92.5% - 107.5% of LA	98.200%

4.4 Evaluation of Bi-layer Tablets

The post compressional parameters of Bi-layer tablets (hardness, friability, weight variation, thickness and drug content) were within the acceptable limits as shown below:

Table-5:.Tablets Evaluation Parameters

S. No	Formulations	Avg. weight/tab (mg)	Hardness (Kg/cm^2)*	Thickness (mm)*	Friability (%)*	Disintegration Time (minutes)*
1	T1	316	4	4.6	0.15	2
2	T2	320	6	4.6	0.16	2

*all the values are mean, n=3

Both batches of Bi-layer tablets fulfilled the official requirements of uniformity of weight. The average percentage deviation of 20 tablets of each formulation was less than ± 5%. The thickness and hardness of the tablet ranged from 4.5mm–4.7mm and 4kg/cm^2 - 6kg/cm^2 respectively. The percentage friability of both batches ranged from 0.15 to 0.16%w/w and the disintegration time of Hydrochlorothiazide (IR) layer was 2 minutes.

Table-6: Weight Variation

S. no	Formulations	Average weight/tab	Deviation	Comments	Inference
1	**T1**	316	±5%	No tablet deviates out of limits	Comply
2	**T2**	320		No tablet deviates out of limits	Comply

4.5 Assay of bi-layer Tablets:

Assay was done as per the procedure given in experimental work chapter. The test was done for T1 and T2 formulations. The labelled amount (LA) of Metoprolol is 50mg and the labelled amount (LA) for Hydrochlorothiazide is 12.5mg. The results are illustrated in the following table 7.

Table-7-: Assay Results of bi-layer tablets

	Assay	IP specification	Results
T1	Metoprolol (ER)	90.0%-110.0% of LA	96.68%
	Hydrochlorothiazide	92.5%-107.5%of LA	101.14%
T2	Metoprolol (ER)	90.0%-110.0% Of LA	98.77%
	Hydrochlorothiazide	92.5%-107.5% Of LA	103.71%

4.6 Dissolution Studies

Table-8: In vitro dissolution profile of Bi-layer Tablets for formulation T-1 (without CARBOPOL 971)

Sustained release layer of Metoprolol Tartrate T1				
Sl. No	Time(hr)	Amount of drug release (mg)	Cumulative % drug release*	Limit (%)
1.	1	8.835	17.67	NMT 25%
2.	4	20.390	40.78	20 – 40
3.	8	32.685	65.37	40 – 60
4.	20	47.940	95.88	NLT 80%
Immediate release layer of Hydrochlorothiazide T1				
Sl. No	Time (hr)	Amount of drug release (mg)	Cumulative % drug release	Limit (%)
1.	½	12.075	96.6	NLT 80%

*all the values are mean, n=6

The above table gives the in vitro dissolution profile of Metoprolol Tartrate extended release and Hydrochlorothiazide immediate release tablet for the formulation T-1 containing only HPMC K-100 as polymer controlling the drug release. The release of Metoprolol Tartrate at 1st, 4th, 8th, 20thhour was found to comply within the limits as shown in the above table. The below Figure shows the graph of in vitro drug release profile of sustained release of Metoprolol Tartrate and immediate release of Hydrochlorothiazide for formulation T-1.

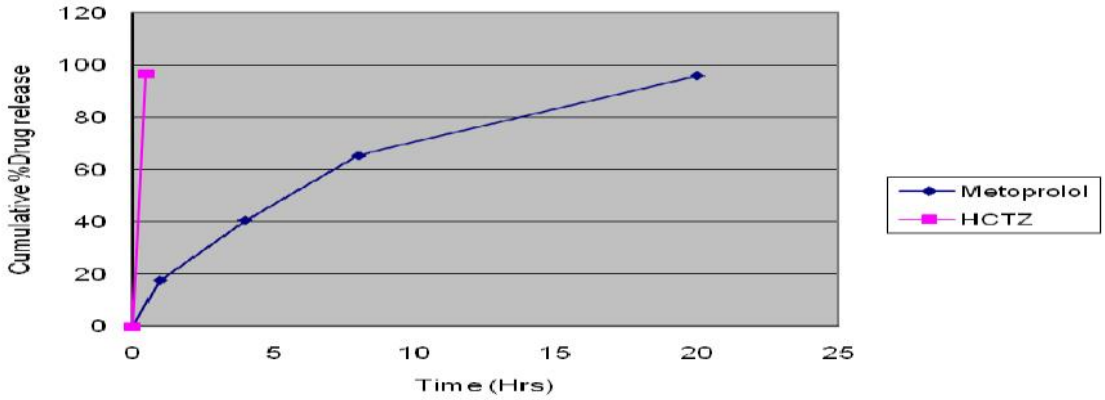

Figure-4-**:** In – Vitro Drug release of Bi-layer Tablets for Trial 1

Table-9: In vitro dissolution profile of Bi-layer tablets for formulation T-2 (with Carbopol 971)

Sustained release layer of Metoprolol Tartrate T2				
Sl. No	Time (hr)	Amount of drug release (mg)	Cumulative % drug release*	Limit (%)
1.	1	8.710	17.42	NMT 25%
2.	4	21.135	42.27	20 – 40
3.	8	34.690	69.38	40 – 60
4.	20	50.645	101.29	NLT 80%
Immediate release layer of Hydrochlorothiazide T2				
Sl. No	Time (hr)	Amount of drug release (mg)	Cumulative % drug release	Limit (%)
1.	1/2	53.450	106.9	NLT 80%

*all the values are mean, n=6

In order to increase the release of the drug, the polymer CARBOPOL971 was introduced in the formula and the previously used polymer HPMC K-100 quantity was adjustably reduced. The above table gives the in vitro dissolution profile of Metoprolol Tartrate extended release and Hydrochlorothiazide immediate release tablet for the formulation F-2. The drug release of Metoprolol Tartrate at 1st, 4th, 8th, 20th hour was found to be 17.42%, 42.27%, 69.38% and 101.29% respectively. Obviously the drug release was enhanced compared to previous T1 results. The release of Hydrochlorothiazide at the end of 1/2 hour was found to be 106.9% which also comprises within limits. The below Figure shows the graph of in vitro drug release profile of Extended release of Metoprolol Tartrate and immediate release of Hydrochlorothiazide for the formulation T-2

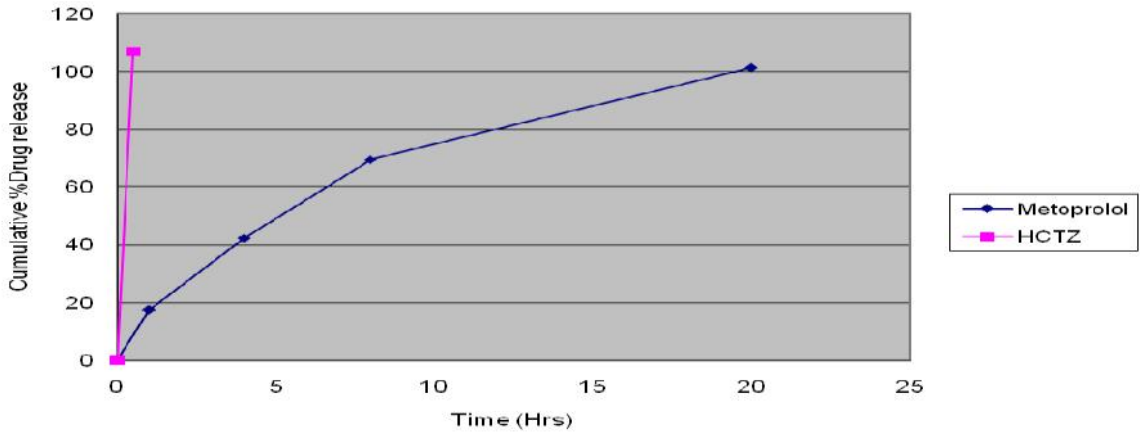

Figure-5-: In – Vitro Drug release of Bi-layer Tablets for Trial 2

Kinetics of Drug release

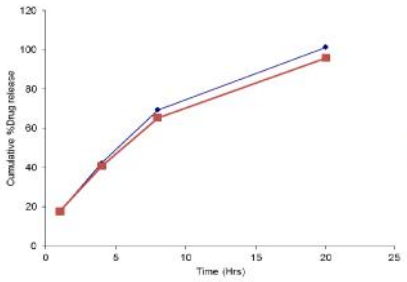

Figure-6: Zero order kinetics

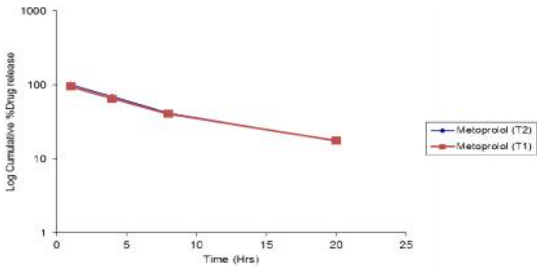

Figure-7: Zero order kinetics

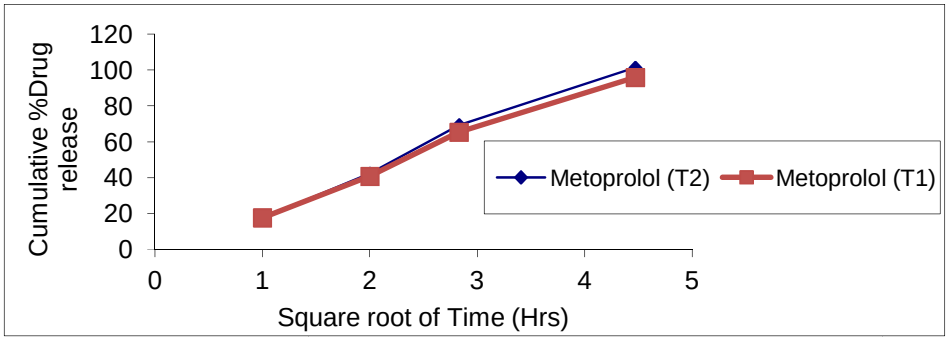

Figure-13- Higuchi diffusion kinetics

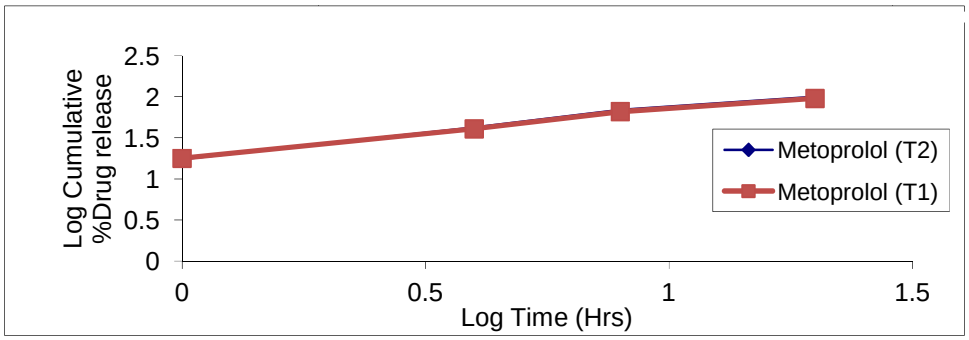

Figure-8: Korsmeyer-Peppas Equation

Table-10: Kinetics studies of Bilayer tablets

Formulated Bilayer tablets code	T1	T2
Release kinetics	R^2	R^2
Zero order	0.929	0.924
First order	0.788	0.725
Higuchi	0.992	0.990
Korsmeyer-peppas	0.888	0.982

4.7 Release Kinetics Study for optimized Bilayer Tablet:

Based on the correlation coefficient (R^2) values obtained from various models Higuchi model fits best as it is closest to one (0.992 for T1 and 0.990 for T2). But also follows first order kinetics which is also close to 1. Hence the release kinetics for T2 was fitted to korsemeyer-peppas equation with R^2 value of 0.982 very close to 1and **'n' value** of 1.2 known as Diffusion or release exponent. It follows non-fickian diffusion model, and the mechanism of drug release is regarded as super case II transport.

4.8 Three Months stability studies observation:

Table11:- Assay Results of bi-layer tablets after accelerated stability studies at 40°C±2°C/75%RH±5%RH

	Assay	IP specification	Results
T1	Metoprolol (ER)	90.0%-110.0% of LA	95.59%
	Hydrochlorothiazide	92.5%-107.5%of LA	101.02%
T2	Metoprolol (ER)	90.0%-110.0% Of LA	98.11%
	Hydrochlorothiazide	92.5%-107.5% Of LA	102.65%

Table12:- Assay Results of bi-layer tablets after real time stability studies at 25°C±2°C/60%RH±5%RH

	Assay	IP specification	Results
T1	Metoprolol (ER)	90.0%-110.0% of LA	96.01%
	Hydrochlorothiazide	92.5%-107.5%of LA	101.10%
T2	Metoprolol (ER)	90.0%-110.0% Of LA	98.30%
	Hydrochlorothiazide	92.5%-107.5% Of LA	103.03%

After 3 months of stability studies as per ICH guidelines assay results from accelerated and real time stability studies at the corresponding storage condition are as shown in the table above and insures good stability of the product as there is no significant change in drug content.

Table 13:- Physical Observation after Accelerated Stability Studies

S. No	Formulations	Thickness (mm)*	Friability (%)*	Description
1	**T1**	4.6	0.17	Round shape, convex faces, one face white, another face orange, no score line or scripture
2	**T2**	4.6	0.16	

5. CONCLUSION

The present research was carried out to improve the efficacy of the polymer controlling the drug release, therefore increasing the bioavailability of bilayered tablets of Metoprolol Tartrate Extended release and Hydrochlorothiazide immediate release by inducing a synergistic interaction after introduction of CARBOPOL 971 hydrophilic polymer in a previously used polymer matrix of HPMC K-100 (Hydroxypropyl methyl cellulose).

Tablets formulation (T2) showed acceptable pharmacotechnical properties and complied with the internal specification for weight variation, thickness, hardness, friability, drug content and in-vitro drug release as well. Drug release from the matrix was found to increase on addition of Carbolpol 971, where the polymer (carbopol 971) concentration employed was 7.88%w/w of the average tablet weight. However, HPMC K100 required was decreasingly adjusted from 36.36% to 18.18% of the tablet average weight (330mg) due to addition of a new polymer.

And the Bioavailability of the drug Formulation (T2) containing a combination matrix polymer of Carbopol 971 and HPMC K-100 showed a better drug release and enhanced Bioavailability compared to Formulation (T1) containing only a single polymer (HPMC K-100).

REFERENCES

[1] Gurvinder Singh Rekhib , Ranjani V. Nellorec, Ajaz S, Hussaind, Lloyd G, Tillmane, Henry J Malinowski, Larry L, Augsburger Identification of critical formulation and processing variables for1 metoprolol tartrate extended-release (ER) matrix tablets. *Journal of Controlled Release,* 1999, 59, 327–342.

[2] Al-Saidana S M, Krishnaiaha Y S R, Satyanarayanab V, P. Bhaskarc, Karthikeyan R S, Pharmacokinetic evaluation of guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug. *Journal of Controlled Release,* 2004, 58, 697–703.

[3] Bjoern, Groenning A, Jens M D, Nilsson C, Lars Sondergaard MD, Thomas Fritz-Hansen MD, Henrik MD, Larsson B W, MD, DMSC, Hildebrandt R, MD, DMSC. Antiremodeling Effects on the Left Ventricle during Beta-Blockade with Metoprolol in the Treatment of Chronic Heart Failure. *Journal of the American College of Cardiology*, 2000, 55, 36-76.

[4] Narendra C, Srinath M S, Prakash Raoa B, Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique. *International Journal of Pharmaceutics,* 2005, 304, 102–114.

[5] Milton packer, Do b-Blockers Prolong Survival in Heart Failure only by inhibiting the b1-Receptor. A Perspective on the results of the COMET trial. *Journal of Cardiac Failure*, 2003, 9, 429-443.

[6] Alan Go S , Jingrong Yang, Jerry, Gurwitz H, John Hsu, Kimberly Lane E, and Richard Platt, Comparative Effectiveness of Beta-Adrenergic Antagonists (Atenolol, Metoprolol Tartrate, Carvedilol) on the Risk of Rehospitalization in Adults with Heart Failure in clinical practice, *American Medical Association*., 2007, 100, 690–696.

[7] Alaa El-Gindy, Ahmed Ashour, Laila Abdel-Fattah Marwan C, Shabana M, Spectrophotometric and HPTLC-densitometricdetermination of lisinopril and hydrochlorothiazide in binary mixtures. *Journal of Pharmaceutical and Biomedical Analysis*, 2001, 25, 923–931.

[8] Hillaert S, Van den Bossche W, Simultaneous determination of hydrochlorothiazide and several angiotensin-II-receptor antagonists by capillary electrophoresis. *Journal of Pharmaceutical and Biomedical Analysis*, 2003, 31, 329-339.

[9] Dindayino F.N. Vervaet C, Van den Mooter G, Remon J.P, Bioavailability of hydrochlorothiazide from isomalt-based moulded tablets. *International Journal of Pharmaceutics*, 2002, 246, 199- 202.

[10] Sam Corveleyn, Jean Paul Remon Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. *International Journal of Pharmaceutics,* 1997, 152, 215–225.

[11] S. Jayaprakash, S. Mohamed Halith, K.Kulathuran Pillai, Priya Balasubramaniyam, P.U. Mohamed Firthouse, M .Boopathi, Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate, *Scholars Research Library Der Pharmacia* Lettre, 2011, 3 (4), 143-154.

[12] Vaijanath G. Dongre, Sweta B. Shah, pravin P. Karmuse,Manisha Phadke, Vivek K. Jadhav Simultaneous determination of metoprolol succinate and amlodipine besylate in pharmaceutical dosage form by HPLC, *Journal of pharmaceutical and Biomedical Analysis* 2008, 46, 583-586.

[13] Ajay L. Barhate, Santosh N. Shinde, Monali S. Sali, Kunal D. Ingale,Vishnu P.Choudhari, Bhanudas S.Kuchekar, Fabrication of Controlled Release Metoprolol Succinate Matrix Tablet : Influence of Some Hydrophilic Polymers on the Release Rate and In Vitro Evaluation**,** *International journal of pharma world research*, 2010, 2 (1).

[14] CH.M.M. Prasada Rao , S.A.Rahaman ,Y.Rajendra Prasad , P. Gangi Reddy, RP-HPLC method of simultaneous estimation of Amlodipine Besylate and Metoprolol in combined dosage form, *International journal of pharma.Research and Development*, 2010, 2(9) 69-76.

[15] Singh Brijesh, D.K Patel and S.K Ghosh, Development of Reverse-Phase HPLC Method for Simultaneous Analysis of Metoprolol Succinate and Hydrochlorothiazide in a Tablet Formulation, *Tropical Journal of Pharmaceutical Research*, December 2009, 8 (6), 539-543.

[16] Raja Kumar Seshadri, Makarand Madhukar desai, Thummala Veera Raghavaraju ,Deepa Krishnan, Dama Venugopala Rao, Ivon Elisha Chakravarthy, Simultaneous Quantitative Determination of Metoprolol, Atorvastatin and Ramipril in Capsules by a Validated Stability-Indicating RP-UPLC Method, *Sci Pharm Research Article.* 2010, 78, 821–834.

[17] V.Rajamanickam, B.Stephen Rathinaraj, N.Thangavelpandian1, Ananda Rajagopal Pandian, A validated RP-HPLC method of Metoprolol Succinate and Amlodipine Succinate from bulk drugs, Amlodipine Succinate from bulk drugs. *Scholars Research Library Der Pharmacia Lettre*, 2010, 2(4), 40-46.

[18] M .Paneerselvam, R.Natarajan, S.Selvarajan and N.N.Rajendran. A Novel drug-drug solid dispersion of Hydrochlorothiazide Losartan Potassium, *International Journal of Pharma and Bio Sciences*, 2010, 1(4), 68-80.

[19] Rekha Gangola, Sunil Kaushik, Paras Sharma, Spectrophotometric Simultaneous Determination of Hydrochlorothiazide and Telmisartan in Combined Dosage Form, *Journal of Applied Pharmaceutical Science*, 2011, 01 (01), 46-49.

[20] Padma Priya, Rajendran.N.N, Lakshmi P K , Umadevi S K, Vijayanthy V, Kausalya J, Ravichandran V. A Novel Captopril Hydrochlorothiazide solid dispersion, *International Journal of Pharmacy and Pharmaceutical Sciences*, 2010, 2(2), 29-32.

[21] Franz H. Messerli, MD, Harikrishna Makani, MD, Alexandre Benjo, MD, Jorge Romero, MD, Carlos Alviar, MD, Antihypertensive Efficacy of Hydrochlorothiazide as Evaluated by Ambulatory Blood Pressure Monitoring, *Journal of the American College of Cardiology*, 2011, 57(5), 590–600.

[22] David E. Clarke, Robert J. Ertel, H. Richard Adams and Joseph P. Buckley, Acute a chronic effects of Hydrochlorothiazide on vascular andregenic mechanisms, *European Journal of Pharmacology*, 1972, 19, 380-384.

[23] Steven G. Chrysant, Daune G. Wombolt, Nancy Felicl ,S and Hongjie Zheng, long term efficacy, safety, and tolerability of Valsartan and Hydrochlorothiazide in patients with essential hypertension, *Current Research Therapeutics*, 1998, 59 (11), 752-762.

[24] Maja Lusinaa, Tanja Cindri´ca, Jadranka Tomaica, Marijana Pekoa, Lidija Pozaica, Nenad Musulinb, Stability study of losartan/hydrochlorothiazide tablets, *International Journal of Pharmaceutics*, 2005, 291, 127–137.

[25] D.S. Desai, B.A. Rubitski, S.A. Varia, N.B. Jain, Povidone- and poloxamer -mediated degradation of hydrochlorothiazide in an antihypertensive combination tablet product**,** *International Journal of Pharmaceutics*, 1996, 142, 61-66.

[26] Y.S.R. Krishnaiah , R.S. Karthikeyan, V. Satyanarayana, A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate, *International Journal of Pharmaceutics*, 2002, 241, 353–366.

[27] Mothilal m, damodharan n, lakshmi k.s, sharanya v.baratharaj, srikrishna, formulation and invitro evaluation of osmotic drug delivery system of metoprolol succinate, *International Journal of Pharmacy and Pharmaceutical Sciences*,2010, 2(2), 64-68.

[28] Manish Ghimire, Lee Ann Hodges, Janet Band, Bridget Mahony, Fiona, McInnes J,Alexander, Mullen B, Howard ,Stevens N.E, In-vitro and in-vivo erosion profiles of hydroxypropylmethylcellulose (HPMC) matrix tablets. *Journal of Controlled Release*, 2010, 147, 70–75.

[29] Chuan-Yu Wu, Jonathan, P.K. Seville P.K, A comparative study of compaction properties of binary and bilayer tablets. Powder Technology, 2009, 189, 285–294.

[30] Jakkie, Van der Watt G, Melgardt, De Villier M, The effect of V-mixer scale-up on the mixing of magnesium stearate with direct compression microcrystalline cellulose. *European Journal of Pharmaceutics and Biopharmaceutics*, 1997, 43, 91-94.

[31] Jenny Herder, Adolfsson , Anette Larsson, Initial studies of water granulation of eight grades of hypromellose (HPMC). International Journal of Pharmaceutics, 2006, 313, 57–65.

[32] Calum R. Park, Dale Munday L, Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. *International Journal of Pharmaceutics*, 2002, 237, 215–226.

[33] Miyazaki S, Kawasaki N, Nakamura T, Iwatsu M, Hayashi T, Hou W M, Attwood D, Oral mucosal bioadhesive tablets of pectin and HPMC: *invitro* and in vivo evaluation. *International Journal of Pharmaceutics*, 2000, 204, 127–132.

[34] Anil Chaudhary, Neha Tiwari, Vikas Jain, Ranjit Singh. Microporous bilayer osmotic tablet for colon-specific delivery, *Eur. J. Pharm. Biopharm.* 2011, 78, 134-140.

[35] Carmen Remun Lopez, Ana Portero, Jose Luis Vila-Jato, Marıa Jose, Alonso Design and evaluation of chitosan ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. *Journal of Controlled Release*, 1998, 55, 143–152.
[36] Yong Shao, Yongdong Jin, Jianlong Wang, Li Wang, Feng Zhao, Shaojun Conducting polymer polypyrrole supported bilayer lipid membranes Dong. *Biosensors and Bioelectronics*, 2005, 20, 1373–1379.
[37] Mina Ibrahim Tadros, Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro–in vivo evaluation inhealthy human volunteers. *European Journal of Pharmaceutics and Biopharmaceutics*, 2010, 74, 332–339.
[38] Panagiotis Barmpalexis, Kyriakos Kachrimanis, Emanouil Georgarakis, Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic programming. *European Journal of Pharmaceutics and Biopharmaceutics*, 2011, 77, 122–131.
[39] Fridrun Podczecka, Emad Al-Mutib the tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. *European Journal of Pharmaceutical Sciences*, 2010, 41, 483–488.
[40] Hema Ravishankar, Preeti Patil, Ashwini Samel, Hans-Ulrich Petereit, Rosario Lizio ,Jayanthi Iyer-Chavan. Modulated release metoprolol succinate formulation based on ionic interactions In vivo proof of concept. *Journal of Controlled Release*, 2006, 111, 65–72.
[41] Hypertension- http://www.medicinenet.com/high_blood_pressure/focus.htm.
[42] Hypertension–wikipedia foundation, http://en.wikipedia.org/wiki/hypertension , https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/diagnosis-treatment/drc-20373417
[43] https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/diagnosis-treatment/drc-20373417
[44] Indian Pharmacopeia 2018
[45] Wikipedia http://en.wikipedia.org/wiki/Hydrochlorothiazide