Available online at www.pharmaresearchlibrary.com/ijrpls

ISSN: 2321-5038
IJRPLS, 2013,1(2):68-76
Research Article

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND LIFE SCIENCES
www.pharmaresearchlibrary.com/ijrpls

Preparation and evaluation of bilayer tablets for Hypertensive patients

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Abstract
The aim of the present work is to design bilayer tablets containing Losartan Potassium for immediate release using sodium starch glycolate as super disintegrant and Metoprolol succinate for extended release using Carbopol 71G, Hydroxy Propyl Methyl Cellulose (HPMC K100M), Xanthan gum and poly ethylene oxide as hydrophilic polymers and Kollidone as binder. The immediate layer was prepared by direct compression and extended release layer by wet granulation method. The tablets were evaluated for physiochemical properties. All the values were found to be satisfactory and were within limits with low standard deviation. *In vitro* release studies were carried out using USP type II paddle apparatus in phosphate buffer (pH 6.8) for 12 h as dissolution medium. The best formulation was subjected accelerated stability studies and the formulation retained its physic chemical characteristics even after stressed storage conditions
Keywords: Metoprolol succinate, Losartan Potassium,Carbopol 71G, HPMC K100M, Xanthan gum, Kollidone

Introduction
Losartan Potassium is chemically described as Mono potassium salt of 2 Butyl 4 chloro -1- [[2'- (1H-tetrazol-5-yl)[1,1'- biphenyl]-4-yl] methyl] 1H- Imidazole- 5- methanol. It is an Angiotensin II receptor antagonist mainly used to treat high blood pressure. It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin angiotensin system. Generally, Losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough. It has a half-life of 1.5-2 h [1].

Metoprolol is a cardio selective β_1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. It has an oral bio-availability of 50% under fasting conditions and it is absorbed slowly. The average elimination half-life in plasma is 3-7 h [2]. Combination therapy has various advantages than mono therapy such as minimized dose dependent side effects, patient compliance. Losartan potassium was formulated as immediate release layer and Metoprolol succinate as extended release layer in order to treat hypertensive patients. Using combination of natural and synthetic polymers has been successfully tried by many researchers for controlled release [3-7].

Materials and Methods
Losartan potassium and Metoprolol succinate were procured as gift samples from Mylan Pharmaceuticals Pvt. Ltd., Hyderabad, India. Carbopol 71G, Kollidone and Xanthan gum were procured from Serin Formulations Pvt. Ltd., Hyderabad, India. Hydroxy Propyl Methyl Cellulose (HPMC K100M) and poly ethylene oxide were obtained from Standard Chemicals, Hyderabad, India. All other chemicals used were of AR grade and double distilled water was used whenever necessary.

Method of preparation of Bilayer tablets
It includes 3 steps in the preparation of Bilayer tablets as follows [8-10].
Step-1: Preparation of Losartan potassium layer (immediate layer)

Losartan potassium along with suitable excipients was mixed uniformly in a glass mortar & pestle. The mixture was passed under the sieve # 30. Later colouring agent (Iron oxide) was added to the preparation and mixed well and followed direct compression.

Step-2: Preparation of Metoprolol succinate layer

Extended release layer containing Metoprolol succinate was prepared by wet granulation technique. Hydrophilic polymer HPMC K 100M was used. Corbopol, kollidone, Xanthan gum, Poly Ethylene Oxide are used in different concentrations for 12 formulations. Metoprolol succinate, polymers and microcrystalline cellulose were used in intra granular material. Corbopol, kollidone, xanthan gum was dissolved in Isopropyl alcohol. The binder solution was mixed with powder to form a damp mass and it is passed through sieve #30. The granules were dried at 55^0 C for 30 min. Then granules were lubricated with magnesium stearate and talc. The powder was compressed in a single station punching machine of 8mm punch.

Step-3: Bilayer tablet manufacturing

The granules of the optimized layers were compressed into bilayer tablets using bilayer tablet punching machine with 8 mm caplet punches. The ER layer was introduced first into the die cavity and a slight compression was made. The IR layer was then introduced over the slightly compressed SR layer and a final compression was made to get the bilayer tablets.

Table 1: Composition for the formulation of Losartan potassium layer

Ingredient (mg)	L1	L2
Losartan potassium	10	10
Micro Crystalline Cellulose	30	30
Sodium starch Glycolate	10	20
Aerosil	2	2
Magnesium stearate	2	2
Ironoxide red	1	1

Table 2: Preparation of Metoprolol layer

Ingredients(mg)	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Carbopol	95	142.5	190	_	_	_	_	_	_	_	_	_
Kollidon	_	_	_	95	142.5	190	_	_	_	_	_	_
Xanthan gum	_	_	_	_	_	_	95	142.5	190	_	_	_
Poly Ethylene Oxide	_	_	_	_	_	_	_	_	_	95	142.5	190
Hydroxy propyl Methyl Cellulose	25	25	25	25	25	25	25	25	25	25	25	25
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Purified Talc	2	2	2	2	2	2	2	2	2	2	2	2

Evaluation parameters

Compatibility Studies

FTIR Studies

The compatibility of drug with the excipients used was tested by FTIR spectroscopy. FTIR spectrums of Metoprolol succinate, Losartan potassium, Metoprolol succinate layer blend, Losartan potassium layer blend and bilayer tablet blend were carried out by using KBr pellet technique. The samples were scanned over from 4,000 to 400 cm^{-1}.Spectral region at a resolution of 4 cm^{-1}.

Evaluation

The prepared bilayer tablets were evaluated for Uniformity of weight, thickness, hardness, friability and uniformity in drug content [11-15]. The thickness of the tablets was measured using vernier caliper. Hardness of the tablets was evaluated using pfizer Hardness tester. Friability of the tablets was determined using Roche friabilator. Drug content was estimated by simultaneous equation method by measuring the absorbance at 256 nm and 222nm respectively using UV Visible Spectrophotometer.

***In vitro* Drug Release studies**

The *in vitro* dissolution study was carried out using USP Type II (paddle) apparatus at 50 rpm. Dissolution study was carried out using 6.8 pH Phosphate buffer solutions for 12 h at 37 ± 0.5^0C. 10 ml of the sample was withdrawn at regular intervals and diluted suitably. The absorbance was measured at 256 nm and 222 nm using UV-Visible Spectrophotometer taking suitably buffer solutions as blank. The in vitro release data was treated mathematically to know the rate of release [16, 17].

Accelerated Stability Studies

The optimized tablets were packed finally in blisters and kept at 40±2^{0}C with 75±5 % RH. The tablets were evaluated for thickness, hardness, friability, uniformity of weight, drug content and *in vitro* drug release [18].

Results and Discussion

The characteristic bands found in FTIR spectrum of drugs were found in FTIR spectrum of the blend, indicating that no physical interaction between the drug and excipients used (fig 1-6).

Fig.1. FTIR spectrum of Losartan potassium

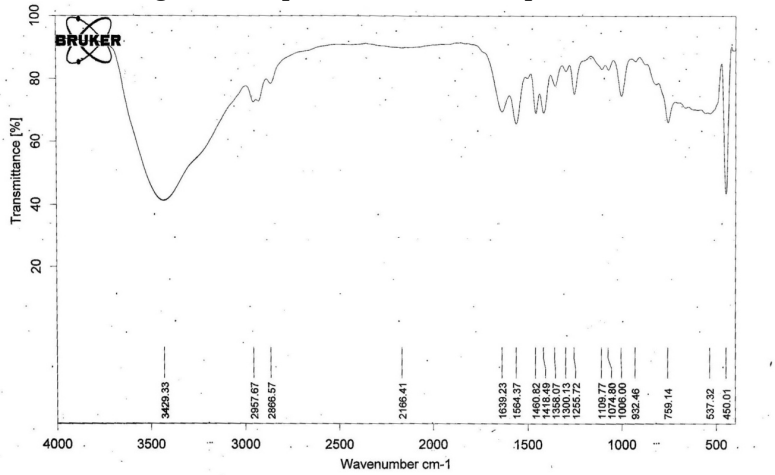


Fig.2. FTIR spectrum of Metoprolol

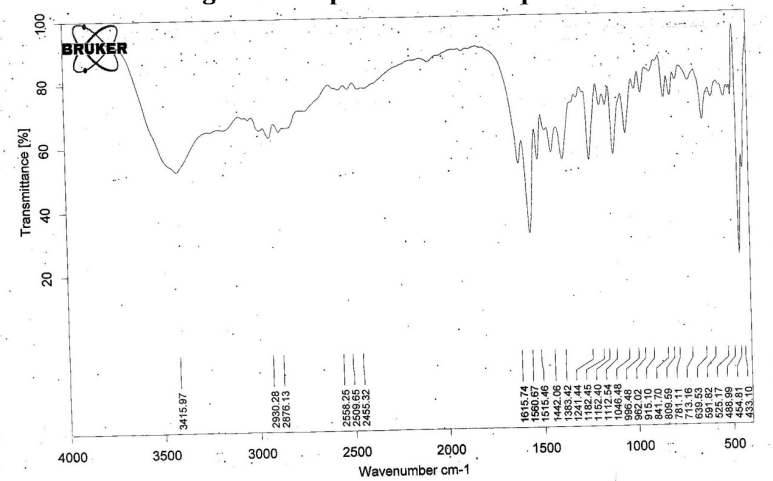


Fig.3. FTIR spectrum of Metoprolol layer blend

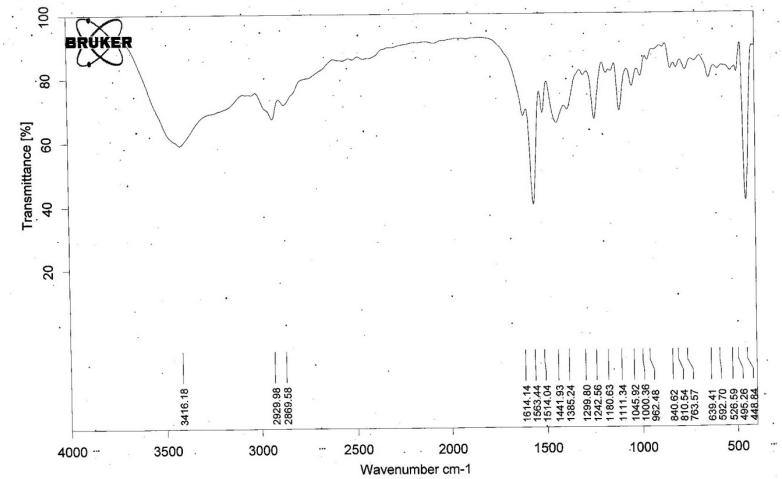


Fig.4. FTIR spectrum of Losartan potassium layer blend

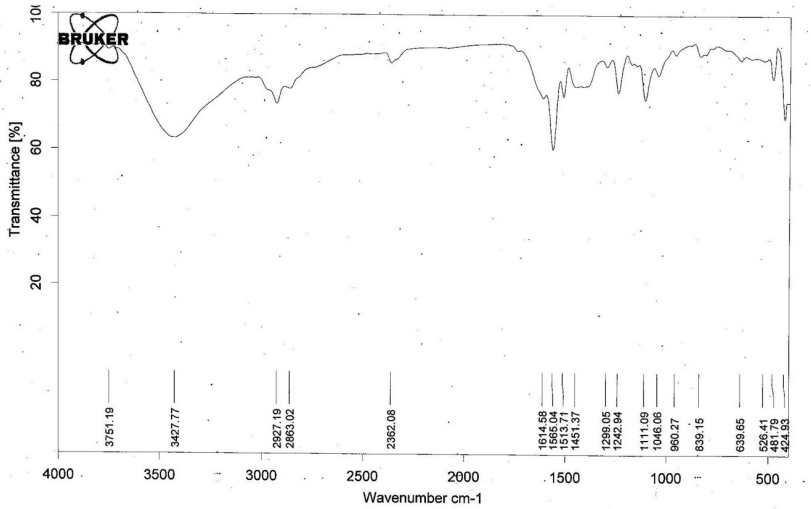
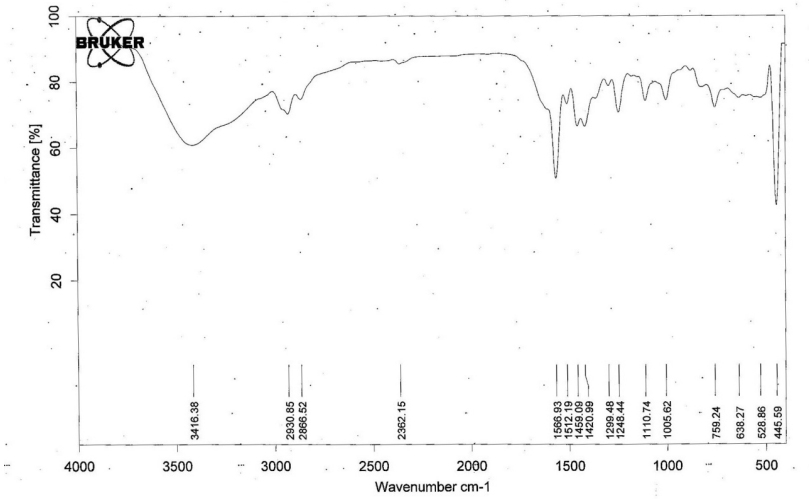


Fig.5. FTIR spectrum of bilayer blend



The result of angles of repose, Carr's Index and Hausner's ratio indicates the good flow ability of the powdered blend. The results of the flow properties were shown in Table 3. The thickness, hardness, uniformity of weight and friability of the prepared tablets were within the limits (table 4). The uniformity of drug content of prepared tablets were shown in table 5.

Table 3: Flow properties of various formulation blends

Parameters	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Angle of Repose (^{0})	28.25±0.703	25.10±1.50	26.75±0.76	27.13±0.89	25.73±0.74	27.34±1.43	26.11±0.41	28.31±0.92	29.01±0.71	29.1±0.78	25.11±0.54	25.32±0.92
Bulk Density (g/ml)	0.65 ±0.03	0.43 ±0.02	0.31±0.02	0.76±0.03	0.61±0.04	0.54±0.03	0.34±0.02	0.42±0.03	0.71±0.01	0.65±0.02	0.52±0.05	0.48±0.04
Tapped Density(g/ml)	0.75±0.02	0.49±0.01	0.39±0.03	0.78±0.02	0.65±0.03	0.59±0.06	0.39±0.03	0.45±0.02	0.73±0.04	0.68±0.02	0.58±0.03	0.56±0.05
Carr's Index	13.33±0.01	12.2±0.08	20.51±0.05	2.56±0.04	6.15±0.04	8.47±0.08	12.8±0.03	6.66±0.04	2.73±0.08	4.41±0.07	10.34±0.03	14.28±0.02
Hausner's Ratio	1.15±0.07	1.13±0.04	1.25±0.04	1.02±0.03	1.06±0.06	1.09±0.07	1.14±0.05	1.07±0.07	1.02±0.03	1.04±0.02	1.11±0.05	1.16±0.07

Table 4: Flow properties of various formulation blends

Formulation	Average weight(g)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1.L1	226.5±0.45	4.2±0.83	3.78±0.32	0.62±0.03
F4.L1	226.3±0.26	4.4±0.78	3.81±0.41	0.58±0.06
F7.L1	226.7±0.23	4.2±0.65	3.64±0.38	0.63±0.07
F10.L1	226.5±0.40	4.83±0.73	3.89±0.26	0.71±0.03
F1.L2	226.5±0.15	4.4±0.66	3.76±0.29	0.64±0.04
F4.L2	226.8±0.28	4.2±0.71	3.90±0.31	0.60±0.05
F7.L2	226.7±0.32	4.7±0.74	3.81±0.33	0.55±0.03
F10.L2	226.5±0.30	4.8±0.70	3.88±0.38	0.61±0.07

All values mentioned as mean ±SD; Number of trials (n)=5

Table 5: Uniformity of drug content of formulations

Formulation	Drug content in pH 6.8 buffer	Drug content in Water
	Metoprolol succinate	**Losartan potassium**
F1.L1	93.24±0.89	94.28±0.82
F4.L1	92.77±0.76	92.84±0.81
F7.L1	93.11±0.81	92.96±0.84
F10.L1	94.12±0.83	93.88±0.83
F1.L2	93.24±0.88	93.67±0.84
F4.L2	91.34±0.74	92.28±0.91
F7.L2	93.69±0.69	94.81±0.83
F10.L2	96.43±0.81	96.55±0.67

All values mentioned as mean ±SD; Number of trials (n)=5

The drug release from formulated tablets was shown in Fig.6 (controlled release) Fig 11 (immediate release). This dissolution was treated with kinetic modeling viz., First order, Korsmeyer Peppas, Higuchi and Hixson Crowell modeling. The graphs were represented in Fig 7 to 10 (for controlled release) and Fig 12 to 15 (for immediate release). The best formulation was subjected to accelerated stability studies as per ICH guidelines. The formulated tablets did not show any changes in all the characters before and after stressed storage conditions.

Conclusion

It was concluded from this study bilayer tablets containing Losartan Potassium for immediate release using sodium starch glycolate as super disintegrant and Metoprolol succinate for extended release using Carbopol 71G, Hydroxy Propyl Methyl Cellulose (HPMC K100M), Xanthan gum and poly ethylene oxide as hydrophilic polymers and Kollidone as binder can be prepared.

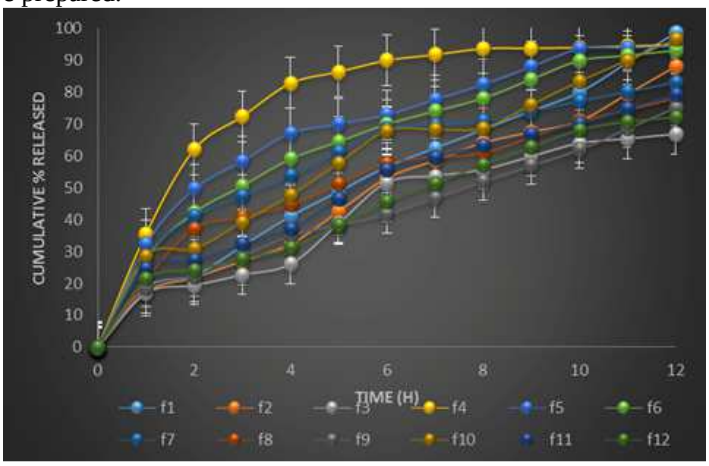


Fig.6. Zero order plots of formulations (controlled release)

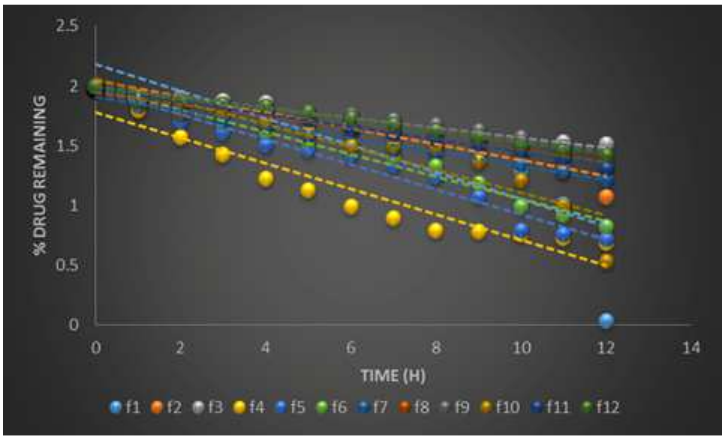


Fig.7. First order plots of formulations (controlled release)

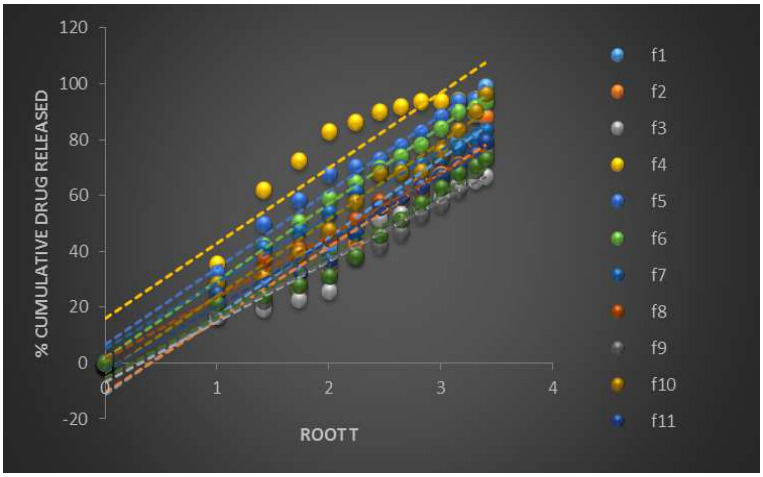


Fig.8. Higuchi plots of formulations (controlled release)

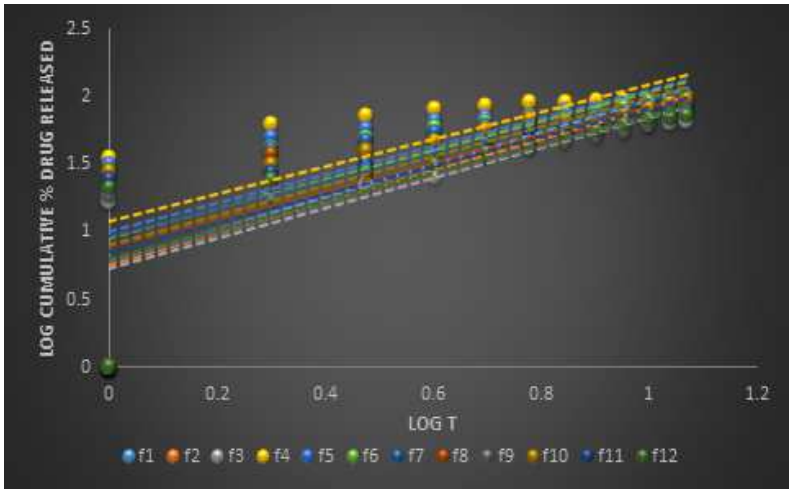


Fig.9. Korsmeyer Peppas plots of formulations (controlled release)

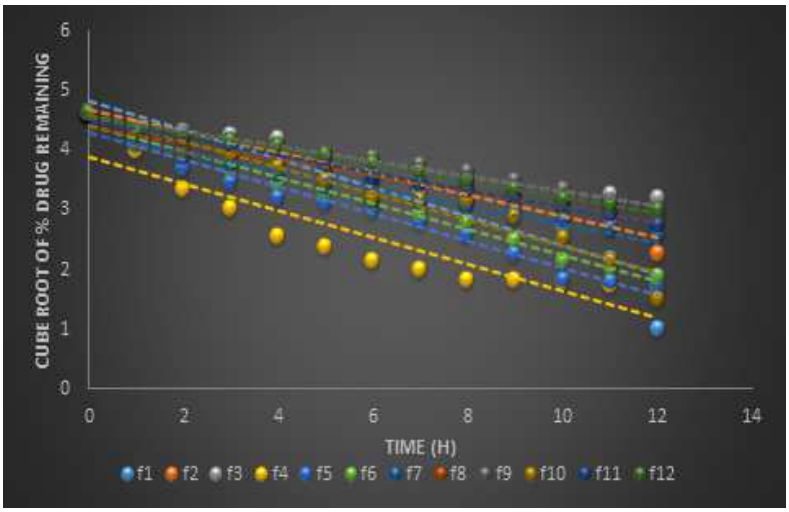


Fig.10. Hixson Crowell's plots of formulations (controlled release)

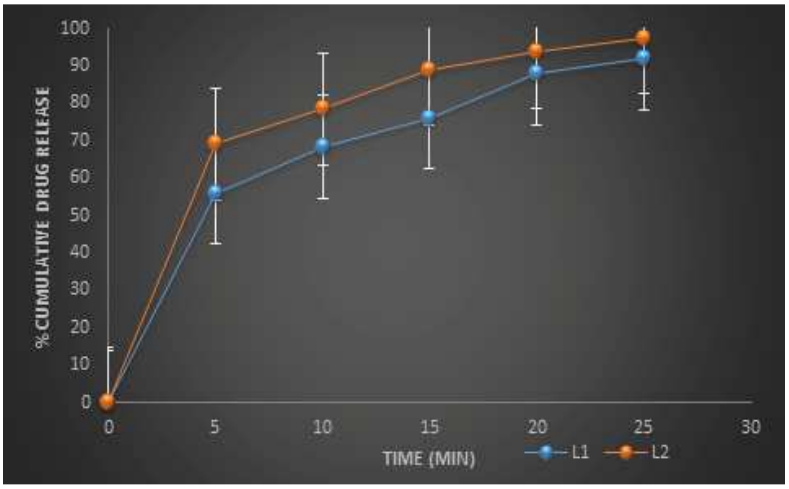


Fig.11. Zero order plots of formulations L1 and L2 (immediate release)

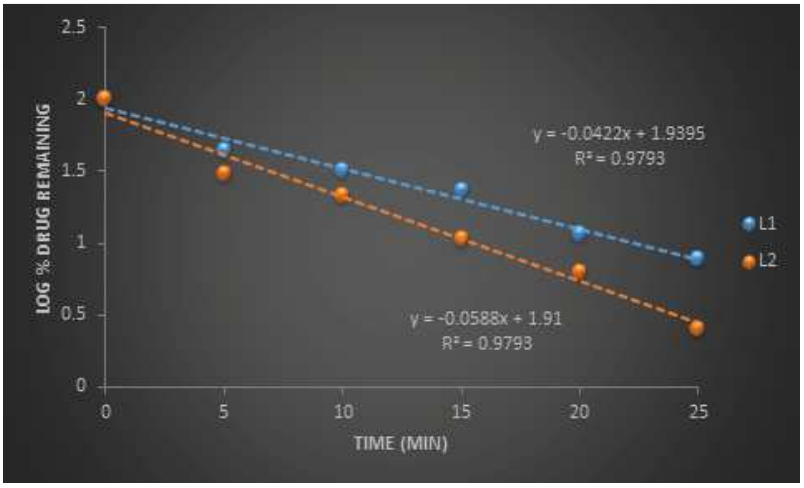


Fig.12. First order plots of formulations L1 and L2 (immediate release)

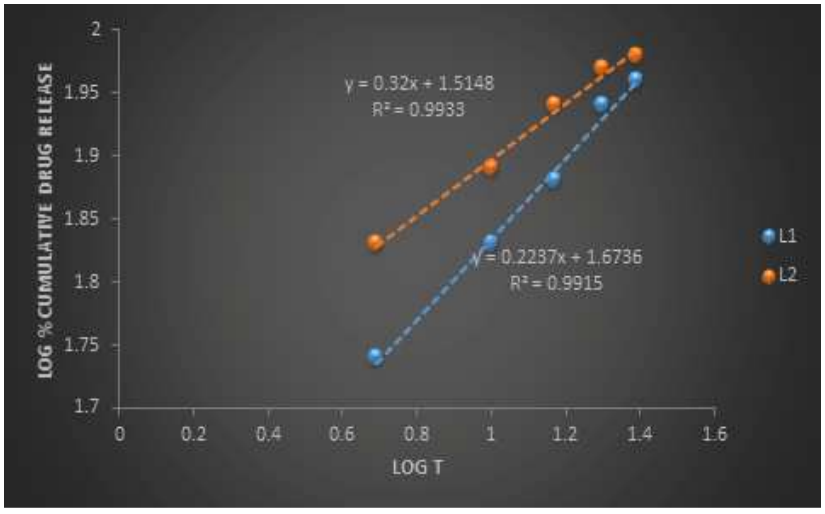


Fig.13. Korsmeyer Peppas plots of formulations L1 and L2 (immediate release)

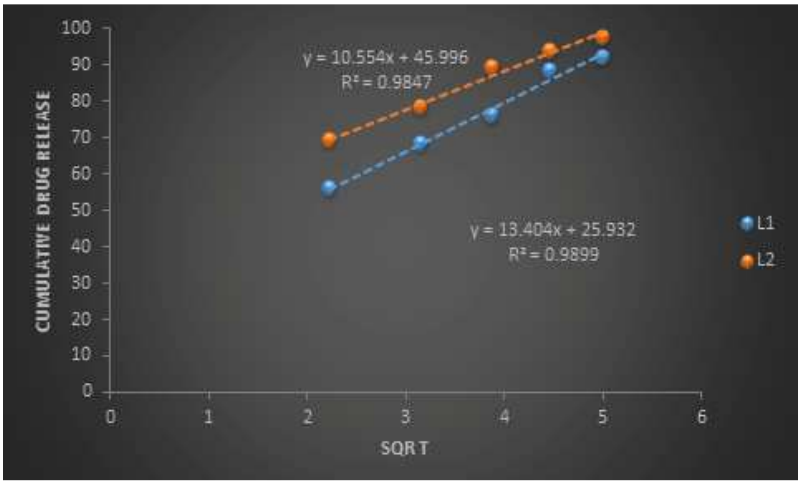


Fig.14. Higuchi's plots of formulations L1 and L2 (immediate release)

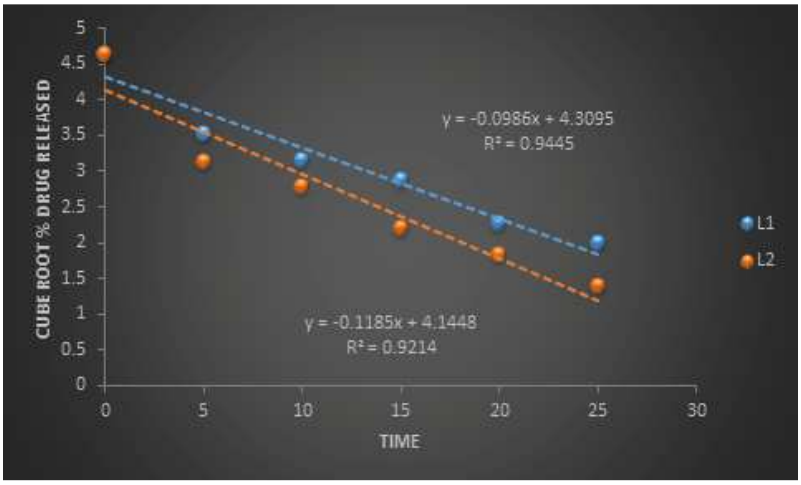


Fig.15. Hixson Crowell's plots of formulations L1 and L2 (immediate release)

References

1. Weinberg MS; Adam J; Weinberg; Raymond B C; Horace Martin, Regression of dilated aortic roots using supramaximal and usual doses of angiotensin receptor blockers. *American Journal of Hypertension*, 16 (5), **2003**, A259, 609.
2. Swaisland HC; Ranson M; Smith RP; Leadbetter J; Laight A; McKillop D et al., Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clinical Pharmacokinetics*, 44 (10), **2005**: 1067–1081.
3. Hindustan AA; Harinath R; Sreenivasulu R; Kishore Kumar Reddy B; Chandrasekhar A; Krishna Mahesh CH et al., Formulation and Evaluation of Glipizide Prosophis cumanensis Fruit Mucilage and Povidone Sustained Release Matrix Tablets, *Int Journal of Pharmaceutical Research and Innovation*, 2: 17-21, **2011.**
4. Abdul Ahad H; Chitta Suresh Kumar; Kishore Kumar Reddy B; Suma Padmaja B; Chandra Sekhar A. Formulation And Evaluation of Ficus glomerata mucilage sustained release matrix tablets of Gliclazide, *Pak. J. Pharm. Sci*., 24 (3), **2011**, 399-404.
5. Ahad HA; Sreeramulu J; Sreenivasulu R; Suma Padmaja B; Narasimha Reddy M. Fabrication of Glimepiride Hibiscus esculentus Fruit Mucilage and Povidone Sustained Release Matrix Tablets: In vitro evaluation, *Der Pharmacia Sinica*, **2011**, 2 (2): 91-100.
6. Lorenzo LML; Remunan LC; Vila JJL; Alonso MJ. Design and evaluation of chitison / ethyl cellulose mucoadhesive bilayered devices for Buccal drug delivery. *J Control Release*. 55, **1988**, 143-152.
7. Hindustan Abdul Ahad; Kishore Kumar Reddy B; Ishaq B Md; Hari Kumar C; Chitta Suresh Kumar. Fabrication and *in vitro* Evaluation of Glibenclamide Abelmoschus esculentus Fruit Mucilage Controlled Release Matrix Tablets, *Journal of Pharmacy Research*, **2010**, 3(5), 943-946

8. Chinam N; Arethi B; Pandit H; Singh SP; Meduri V. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, Acta Pharm,. 2007, 57, 479–489.
9. Sonara G; Jaina D; Moreb D; Preparation and *in vitro* evaluation of bilayer and floatingbioadhesive tablets of rosiglitazone maleate, *Asian Journal of Pharmaceutical Sciences*, **2007**, 2 (4), 161-169.
10. Kulkarni A; Bhatia M; Development and evaluation of regioselective bilayer floatingtablets of Atenolol and Lovastatin for biphasic release profile, *Iranian Journal of Pharmaceutical Research*, **2009**, 8 (1), 15-25.
11. Narasimha Reddy D; Srinath MS; Hindustan Abdul Ahad, Sudharani MV. Formulation and in vitro evaluation of glimepiride mucoadhesive tablets for diabetics, *Instasci Journal of Pharmaceutical Sciences*, **2012**, 2 (1), 1-9.
12. Lachman L; Lieberman HA; Kanig JL. The Theory and Practice of Industrial Pharmacy. 4th edition, Philadelphia: PA: Lea & Febiger, **1986**, pp293-45.
13. Naresh Gorantla; Sambasiva rao A; Hindustan Abdul Ahad; Rajesh Pawan A. Fabrication and Characterization of Bilayer Sustained Release Tablets Using Ibuprofen and Methocarbamol as Model Drugs, *Int. J. Chem. and Life Sciences*, **2013**, 2 (3), 1132-1135
14. Narasimha Reddy D; Srinath MS; Hindustan Abdul Ahad; Formulation and in vitro Evaluation Glimepiride and Parecoxib Mucoadhesive Tablets for diabetics associated with pain and inflammation, *Der Pharmacia Sinica*, **2011**, 2 (2): 101-109
15. Narasimha Reddy D; Srinath MS; Hindustan Abdul Ahad; Fabrication and Evaluation of Glimepiride and Valdecoxib Combination Mucoadhesive Tablets; *Journal of Pharmacy Research*, **2011**,4(1),93-96
16. Korsmeyer RW; Gunny R; Doelker EM; Buri P; Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*, **1983**; 15: 25-35.
17. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* **1963**; 52, 1145-1149.
18. Remunan C; Bretal M; Nunez A; Bila Jato JL. Accelerated stability of sustained release tablet prepared with Gelucire. *Int J Pharm*, **1992**; 80: 151-159.