Design, Formulation Development and Evaluation of Matrix Tablet Containing Labetalol HCL

Dileep Kumar Awasthi[1*], Sangamesh B. Puranik[2], Rohit Saraswat[3], Mahesh Kumar Jhajharia[4], Prashant Sharma[5]

School of Pharmacy, OPJS University, Churu, Rajasthan, India
*Corresponding Author

Abstract— *The objective of present work was to design and develop sustained release matrix tablets of anti-hypertensive drug Labetalol hydrochloride. Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide used as a rate retarding polymer. Whereas Polyvinyl Pyrrolidone and Microcrystalline cellulose are used as granulating agent and diluent. The influence of variable concentration of polymers on the release rate of drug was investigated. The results of the present work point out that the rate of Labetalol hydrochloride release from polymers like Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide are mainly controlled by the drug–polymer ratio. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content and in vitro drug release studies.*

Keywords— Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, Sustained-release, Labetalol hydrochloride Formulation.

I. INTRODUCTION

Sustained release system includes any drug delivery system that "achieves slow release of drug over an extended period of time." The term sustained release has become associated with those systems from which therapeutic agent may be automatically delivered over a long period of time. A simple dosing scheme with a once or twice daily administration of the antihypertensive agent is known to increase patient compliance. For this reason, the pharmaceutical industry is intensively searching for longer-acting antihypertensive drugs, either by the development of novel agents with a longer elimination half life, or by the improvement of the dosage form of existing shorter acting compounds, so that plasma concentrations compatible with a blood pressure lowering activity are maintained during the whole day. Sustained drug delivery has been introduced to overcome the drawback of fluctuating drug level associated with conventional dosage form [1-3].

The goal in designing oral sustained or controlled delivery is to reduce the frequency of the dosing or to increase effectiveness of the drug by localizing at the site of action, reducing the dose required or provide uniform drug delivery, thereby also improving patient compliance. Controlled or sustained release dosage forms provide a better control drug levels, less dosage frequency, less than effects, increased efficiency and constant delivery [4].

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of sustained release drug delivery system like application of different polymers to achieve sustained delivery that could revolutionize method of medication and provide a number of therapeutic benefits. To fabricate matrix tablet of Labetalol HCl using polymers like Hydroxypropylmethylcellulose (HPMC), Sodium CMC, Xanthan gum and Tamarind seed polysaccharide (carried out the Isolation and Extraction of Tamarind seeds polysaccharide from tamarind husk kernels).

II. MATERIALS & METHODS:

Labetalol hydrochloride was obtained as a gift sample from Yarrow chem. distributor, Mumbai and ingredients like HPMC K 15, Sodium CMC, Microcrystalline Cellulose, and Talc, obtained from loba chemicals Mumbai. Tamarind seed polysaccharide is used.

2.1 Preparation of Matrix Tablets of Labetalol Hydrochloride:

In the present work, wet granulation method has been used to prepare matrix tablets of Labetalol hydrochloride and the polymer used is:

Hydrophilic swellable polymer i.e., hydroxypropyl methyl cellulose with grade K15. Sodium CMC Xanthan gum TSP (Starch).

2.2 Diluents (bulking agent or compression vehicles) used are

- Microcrystalline cellulose
- Binder**:** Polyvinyl pyrrolidone K30 (PVPK30) in water.
- Lubricant**:** Magnesium stearate Glidant**:** Talc

2.3 Method:

In the present work, drug with different polymer in their variable concentration is used to give a drug- polymer proportion of 1:0.5, 1:0.75 and 1:1 for the preparation of matrix tablet. Among the three drug polymer ratios studied drug-polymer ratio 1:1 released approximately 90% of the drug in 11.5 hours.

2.3.1 Procedure for Preparation of Matrix Tablets

Matrix tablets were prepared by wet granulation method. The composition with respect to drug- polymer ratio 1:0.5, 1:0.75 and 1:1 was selected. Weighed all the ingredients accurately. Drug, Polymer and diluents were mixed in a poly bag and the mixture was passed through a mesh No. 44.Granulation was done with a solution of PVP K30 in sufficient quantity of distilled water. The wet mass was passed through mesh No. 22 to get granule of desired size. The wet granules were dried at 50°C for about 2 hours. The dried granules were seized by a mesh No. 20 and mixed with magnesium stearate and talc. Granules thus obtained weighing equivalent to required weight were compressed into tablets by using 8mm flat round punches on a single punch sixteen station Cadmach tablet machine.

TABLE 1
FORMULATION CHART OF LABETALOL HCL MATRIX TABLET

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Labetalol HCl	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K 15	50	75	100	-	-	-	-	-	-	-	-	-
Sodium CMC	-	-	-	50	75	100	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-	50	75	100	-	-	-
TSP(Starch)	-	-	-	-	-	-	-	-	-	50	75	100
Microcrystalline cellulose	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight (mg)	300	300	300	300	300	300	300	300	300	300	300	300

III. RESULT AND DISCUSSION:

3.1 Preformulation study of Labetalol HCl:-

3.1.1 Description

Test	Specification	Result
Description	White crystalline powder	White crystalline powder.

3.1.2 Solubility

Parameter	1 Trial	2 Trial	3Trial	Mean
Solubility* (mg/ml)	20	19.5	20.5	20

Solubility in water at $25^{O}C$

3.1.3 Melting point

3.1.3.1 Melting point of Labetalol HCl was found to be 1950c

Evaluation of Formulation Parameters:

Evaluation was divided in mainly

- Pre-compression Parameters.
- Post-compression Parameters.

3.2 Precompression Study

TABLE 2
RESULTS OF FLOW PROPERTIES

BATCH	ANGLE OF REPOSE(º)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/)	COMPRESS-BILITY INDEX	HAUSNER'S RATIO
F1	24.6	0.537	0.610	12.23	1.13
F2	23.7	0.524	0.601	12.83	1.14
F3	24.7	0.541	0.626	13.55	1.15
F4	24.8	0.560	0.630	11.55	1.12
F5	23.5	0.580	0.658	11.85	1.13
F6	24.0	0.579	0.670	12.18	1.15
F7	23.5	0.565	0.637	12.80	1.12
F8	22.5	0.540	0.626	11.95	1.15
F9	23.6	0.559	0.631	12.63	1.12
F10	22.4	0.584	0.659	12.45	1.12
F11	25.2	0.545	0.625	11.82	1.14
F12	24.2	0.572	0.664	13.15	1.16

The formulated granules were characterized with respect to angle of repose, bulk density and tapped density. All granules from all formulation show excellent flow property.

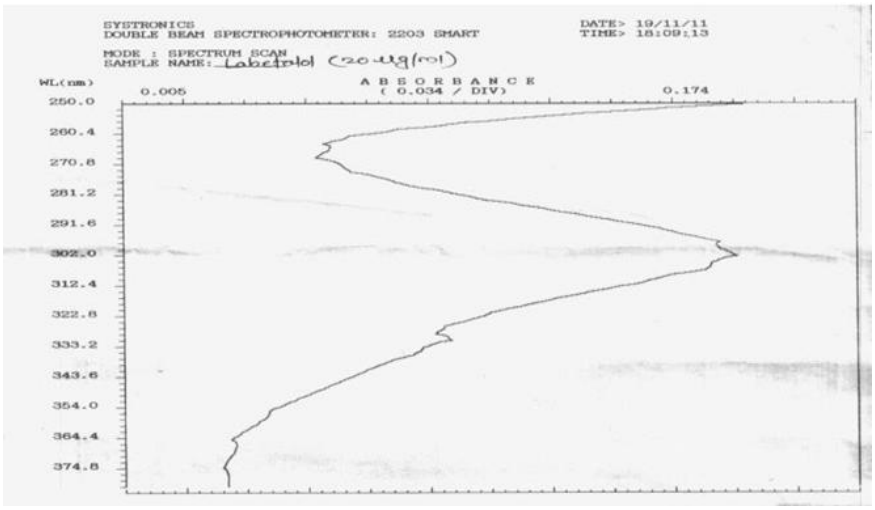


FIGURE 1: UV spectra of Labetalol HCl

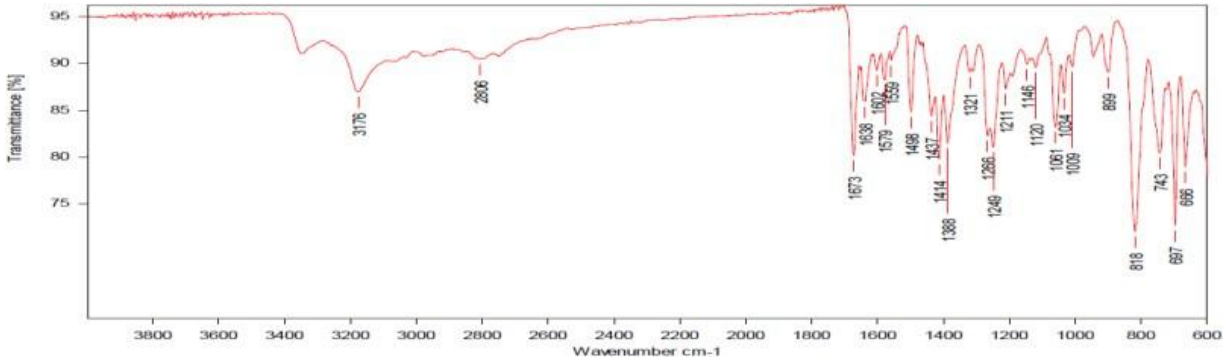


FIGURE 2: IR spectra of Labetalol HCl

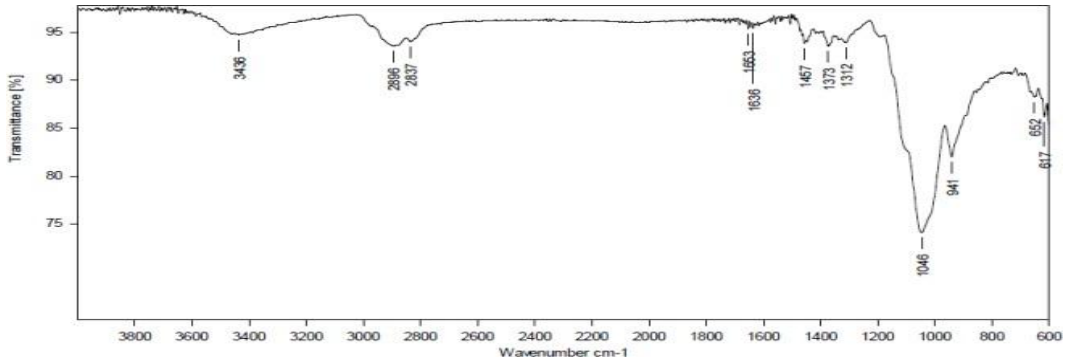


FIGURE 3: IR spectra of HPMC K 15

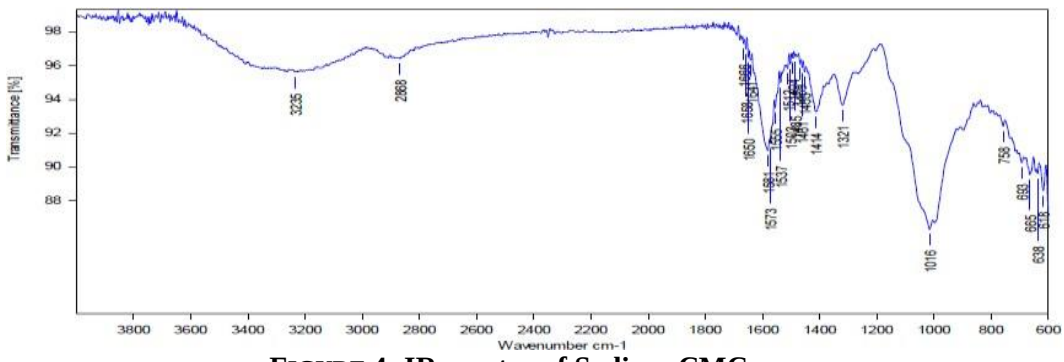


FIGURE 4: IR spectra of Sodium CMC

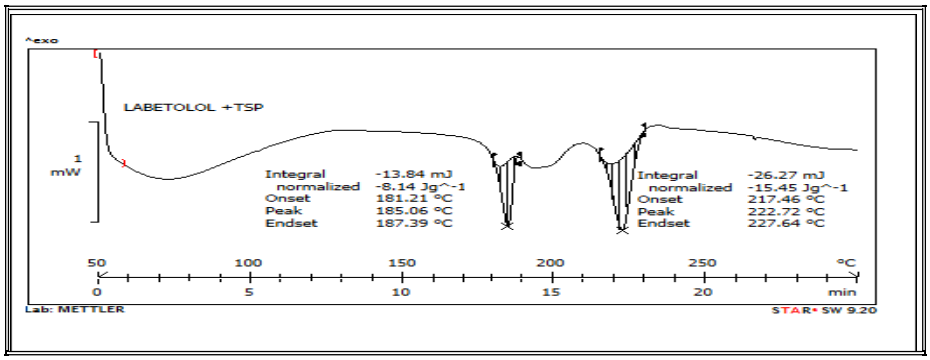


FIGURE 5: DSC SPECTRA OF LABETALOL + TAMARIND SEED POLYSACCHARIDE

TABLE 3
EVALUATION PARAMETERS OF FORMULATIONS

Formulation code	Evaluation parameter				
	Thickness ± S.D. (mm) (n = 5)	Hardness ± S.D. (kg/cm^2) (n = 5)	Friability (%)	Average weight variation (n=20)	Drug content (%)
F1	4.64±0.13	5.86±0.21	0.03	310±1.153	99.24
F2	4.55±0.11	5.74±0.41	0.07	295±2.111	95.41
F3	4.62±0.23	5.72±0.25	0.11	305±2.172	99.5
F4	4.52±0.15	5.82±0.25	0.63	310±1.183	96.87
F5	4.53±0.27	5.68±0.13	0.18	310±2.211	97.71
F6	4.44±0.19	5.66±0.23	0.21	290±1.121	98.47
F7	4.52±0.16	5.96±0.28	0.29	310±3.189	96.45
F8	4.53±0.19	5.44±0.23	0.17	290±1.198	98.98
F9	4.56±0.22	5.74±0.11	0.29	295±1.143	95.87
F10	4.65±0.21	5.62±0.19	0.27	290±0.102	97.33
F11	4.53±0.23	5.70±0.15	0.25	310±3.172	98.41
F12	4.43±0.21	5.72±0.23	0.67	290±2.173	97.07

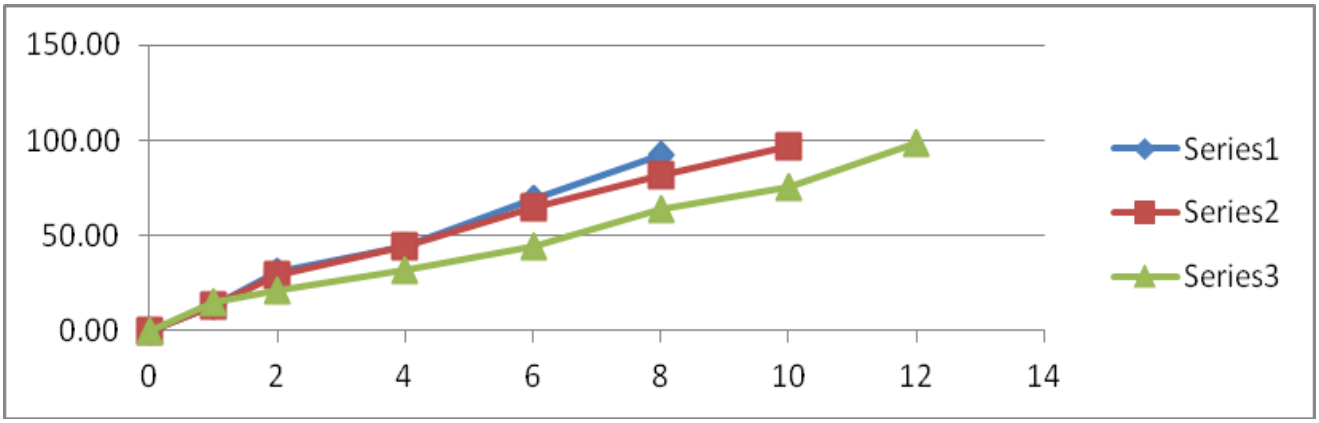
3.3 *In vitro* drug release of Labetalol HCl through HPMC K 15

TABLE 4
***IN VITRO* RELEASE PROFILE OF FORMULATION F1 &F2**

Time	F1					F2				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	Mg	Mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.07	13.32	0.00	13.32	13.32	0.07	13.20	0.00	13.20	13.20
2	0.17	31.44	0.07	31.51	31.51	0.16	29.64	0.07	29.71	29.71
4	0.25	44.46	0.25	44.71	44.71	0.25	44.46	0.24	44.70	44.70
6	0.38	68.52	0.50	69.02	69.02	0.36	64.26	0.49	64.75	64.75
8	0.51	91.08	0.88	91.96	91.96	0.45	81.12	0.84	81.96	81.96
10	-	-	-	-	-	0.53	95.52	1.29	96.81	96.81

TABLE 5
***IN VITRO* RELEASE PROFILE OF FORMULATION F_3**

Time	F3				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	Mg	%
0	0	0	0	0	0
1	0.09	15.54	0.00	15.54	15.54
2	0.12	21.48	0.09	21.57	21.57
4	0.18	31.98	0.21	32.19	32.19
6	0.24	43.86	0.38	44.24	44.24
8	0.35	63.36	0.63	63.99	63.99
10	0.42	74.88	0.98	75.86	75.86
12	0.54	96.78	1.40	98.18	98.18



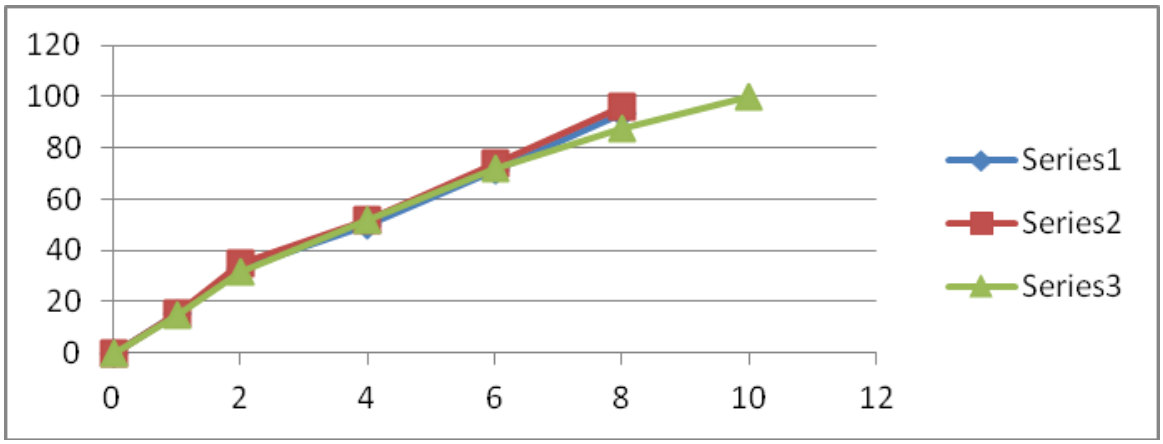
GRAPH 1: In vitro drug release of Labetalol HCl through HPMC K 15 (F1, F2, F3)

TABLE 6
***IN VITRO* DRUG RELEASE OF LABETALOL HCL THROUGH SODIUM CMC**

Time	F4					F5				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	13.32	0.00	15.48	15.48	0.09	15.48	0.00	15.48	15.48
2	0.18	31.44	0.09	32.97	32.97	0.19	34.98	0.09	35.07	35.07
4	0.28	44.46	0.27	50.07	50.07	0.29	51.30	0.28	51.58	51.58
6	0.39	68.52	0.55	71.47	71.47	0.41	73.50	0.57	74.07	74.07
8	0.51	92.52	0.93	93.45	93.45	0.53	94.86	0.97	95.13	95.13

TABLE 7
IN VITRO RELEASE PROFILE OF FORMULATION F_6

Time	F6				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	mg	%
0	0	0	0	0	0
1	0.08	14.94	0.00	14.94	14.94
2	0.17	31.38	0.08	31.46	31.46
4	0.29	51.42	0.26	51.68	51.68
6	0.40	71.16	0.54	71.70	71.70
8	0.48	86.46	0.94	87.40	87.40
10	0.55	98.34	1.42	99.76	99.76



GRAPH NO. 2 *In vitro* drug release of Labetalol through Sodium CMC (F4, F5, F6)

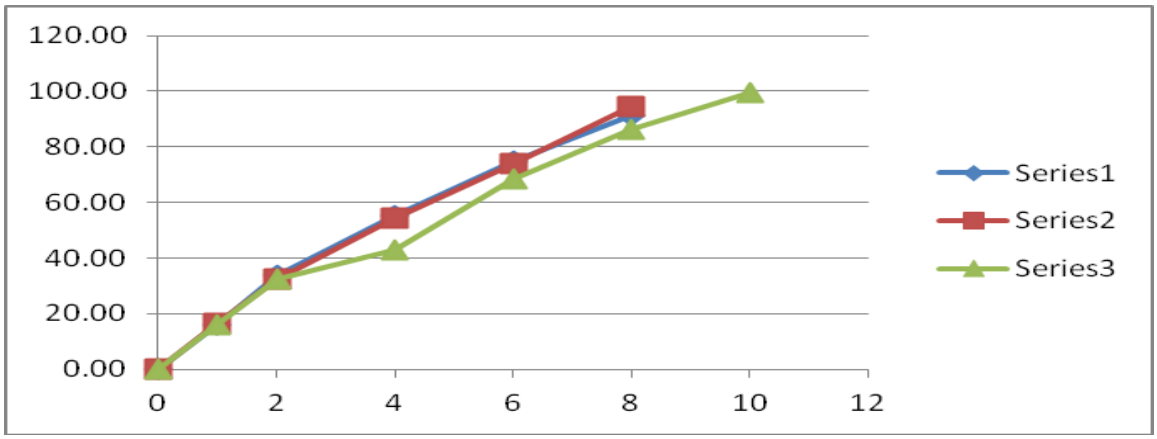
3.4 *In vitro* drug release of Labetalol through Xanthan gum

TABLE 8
***IN VITRO* RELEASE PROFILE OF FORMULATION F_7 & F_8**

Time	F7					F8				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26	0.09	16.56	0.00	16.56	16.56
2	0.19	33.78	0.09	33.87	33.87	0.18	32.28	0.09	32.37	32.37
4	0.31	55.08	0.28	55.36	55.36	0.30	54.00	0.27	54.27	54.27
6	0.41	74.52	0.58	75.10	75.10	0.41	73.62	0.57	74.19	74.19
8	0.50	90.18	1.00	91.18	91.18	0.52	93.48	0.98	94.46	94.46

TABLE 9
IN VITRO RELEASE PROFILE OF FORMULATION F_9

Time	F9				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	Mg	mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26
2	0.18	32.28	0.09	32.37	32.37
4	0.24	42.78	0.27	43.05	43.05
6	0.38	67.98	0.51	68.49	68.49
8	0.48	85.50	0.89	86.39	86.39
10	0.54	97.98	1.36	99.34	99.34



GRAPH NO. 3: *In vitro* drug release of Labetalol through Xanthan gum (F7, F8, F9)

3.5 *In vitro* drug release of Labetalol HCl through the Tamarind seed polysaccharide.

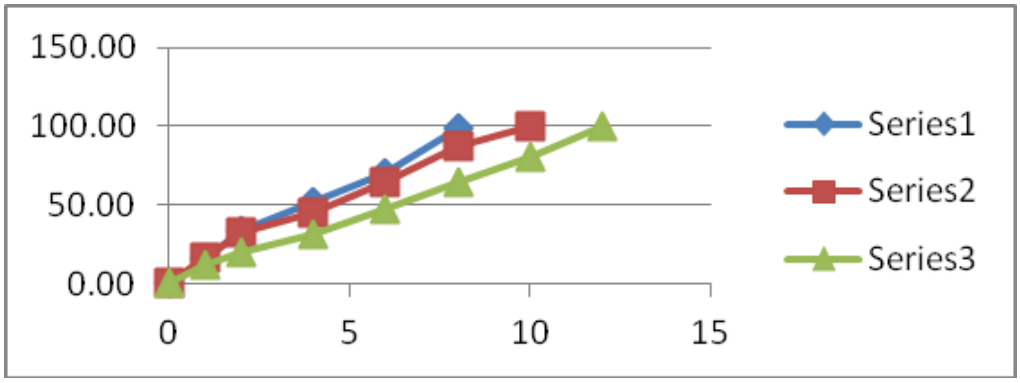
TABLE 10
***IN VITRO* RELEASE PROFILE OF FORMULATION F_{10} & F_{11}**

Time	F10					F11				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	15.30	0.00	15.30	15.30	0.09	16.02	0.00	16.02	16.02
2	0.19	33.30	0.09	33.39	33.39	0.18	32.76	0.09	32.85	32.85
4	0.29	52.08	0.27	52.35	52.35	0.25	44.28	0.27	44.55	44.55
6	0.39	69.66	0.56	70.22	70.22	0.36	64.32	0.52	64.84	64.84
8	0.55	98.10	0.95	99.05	99.05	0.48	86.76	0.87	87.63	87.63
10	-	-	-	-	-	0.54	97.98	1.36	99.34	99.31

TABLE 11

***IN VITRO* RELEASE PROFILE OF FORMULATION F_{12}**

Time	F12				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.07	12.12	0.00	12.12	12.12
2	0.11	19.62	0.07	19.69	19.69
4	0.17	30.72	0.18	30.90	30.90
6	0.26	46.80	0.35	47.15	47.15
8	0.36	64.20	0.61	64.81	64.81
10	0.44	79.44	0.96	80.40	80.40
12	0.55	98.22	1.41	99.63	99.63



GRAPH NO. 4: in vitro drug release of Labetalol through Tamarind seed polysaccharide (F_{10}, F_{11}, F_{12})

IV. CONCLUSION

From the present study, The sustained release matrix tablet of Labetalol HCl using polymers such as HPMC K 15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, prepared by wet granulation method were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug within the matrices.IR and DSC studies indicated that the drug and polymers are in the pure form and compatible with each other. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer concentration is increased, the drug release rates were found to be decreased. Formulation F3 and F12 with drug-polymer ratio 1:1 containing PVP K30 and MCC as binder and diluents respectively have shown promising results as per USP Test-I requirements. Sustained release matrix tablets of Labetalol hydrochloride can be prepared using HPMC K 15 and Tamarind seed polysaccharide achieve a desired drug release rates over a period of 12 hours, which can help to reduce the dose and frequency. Among the various formulations prepared, F3 and F12 appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

REFERENCES

[1] Leon Shargel, Susanna Pong et al., Applied Biopharmaceutics and Pharmacokinetics, Modified- Release Drug Products, Fifth Edition, 2004; 515.

[2] Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained and Controlled release drug delivery systems, Fourth Edition, 2002; 513

[3] Alfred Martin, Textbook Of Physical Pharmacy, Fifth edition:285 – 289

[4] Mohd. Azharuddin, Krishnanda Kamath et al., "Formulation and Evaluation of controlled release matrix tablet of hypertensive drug using natural & synthetic polymer." Mar 2011; Vol.2, Issue 4: Mar 2011; 26-32

[5] Ganesh G. N. K, Manjusha Pallaprola, Gowthamarajan K, Suresh Kumar R, "Design and development of buccal drug delivery system for Labetalol HCl using natural polymer" International journal of pharmaceutical research and development, 2011;Vol.3(3): 37-49

[6] Abdul Ahad sreeramulu et al., "Design and evaluation of sustained release matrix tablets of Glimepiride based on combination of natural and synthetic polymer" International journal of applied biology and pharmaceutical technology, Nov-Dec- 2010; Vol.1 Issue3.

[7] Subramaniam Kannan, Rangasamy Manivannam et al., "Formulation and Evaluation of Sustained Release Tablets of Aceclofenac using Hydrophilic Matrix System" International journal of Pharma Research, july-sept 2010; vol.2,Issue3: 1775.

[8] Rakesh Patel, Ashok Baria et al., "Formulation development & process optimization of Theophylline sustained release matrix tablet." International Journal of pharmaceutical sciences, Oct.2009; Vol.1 Issue 2.

[9] Mohd. Hasanuzzaman et al.; "Formulation, Evaluation and optimization of sustained release matrix tablet of Indapamide using hydrophillic matrix system" International Journal PharmaTech Research, July-Sept.2011;Vol.3 Issue3:183.

[10] Afrasim Moin & HG Shivakumar, "Formulation of Sustained-Release Diltiazem Matrix Tablets Using Gum Blends" Tropical Journal of Pharmaceutical Research, June 2010; Vol.9 Issue 3: 283-291.

[11] Rajesh Gollapudi, Harika Javvaji, Rama Rao Tadikonda & Vajaja Arpineni "Formulation & In vitro evalution of sustained release matrix tablet of Losartan potassium" An International Journal of Advances in Pharmaceutical Sciences Jan-Feb 2011; Vol.9 Issue1.

[12] Shantveer V. Salgar, Lingaraj S.Danki, Shivanand Hiremath, Abdul Sayeed, "Preparation & evalution of sustained release matrix tablets of Propanolol hydrochloride" International Journal of Pharma & Bio Science, Oct-Dec.2010 Vol.1 Issue 4.

[13] B. Chatterjee, T.K. Pal et al., "Development and in vitro evalution of micronized sustained release matrix tablet of Carvediol" IJPSER, Jun. 2010; Vol.1, Issue10.

[14] Klaus florey., analytical profiles of drug substances volume no:2001: 477

[15] Indian Pharmacopeia Volume I, government of India, Ministry of Health and Family Wale fare, New Delhi, Controller of publication, 1996, 425, 426.

[16] Raymond C Rowe, Paul J Sheskey and Sian C Owen ,Handbook of pharmaceutical excipients, 6th edition, :728

[17] Ganesh G.N.K, Manjusha Pallaprola, Gowthamarajan K, Suresh Kumar R, "Design and development of buccal drug delivery system for Labetalol HCl using natural polymer" International journal of pharmaceutical research and development, May 2011;Vol.3(3):37-49

[18] Rajesh Gollapudi, Harika Javvaji, Rama Rao Tadikonda & Vajaja Arpineni "Formulation & In vitro evalution of sustained release matrix tablet of Losatan potassium" An International Journal of Advances in Pharmaceutical Sciences, Jan-Feb 2011; Vol.9(1)

[19] N. K. Ebube et al. Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks,: International Journal of Pharmaceutics volume 196, 2000:27–35.

[20] Edward Lau, Preformulation studies, E.L. Associates, Wilmington DE 19807:173- 233.

[21] Remington, The Science and Practice of Pharmacy, 19th edition Volume II, Mack Publication Company :1644,1660.

[22] Lachman L, Liberman HA The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Bombay, 1987.