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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF LABETALOL HYDROCHLORIDE USING NATURAL AND SYNTHETIC POLYMERS AND COMPARISON OF RELEASE RETARDING PROPERTY OF POLYMRS.

Nilam Krishana Thakare*

MGV'S College of Pharmacy, Panchavati, Nashik-422003.

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***Correspondence for Author**
Nilam Krishana Thakare
MGV'S College of Pharmacy, Panchavati, Nashik-422003.

ABSTRACT

Labetalol hydrochloride is used in treatment of hypertension. It has a short half life and undergoes extensive first pass metabolism. In present study matrix tablets of Labetalol HCL were prepared by direct compression method using HPMC K100 as synthetic polymer, Xanthan gum and Guar gum as natural polymers. All these prepared formulations were evaluated for weight variation, hardness, thickness, drug content and drug release pattern which showed satisfactory results. *In-vitro* drug release was carried out using USP Type II dissolution apparatus at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, followed by 900 ml phosphate buffer medium (pH 6.8) up to 12 hours. Among all the formulations F-6 and F-13 showed better release and could extend the release up to 12 hours. When natural polymers like Xanthan gum and Guar gum used in combination in different concentration ranges, their drug release retarding property get increased as compared when they are used in single. Several kinetics models were applied to the dissolution profiles to determine the drug release kinetics.

KEYWORDS: Labetalol Hydrochloride, HPMC K100, Xanthan Gum, Guar Gum.

INTRODUCTION

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems, because of many drawbacks of conventional dosage forms. Some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme

solubility problems, require localization to a particular site in the body or long-term use.[1] The important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and targeting the drug to desired site.[2] The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve and then maintain the desired drug concentration.[2] The basic goal of sustained drug delivery system is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time.[3] Sustained release dosage form is a "dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ". Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.[4] Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release rate of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymer by the sustained release method therapeutically effective concentration can be achieve in the systemic circulation over an extended period of time, thus achieving better compliance of patient.[1,5]

MATERIAL AND METHODS

Labetalol hydrochloride was obtained as gift sample from Meyer Organics Pvt.Ltd.Thane, Maharashtra. Xanthan Gum, HPMC K100, Guar Gum obtained from Modern science laboratory. Other materials used were of analytical grade and procured from commercial sources.

Preparation of Sustained Release Matrix Tablets of Labetalol Hydrochloride[6,7,8]

Sustained release tablets were prepared by direct compression technique. HPMC K100M, Xanthan gum, Guar gum, were used as release retarding polymers. Other ingredients like Polyvinyl pyrrlidone as dry binder, Magnesium Stearate as lubricant, Talc as a glidant, starch DC as a diluent. All batches containing Labetalol Hydrochloride, HPMC K100, Xanthan gum, Guar gum, were passed through sieves of 40 mesh screen. Weighed amounts of drug as well as all other ingredients were mixed and blended for 10 minutes. The blend was compressed using 7-station rotary press using round shaped punches. Punches measuring 11 mm diameter were used for compression of the tablets. In total 13 formulations containing HPMC K100 (F1,F2,F3), Xanthan gum (F4,F5,F6), Guar gum (F7,F8,F9) and combination of

Xanthan gum and Guar gum were prepared (F10,F11,F12,F13).The formula for various formulations attempted have been given in table-1,2.

Physical Characterization of Fabricated Tablets[6,7,8]

The quality control test for the tablets such as hardness, friability, weight variation were determined using reported procedure. The tablet crushing strength was tested by commonly used Dial tablet hardness tester. Friability was determined by Roche®friabilator, which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets were recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the average weight physical characters observed for various batches is given in table-3.

Estimation of Drug Content by Assay Method[9,10]

Drug content of the matrix tablet was determined by assay method. Weight and powder 20 tablets, weigh accurately a quantity of powder equivalent to 0.5 gm of labetalol HCL. Shake with 200ml of 0.05 M sulphuric acid. For 30 min and dilute to 250 ml with 0.05M sulphuric acid mix and filter. Dilute 10 ml of the filtrate to 250 ml with same solvent and measure the absorbance of resulting solution at the maximum at about 302 nm. (calculate the content of $C_{15}H_{24}N_2O_3Hcl$ taking 86 as the value of A).

***In vitro* release studies[7,8]**

In vitro drug release study of the samples was carried out using USP – type II dissolution apparatus (Paddle type).The dissolution medium, 900ml of HCl buffer p^H1.2 and phosphate buffer of p^H 6.8 were used for test. Firstly, place HCL buffer p^H 1.2 into the dissolution flask maintaining the temperature of 37 ± 0.5^0C and rpm of 50 for 2 hrs. SR tablet placed in each basket of the dissolution apparatus. After 2 hrs HCL buffer was replace by phosphate buffer p^H6.8.The apparatus was allowed to run for 12 hours. Samples measuring 5 ml were withdrawn after every 1 hour up to 12 hours manually. During sampling, samples were filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at 302nm using HCL buffer p^H 1.2 and phosphate buffer p^H 6.8 respectively as blank by UV-Spectrophotometer. Results are given in table-5,6.

Kinetics of *In-vitro* Drug Release[13]

In-vitro release obtained treated to zero order rate equation, First order rate equation, Higuchis equation, Hixson Crowell Cube Root equation and Korsmeyer-peppas equation to know precisely the mechanism of drug release from matrix tablet. Release data obtained is treated with following modes of data treatment. Zero-order equation-cumulative percentage drug release vs. time in hours. First order equation-log cumulative percentage remained vs. time in hours.Higuchi's Diffusion equation-cumulative percentage drug release vs. square root time. Hixson Crowell Cube Root equation- cumulative cube root drug release vs. time. Korsmeyer-Peppas equation-Log cumulative percentage of drug release vs. Log time. Results are given in table-7.

RESULT AND DISCUSSION

In present work formulate and evaluated sustained release matrix tablets of labetalol hydrochloride using polymers like HPMC K100, Xanthan gum, Guar gum as rate controlling polymers and effect on in vitro drug dissolution were studied by addition of these polymers.

Pre compressional studies

The results obtained by evaluating the powder blends of drug and excipients are shown in table-3.Bulk density and tapped density were found in the range of 0.16-0.21 g/cc and 0.20-0.26 gm/cc respectively. The haursner's ratio was with in between 1.0-1.52 indicating that all batches of powder blends were having good compressibility. Value of angle of repose was found in the range of 28.92-34.41 showing that blend of powder mass was good flowing.

Weight variation and Thickness

The average weight in all the formulation was found to be 440.6 mg to 443.7 mg. In all formulations no tablets were outside the ± 5% of the tablet weight in weight variation test. The thickness of all formulation found 5.0mm. Friability value was less than 1% in all cases. Hardness of all the tablets was maintained at 5.4 to 5.9 kg/cm^{2}for all the formulation. Assay was performed and percent drug content of all the tables were found to be 90.81% and 105.46% of labetalol hydrochloride which was within the acceptable limit, see in the table-4.

***In vitro* dissolution**

In vitro dissolution studies are performed for sustained release tablets of labetalol mixture. From all 13 formulation F6 and F13 are optimized formulation. Formulation F-6 containing Xanthan gum at lower concentration retard drug release up to 12 hrs. After 12 hrs drug

release was found to be 90.00%.In case of F-13 containing Xanthan gum and Guar gum as release retarding polymers at lower concentration drug release was found to be 88.47% at 12 hrs.

Kinetics of drug release

The in-vitro release data were fitted to zero order, first order, Hixson Crowell, krosmeyer Peppas and diffusion controlled release mechanism according to simplified Higuchi model. The preference of a certain mechanism was based on the correlation coefficient "r" for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release. In Case of F-6 highest "R^{2}" value was obtained for Hixson Crowell, and In Case of F- 13 it was found for highuchi, shown in table. The value of release exponent "N" obtained from Krosmeyer equation was greater than 1, indicate Super case II transport. So the final mechanism of drug release was mixed type followed by diffusion and erosion.

Table No-1: Composition of Formulations of SR Tablet of labetalol Hydrochloride.

Sr.No	Ingredients(Mg)	F_1(H)	F_2(M)	F_3(L)	F_4(H)	F_5(M)	F_6(L)	F_7(H)	F_8(M)	F_9(L)
1	Labetalol Hcl.	204	204	204	204	204	204	204	204	204
2	HPMC K_{100}	164	92	20.5	_	_	_	_	_	_
3	Xanthan gum	__	__	__	82	61.5	41	__	_	_
4	Guar gum	__	__	__	__	__	__	143	92	41
5	PVP K_{30}	5	5	5	5	5	5	5	5	5
6	Magnesium Stearate	10	10	10	10	10	10	10	10	10
7	Talc	10	10	10	10	10	10	10	10	10
8	Starch DC	57	129	200	139	160	180	78	129	180
9	Total Weight	450	450	450	450	450	450	450	450	450

Table No-2: Composition of Sustained Release Tablet of Labetalol Hcl Using Xanthan Gum and Guar Gum in Combination.

Sr.No	Ingridents	F_{10}(H+H)	F_{11}(H+L)	F_{12}(L+H)	F_{13}(L+L)
1	Labetalol HCl	204	204	204	204
2	Xanthan Gum	82	82	41	41
3	Guar Gum	102	41	102	41
4	PVP K_{30}	5	5	5	5
5	Magnesium Stearare	10	10	10	10
6	Talc	10	10	10	10
7	Starch DC	37	98	78	139
8	Total Weight	450	450	450	450

Table No-3: Evaluation of Powder Blend for Flow Properties.

Batch	Angle of Repose(θ)	Bulk density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Hausner's Ratio	Inferences (Flow Character)
F1	34.21	0.17	0.20	14.15	1.16	Good
F2	32.23	0.18	0.21	12.96	1.14	Good
F3	32.23	0.21	0.23	8.69	1.0	Excellent
F4	33.32	0.18	0.20	9.1	1.10	Excellent
F5	32.91	0.19	0.22	15.38	1.18	Good
F6	32.39	0.16	0.20	16.7	1.23	Good
F7	32.61	0.16	0.20	22.59	1.29	Passable
F8	31.60	0.17	0.26	22.59	1.52	Very poor
F9	34.41	0.17	0.23	34.48	1.35	Poor
F10	29.54	0.18	0.21	12.96	1.14	Good
F11	32.94	0.16	0.20	16.7	1.23	Good
F12	28.92	0.19	0.22	15.38	1.18	Good
F13	29.56	0.21	0.23	8.69	1.09	Excellent

Table No.4: Evaluation of Tablets Parameters.

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation in (Mg)	Friability (%)	Drug Content (%)
F1	5.0±0.0	5.6±0.65	441.6±5.08	0.56±0.10	98.13±0.66
F2	5.5±0.0	5.5±0.52	442.7±5.3	0.44±0.14	90.81±0.91
F3	5.0±0.0	5.7±0.42	442.8±6.2	0.81±0.11	102.79±0.91
F4	5.0±0.0	5.8±0.84	440.1±6.4	0.44±0.18	96.86±1.03
F5	5.0±0.0	5.9±0.31	443.7±4.8	0.90±0.10	103.72±1.21
F6	5.0±0.0	5.7±0.58	442.5±4.2	0.69±0.11	106.56±1.1
F7	5.0±0.0	5.4±0.43	441±5.2	0.44±0.12	104.41±1.1
F8	5.0±0.0	5.5±0.46	442.5±4.2	0.52±0.10	96.04±2.09
F9	5.0±0.0	5.6±0.57	441.6±5.7	0.5±0.13	95.52±1.04
F10	5.0±0.0	5.6±0.40	440.6±6.4	0.76±0.12	104.82±1.2
F11	5±0.0	5.4±0.39	443.1±5.7	0.56±0.1	95.52±1.64
F12	5±0.0	5.6±0.45	442.2±6.1	0.68±0.1	96.51±1.69
F13	5±0.0	5.7±0.53	442.5±4.00	0.56±0.1	105.46±1.03

Table No-5: In-Vitro Drug Release of SR Tablets.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	**0**	0	0	0
1	1.36±0.03	6.99±0.02	4.19±0.02	1.92±	8.73±	**7.60±0.02**	0.22±0.09	4.19±0.02	2.49±0.04
2	2.85±0.01	17.29±0.03	11.06±0.03	3.07±0.01	9.91±0.04	**8.77±0.05**	2.49±0.06	7.05±0.04	7.61±0.01
3	22.81±0.02	40.56±0.01	23.43±0.02	32.96±0.04	19.93±0.05	**22.76±0.05**	20.15±0.03	27.29±0.06	23.30±0.03
4	25.23±0.02	42.28±0.02	24.13±0.01	39.41±0.01	26.30±0.07	**29.73±0.02**	28.60±0.06	35.42±0.01	25.14±0.01
5	25.96±	47.43±0.	33.43±0.	40.19±	29.87±	**31.03±**	32.74±	41.31±	36.67±

	0.02	02	02	0.04	0.08	**0.04**	0.02	0.01	0.04
6	32.35± 0.02	59.99±0. 02	46.79±0. 04	42.69± 0.02	32.31± 0.07	**43.73± 0.03**	36.34± 0.03	43.25± 0.04	49.98± 0.05
7	42.78± 0.03	66.04±0. 9	60.22±0. 01	52.04± 0.03	37.16± 0.04	**52.57± 0.04**	55.91± 0.05	51.46± 0.04	53.67± 0.04
8	45.78± 0.04	64.05±0. 3	68.58±0. 02	55.18± 0.04	51.49± 0.06	**64.89± 0.04**	57.92± 0.02	58.01± 0.06	63.06± 0.02
9	51.22± 0.01	65.19±0. 09	73.48±0. 03	61.17± 0.03	61.42± 0.05	**76.13± 0.04**	59.93± 0.02	63.46± 0.04	66.26± 0.04
10	64.35± 0.03	65.21±0. 01	80.70±0. 01	67.77± 0.02	69.10± 0.01	**78.26± 0.04**	60.25± 0.03	66.65± 0.06	71.75± 0.03
11	64.37± 0.01	69.78±0. 05	85.13±0. 04	69.29± 0.02	71.75± 0.09	**84.99± 0.05**	63.99± 0.06	75.56± 0.07	77.81± 0.01
12	67.59± 0.02	71.50±0. 02	89.55±0. 04	75.93± 0.02	78.92± 0.02	**90.00± 0.08**	73.45± 0.03	79.95± 0.03	86.74± 0.02

Table No-6: In-Vitro Drug Release of SR Tablets Made Using Xanthan Gum and Guar Gum.

Batches	F10	F11	F12	F13
0	0±0	0±0	0±0	**0±0**
1	4.19±0.06	1.92±0.02	0.79±0.06	**5.33±0.04±**
2	6.48±0.04	3.07±0.02	1.93±0.03	**7.63±0.02**
3	25.01±0.06	18.14±0.07	22.69±0.06	**26.16±0.02**
4	30.85±0.03	19.38±0.04	25.66±0.06	**28.59±0.07**
5	36.71±0.04	25.76±0.04	29.22±0.01	**33.87±0.04**
6	39.76±0.04	33.30±0.03	37.93±0.03	**44.31±0.04**
7	42.26±0.04	40.32±0.04	48.05±0.03	**57.66±0.04**
8	49.90±0.03	47.38±0.05	48.05±0.05	**61.40±0.02**
9	58.15±0.03	55.62±0.04	56.86±0.04	**70.28±0.05**
10	65.30±0.07	62.76±0.04	58.31±0.04	**76.90±0.08**
11	69.64±0.02	68.81±0.01	71.16±0.02	**81.24±0.03**
12	73.08±0.02	74.86±0.04	75.53±0.05	**88.47±0.01**

Table No-7: Data Treatment.

Batches	Regression Coefficient (R^2)				Korsermeyers - Peppas plot	
	Zero Order Plot	First order Plot	Hixon-Crowell Plot	Higuchi Plot	R^2	N
F6	**0.9854**	0.8875	**0.9731**	0.9603	0.9668	**1.103**
F13	**0.9869**	0.9858	0.8679	**0.9199**	0.9634	**1.1842**

Data Kinetics F-6

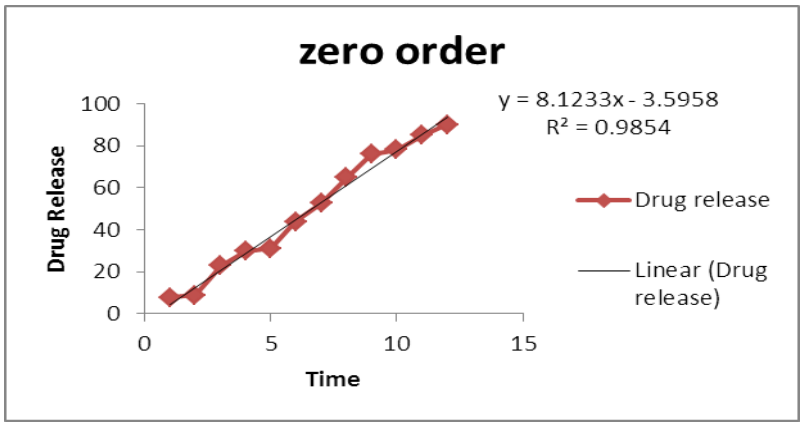

Fig No 1:- Zero Order Kinetic Treatment of Dissolution Data of F-6 Batch.

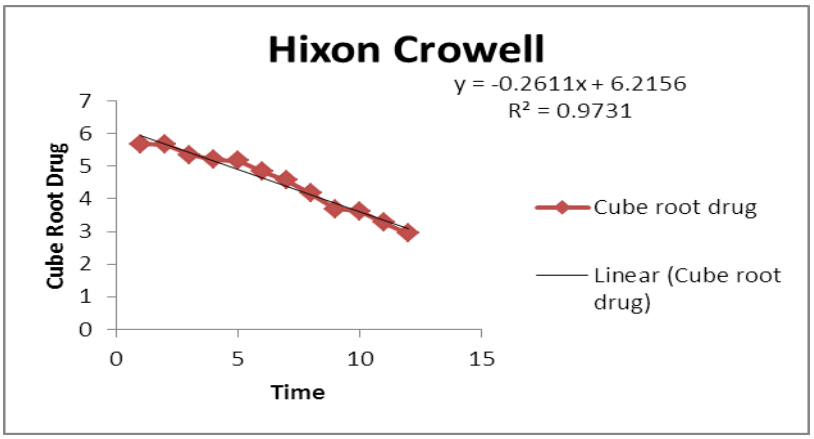

Fig No2:- Hixson Crowell Cube Root Kinetic Treatment of Dissolution Data of F-6 Batch.

Data Kinetics F-13

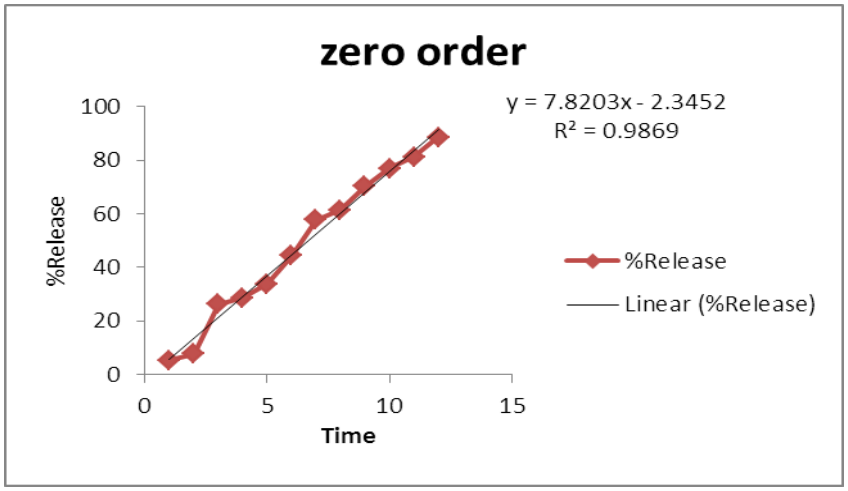

Fig No 3:- Zero Order Kinetic Treatment of Dissolution Data of F-13 Batch.

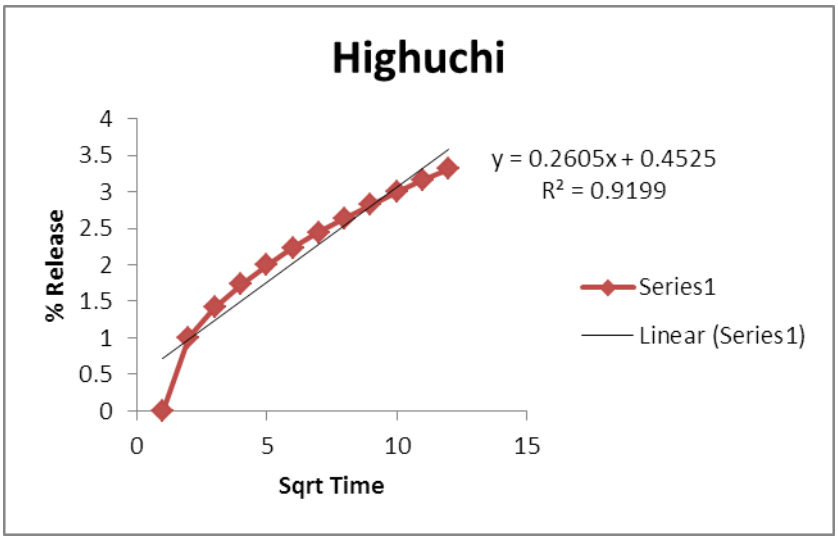

Fig No 4:-Higuchi Square Root Kinetic Treatment of Dissolution Data of F-13 Batch

CONCLUSION

In present study matrix tablets of labetalol HCL were prepared by direct compression method using HPMC K100, Xanthan gum and Guar gum. All these prepared formulations were evaluated and showed satisfactory results. Among all the formulations F-6 and F-13 showed better release and could extend the release up to 12 hours. When natural polymers like Xanthan gum and Guar gum used in combination in different concentration ranges (F10,F11,F12,F13) their drug release retarding property get increased as compared when they are used in single. Combination of Xanthan gum and Guar gum has greater retarding property in combination. These polymers retard drug release up to 12 hrs. From obtained results, it is concluded that natural polymers have equal retarding property to that of synthetic polymers. So, one can replace synthetic polymers by natural polymers.

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