CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF LABETALOL HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLET BY USING *HIBISCUS ROSA-SINENSIS* LEAVES MUCILAGE AND POVIDONE

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Abstract:

The purpose of the present work was to develop matrix tablets of Labetalol HCl with Hibiscus rosa-sinensis leaves mucilage and povidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Mucilage from the Hibiscus rosa-sinensis leaves was extracted, isolated, and characterized. Physicochemical properties of dried mucilage powder of Hibiscus rosa-sinensis leaves were studied. Sustained release formulations of Labetalol HCl were prepared by using mucilage and povidone. The formulated tablets were tested for mechanical properties, friability, swelling behavior, in-vitro drug release pattern and the dissolution data (subjected to mathematical modeling). The formulated tablets were found to have good mechanical properties and good swelling properties. The in-vitro dissolution data was fitting to zero order kinetics and the release of drug from the formulation was found to follow Korsemeyer Peppas release. From this study it was concluded that the dried mucilage of Hibiscus rosa-sinensis leaves and povidone combination can be used as an effective matrix forming material for making sustain release matrix tablets of Labetalol HCl.

Key Words: - *Sustain release, Matrix tablets, Labetalol HCl, Hibiscus rosa-sinensis, Povidone.*

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Please cite this article in press as Hangargekar Chitra et al, ***Formulation and Evaluation of Labetalol Hydrochloride Sustained Release Matrix Tablet by Using Hibiscus Rosa-Sinensis Leaves Mucilage and Povidone****, Indo Am. J. Pharm. Sci, 2015; 2(12).*

INTRODUCTION:

Sustained-release oral delivery systems achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, which provides better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. Among the different approaches, matrix systems still appear as one of the most attractive from the economic as well as the process development and scale up points of view [1]. According to the joint national committee (JNC) VI, "Hypertension is when the diastolic blood pressure (DBP) measures 90 mm of hg or higher and systolic and systolic (SBP) measures consistently greater than 140 mm of Hg" [2]. Antihypertensive drugs are used for prevention of stroke. Stroke is associated with a wide variety of reasons and hence the presence of adequate amounts of plasma drug levels becomes very necessary for efficient treatment of hypertension. Antihypertensive drugs have short half-lives, extensively metabolized in the liver and are highly bound to plasma proteins. Hence if the release of drug is sustained for a longer period of time, will result in efficient management of hypertension [3] .Labetalol hydrochloride, 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]-benzamide, a non-selective α, β-adrenoceptor antagonist which is used in the treatment of hypertension. It is appreciably soluble in lower and higher pH solutions, with minimum solubility between pH 6 to 10. The drug shows variable bioavailability that is ranging from 10-80% which may be attributed to its instability in alkaline pH and poor absorption due to precipitation. It is administered in doses ranging from 50-200 mg twice a day due to its shorter half-life of 3-6 hrs. suggesting the need for sustained release formulation [4].*Hibiscus rosa-sinensis*, (Malvaceaefamily) commonly known as China rose is a popular landscape shrub, creates a bold effect with its medium-textured, glossy dark green leaves and with 4-6 inch wide and up to 8 inch long, showy flowers, produced throughout the year and grows up to 7-12 feet[5].The purpose of present work was to design and evaluate sustained release matrix tablets of Labetalol HCl using *Hibiscus rosa-sinensis* leaves mucilage and povidone combination as release retardant.

MATERIALS AND METHODS:

Materials:

Labetalol HCl was obtained as a gift sample from M-Cure Pharmaceuticals, Pune, India. *Hibiscus rosa-sinensis* leaves were collected from plants growing in local areas of Osmanabad, Maharashtra. Povidone, Microcrystalline cellulose (Avicel), Magnesium stearate were procured from Alkem Pharmaceuticals (Mumbai, India). Acetone and all other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiment.

Methods:

Extraction of Mucilage:

The fresh *Hibiscus rosa-sinensis Linn* leaves were collected and washed with water to remove dirts and debris. Leaves were powdered and soaked in water for 5-6 hrs, boiled for 30 minutes and left stand for 1hour to allow complete release of mucilage into water. The mucilage was extracted using multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried, in an oven at 40ºC, collected, ground, passed through #80 sieve and stored in desiccator at room temperature for further use.

Preparation of Sustained Release Matrix Tablets:

Matrix tablets containing Labetalol HCl were prepared by direct compression technique using variable concentrations of dried *Hibiscus rosa-sinensis* leaves mucilage and povidone.Different formulations were prepared by direct compression method. All the powders were passed through 85 mesh sieve shown in table 1.

Evaluations:

Weight Variation Test:

To study weight variation 10 tablets of the formulation were weighed using an electronic balance and the test was performed according to the official method. Ten tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug Content:

For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer pH 6.8. Then aliquot of the filtrate was diluted suitably and analysed spectrophotometrically at 304.50 nm against blank. Drug content was calculated using standard curve.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using digital hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness:

The thickness of the tablet was measured using vernier caliper. Thickness of selected tablets from each batch was measured and average of reading taken in triplicate was calculated.

Friability Test:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again.

The % friability was then calculated by,

Percentage friability = $W - W_0 / W \times 100$

Where, W0 = initial weight

W = weight after friability

***In-vitro* Dissolution Studies:**

The *in-vitro* release of Labetalol HCl from the formulated tablets was carried out in tablet dissolution tester USP – Electro lab using 900 ml of dissolution medium maintained at 37.0 ± 0.5^0 C and stirring rate of 100 rpm. Nine tablets from each formulation were tested individually in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer (pH 6.8) for the following 10 h. at every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of Labetalol HCl present in each sample was determined spectrophotometrically at 304.50 nm.

Swelling index:

The swelling index of tablets was determined in pH 6.8 phosphate buffer at room temperature. The swollen weight of the tablets was determined at predefined time intervals.

The swelling index (SI) was calculated by the following equation:

SI % = (weight of swollen tablet – initial weight of tablet) / (initial weight of tablet) ×100

Table 1: Formulation of Sustained Release Matrix Tablets of Labetalol HCl

Formulation	H1	H2	H3	P4	P5	P6	HP7	HP8	HP9
Labetalol HCl	200	200	200	200	200	200	200	200	200
Hibiscus rosa sinensis leaves mucilage	30	60	90	-	-	-	-	-	-
Povidone k-25	-	-	-	12	16	20	-	-	-
Mucilage+ Povidone	-	-	-	-	-	-	30	35	40
Microcrystalline cellulose	165	135	105	183	179	175	165	160	155
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight	400	400	400	400	400	400	400	400	400

RESULTS AND DISCUSSION:

The DSC thermogram obtained from these studies shows the sharp endothermic peak at 203.35ºC for pure Labetalol HCl corresponding to its melting point. The endothermic peak of formulation HP9 showed at 258.22ºC, due to various concentrations of the polymers which is shown in figure 1 and 2 respectively.A total of nine formulations of matrix tablet were design. These powder blend were evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio shown in table 2. All are within the accepted limits. The prepared tablets were tested for physical parameters like hardness, weight variation, friability, drug content uniformity. The results of all these evaluations are given in table 3. The percent deviation from the average weight was found to be within the prescribed official limits.Hardness of tablets was found to be in the range of 5.42 to 5.93 Kg/cm^2 and is given in table 3. The friability of all the prepared tablets was found to be in the range of 0.57 to 0.64, fulfilling the official requirements (not more than 1%).Drug content estimation data for all batches are given in table III it was found to be in the range of 95.41 to 99.24% with low values of standard deviation indicates uniform drug content in the tablets prepared.The formulations H1, H2, H3 are formulated with different concentrations of *Hibiscus rosa-sinensis* leaves mucilage with varying concentrations. The swelling index of tablet was performed in the terms of percentage weight gain by matrix tablet shown in figure 3, as time increases the swelling index was increased, because weight gained by tablet was increased proportionally with the rate of hydration up to 6hrs. Later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium.The *in-vitro* drug release of formulation H1-HP9 is shown in figure 4. In H1 formulations 89.59% of the drug release was within 12 hours. And in H2 formulations 91.41% of the drug was released within 12 hours. Where as in H3 formulations 92.22% of the drug was released was within 12 hours. The formulations P4, P5, and P6 are formulated with different concentrations of Povidone with varying concentrations. In P4 and P5 formulations 82.08 %, 84.21% release of drug was occurred within 12hours respectively. In P6 formulations 99% release of drug was occurred within 12hours. The desired release is not achieved in P4, P5 and P6 formulation. The formulations HP7, HP8, and HP9 are formulated with different concentrations of *Hibiscus rosa-sinensis* leaves mucilage and Povidone combination with varying concentrations and. In all these formulations 93.64%, 94.25%, 96.89% drug release was occurred in 12 hours. The release was highly sustaining as the concentration of the polymer is increasing. The desired release achieved in HP9 formulation. From the entire above plot it was confirmed that **HP9** batch is the best batch. As coefficient of regression (r^2 =0.998) is linear for **Korsemeyer Peppas.** The best fit model is **Korsemeyer Peppas**model and according to Peppas equation (n=0.655) confirms diffusion mechanism is **Anomalous** (non Fickian) diffusion shown in table 4.

Table 2: Results of Flow Properties:

Batch	Angle of Repose (º)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index	Hausner's Ratio
H1	31.6	0.537	0.610	12.23	1.13
H2	33.7	0.524	0.601	12.83	1.14
H3	32.7	0.541	0.626	13.55	1.15
P4	30.8	0.560	0.630	11.55	1.12
P5	31.5	0.580	0.658	11.85	1.13
P6	29.0	0.579	0.670	12.18	1.15
HP7	33.2	0.565	0.637	12.80	1.12
HP8	32.5	0.540	0.626	11.95	1.15
HP9	34.6	0.559	0.631	12.63	1.12

Table 3: Evaluation Parameters

Formulation code	Evaluation parameter				
	Thickness ± S.D. (mm) (n = 3)	Hardness ± S.D. (kg/cm2) (n = 3)	Friability (%)	Average weight variation (n=10)	Drug content (%)
H1	4.07±0.02	5.82±0.03	0.03	404.4±0.5	99.24
H2	4.83±0.03	5.75±0.02	0.07	404.1±0.7	95.41
H3	4.75±0.04	5.72±0.02	0.11	404.9±0.6	99.5
P4	4.02±0.03	5.83±0.02	0.63	404.3±0.5	96.87
P5	4.03±0.03	5.65±0.02	0.18	405.2±0.4	97.71
P6	4.13±0.03	5.67±0.01	0.21	404.9±0.7	98.47
HP7	4.02±0.02	5.93±0.02	0.29	405.5±0.4	96.45
HP8	4.87±0.03	5.42±0.02	0.17	405.1±0.9	98.98
HP9	4.03±0.04	5.74±0.02	0.29	404.2±0.4	95.87

Table 4: Kinetic Model Fitting

Formulation Code	r^2 Value				
	Zero order	First order	Higuchi model	Korsemeyer & Peppas model	Hixson Crowell model
H1	0.996	0.944	0.997	0.997	0.978
H2	0.998	0.940	0.930	0.998	0.976
H3	0.996	0.907	0.928	0.996	0.957
P4	0.997	0.956	0.930	0.997	0.980
P5	0.998	0.956	0.934	0.996	0.981
P6	0.998	0.952	0.936	0.997	0.981
HP7	0.997	0.924	0.938	0.997	0.970
HP8	0.999	0.904	0.926	0.998	0.960
HP9	0.998	0.887	0.937	0.997	0.954

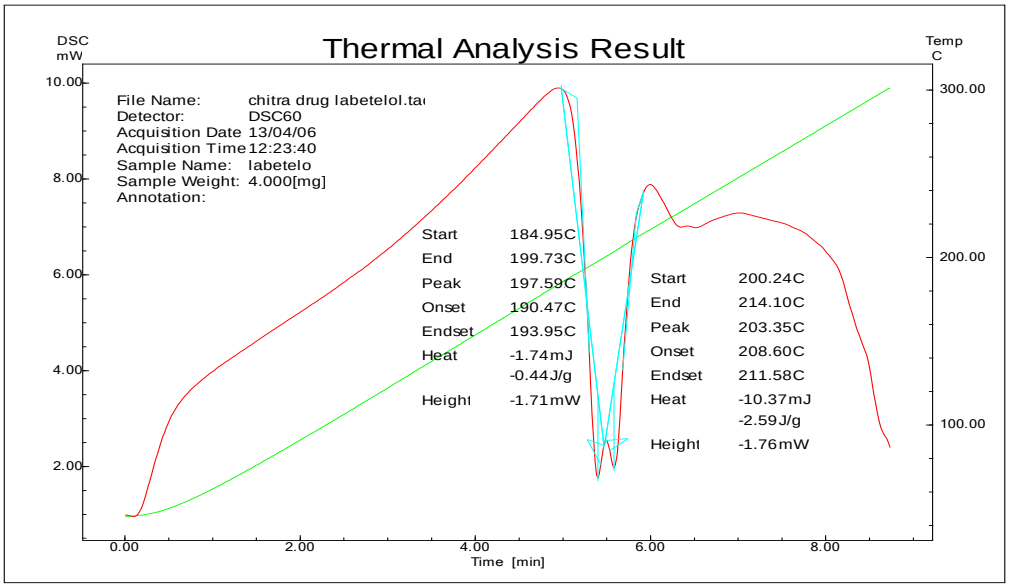

Fig. 1: DSC of Pure Drug (Labetalol HCl)

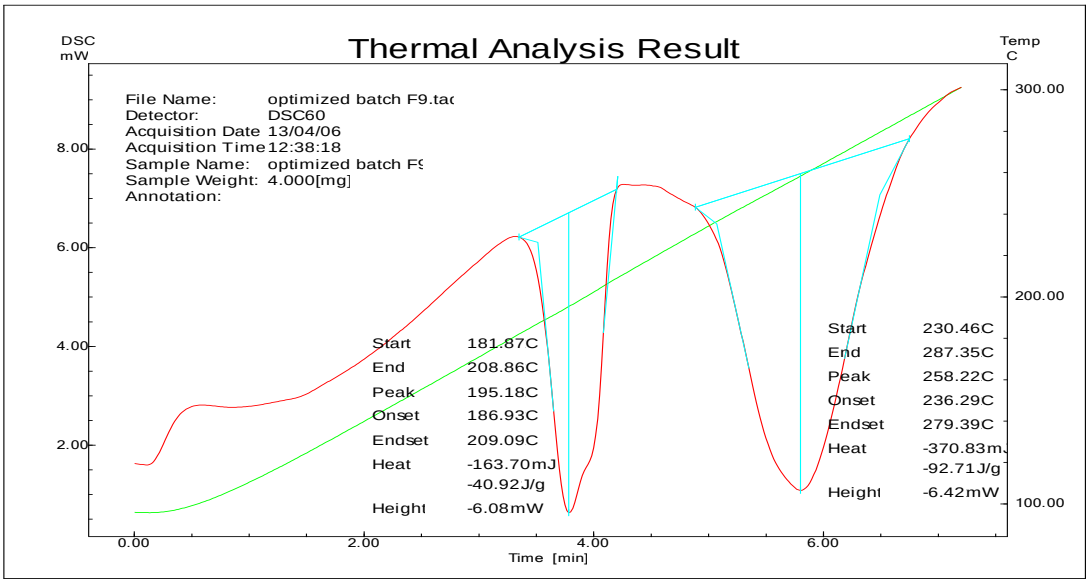

Fig.2: DSC of Optimized Batch (HP9)

The % Swelling Index Study of Batch H1 to Batch HP9 Shown in Graph

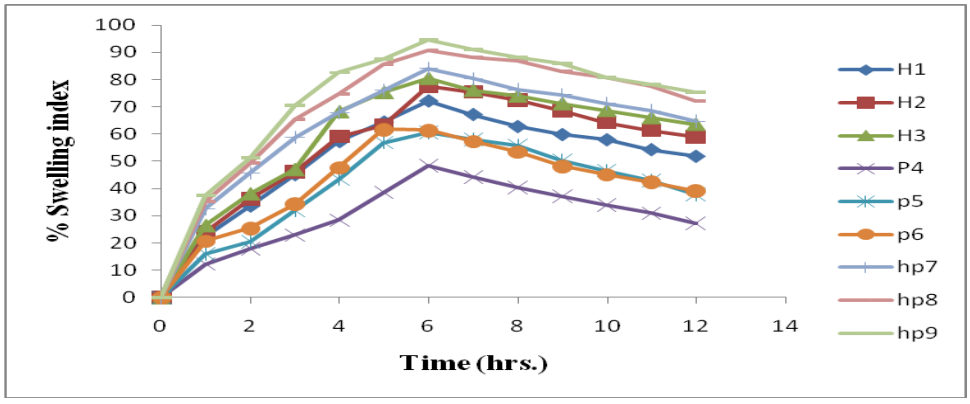

Fig. 3: Swelling Index of Batch H1-HP9.

The *In-Vitro* Drug Release Study of Batch H1 to Batch HP9 Shown In Graph

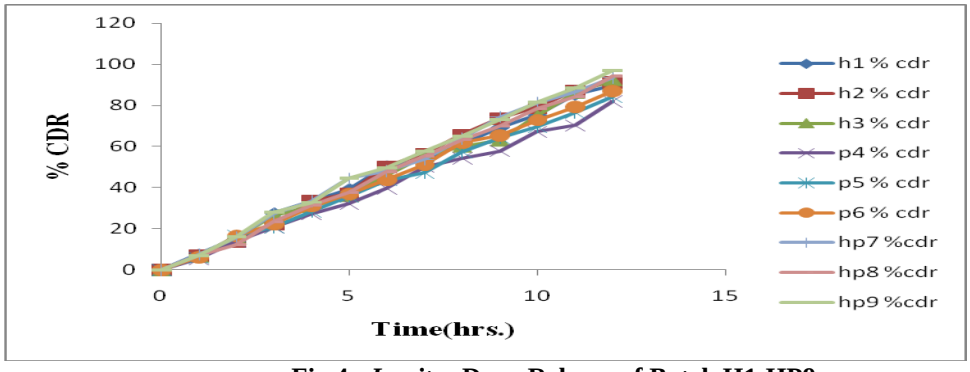

Fig 4: *In-vitro* Drug Release of Batch H1-HP9.

CONCLUSION:

The study deals with the investigation of release retardant effect of *Hibiscus rosa-sinensis* Mucilage when formulated as a matrix tablet. The mucilage exhibited an appreciable physicochemical properties and suited best for the development of sustained release tablets as indicated by the drug release studies. This can be used as a potential natural source over the synthetic release retardant. Hence, *Hibiscus rosa-sinensis* could be employed as a release rate retardant for sustaining the drug release from the formulation. The present study revealed that *Hibiscus rosa-sinensis* leaves mucilage and povidonecombination appears to be suitable for use as a release retardant in the manufacture of sustainedrelease matrix tablets because of its good swelling,good flow and suitability for matrix formulations. From the dissolution study, it was concluded thatdried mucilage of *Hibiscus rosa-sinensis* leaves in combination with povidone can beused as an excipient for making sustained releasematrix tablets.

ACKNOWLEDGEMENT:

The authors are thankful to K.T.Patil College of Pharmacy, Osmanabad, for providing necessary facilities, also thanks to M-Cure Pharmaceuticals, Pune, Alkem Pharmaceuticals, Mumbai to provide gift sample of drug and polymers to carry out this research work.

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