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Formulation and Evaluation of Extended Release Tablets of Labetalol Hydrochloride

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ABSTRACT:

Extended-release preparations are long-acting, broad-acting preparations that release the active ingredient over an extended period of time. Labetalol hydrochloride is used to treat high blood pressure. This drug is characterized by a short half-life (3-6 hours) and rapid metabolism. It depends on the solubility and pH range from 6 to 10. In this study, 200 mg labetalol hydrochloride extended-release tablets were prepared by wet granulation method using polymers Eudragit RSPO and Lubritab in different variations to extend the drug delivery up to 12 hours and to improve bioavailability. These formulations were evaluated for changes in weight, hardness, thickness, drug content and drug release pattern, with positive results. In vitro drug release was performed in 900 mL of acidified medium (pH 1.2) at 50 rpm for 2 hours, and then in 900 mL of phosphate-buffered medium (pH 6.8) for 12 hours using a USP Type II degassing apparatus. Mean dissolution time is used to describe the rate of drug release from the dosage form and to indicate the effectiveness of delaying drug release from the polymer. As a result of comparing the elimination data and the new drug, it was found that in eight formulations, formulation F7 was the best formulation. To determine drug release kinetics, several kinetic models have been used in the elution literature. Drug release from F7 formulation followed first-order and Higuchi kinetics and Fickian diffusion mechanism.

Keywords: Extended release tablets, Labetalol HCl, Lubritan, Eudragit RSPO, Magnesium stearate and Lactose monohydrate

1. 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. 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. Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs . The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration.

The drug such as Labetalol HCl was selected taking in to consideration of their physicochemical, biopharmaceutical properties and rationale of clinical efficacy. 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.

Labetalol hydrochloride is a selective α- and nonselective β-adrenergic blocking agent. It is used in management of hypertension, alone or in combination with other classes of antihypertensive agents. Labetalol hydrochloride is one of several preferred initial therapies in hypertensive patients with heart failure, post-MI, high coronary disease risk, or diabetes mellitus. It can be used as monotherapy for initial management of uncomplicated hypertension. Labetalol hydrochloride is also effective in controlling blood pressure in pregnant women with moderate to severe hypertension and severe pregnancy induced hypertension.

The present study is aimed to formulate extended release matrix tablets of Labetalol hydrochloride using various hydrophilic and hydrophobic polymers and the effect of various hydrophilic and hydrophobic polymers on drug release and other parameters were studied to optimize the final formulation.

2. Materials:

Materials used in this study were obtained from the different sources. Labetalol HCl was a gift sample from Teva. Eudragit RSPO obtained from Evonik , Lubritab manufactured by JRS Pharma, Magnesium stearate were procured from Polymer additives Inc and Lactose monohydrate purchased from DFE pharma. Other materials used were of analytical grade and procured from commercial sources.

3. Methods:

3.1. Solubility:

weigh 1mg of standard in 6 different eppendrof tubes and see the solubility of Labetalol HCl and select suitable solvents.

3.2. UV analysis of drug:

a. Preparation of 0.1 N HCl solution: 8.5 ml of concentrated hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

b. Phosphate buffer: Mix 10.5 mL of 1.0 M Sodium dihydrogen phosphate dihydrate buffer and 60 mL of 0.5 M Disodium hydrogen phosphate anhydrous buffer. Make up to 1000 mL with ultrapure water, if necessary adjust the pH of solution to 7.1 ± 0.05 with 10 % Orthophosphoric acid solution. Filter through 0.45 µ membrane filter.

c. Preparation of standard stock solution: Accurately weighed 10mg of Labetalol HCl was dissolved in 100 ml of 0.1 N HCl which gives 100 µg/ml standard stock solution.

d. Determination of Analytical Wavelength (λmax): The standard stock solution of 100 µg/ml of Labetalol HCl was estimated by UV-Visible Spectrophoto metric method and the absorption maxima were determined. The λmax of Labetalol HCl was found to be 219 nm.

3.3. Fourier Transform Infra-Red (FT-IR) spectral analysis:

Fourier–Transform Infrared (FT–IR) spectrums of pure Labetalol HCl were obtained by a Fourier-Transform Infrared spectrophotometer, (FTIR-8300, Shimadzu, Japan) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm-1 and the resolution was $1cm^{-1}$.

3.4. Preparation of Extended Release Matrix Tablets of Labetalol Hydrochloride:

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and Eudragit RSPO or Lubritab were blended geometrically in a mortar and pestle for 15 minutes then Magnesium stearate and Lactose monohydrate were mixed one by one. After mixing these ingredients, the powder blend was passed through # 44 mesh. The resulting powder mixture was compressed using 7-station rotary press using round shaped punches. Punches measuring 11 mm diameter were used for compression of the tablets. Sustained release tablets were prepared by wet granulation technique. Cemach tablet compression machine. The tablets were dried at 60°C in oven till constant weight obtained. The formula for various formulations attempted have been given in Table.1

Table.1.Composition of Extended Release Labetalol Hydrochloride Tablets

Quantity per tablet (mg)								
Ingredients	**F1(1:0.5) lubritab**	**F2(1:0.5) Eudragit RSPO**	**F3(1:0.3) Lubritab**	**F4(1:0.3) Eudragit RSPO**	**F5(1:0.2) lubritab**	**F6(1:0.2) Eudragit RSPO**	**F7(1:0.1) Lubritab**	**F8(1:0.1) Eudragit RSPO**
Dry mix								
Labetalol Hcl	200	200	200	200	200	200	200	200
Lubritab	100	-	60	-	40	-	20	-
Eudragit RSPO	-	100	-	60	-	40	-	20
Lactose monohydrate	50	50	62	62	68	68	68	68
Binder solution								
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Lubrication								
Mg stearate	10	10	38	38	52	52	60	60

3.5. Evaluation of Powder Blend of tablets:

The flow properties of powder blend were characterized in terms of angle of repose, Carr's index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.

a.Bulk Density: The mass of the powder divided by the volume of the powder is called bulk density. 20 g of api powder sample was added to a 50 ml vial. The volume is recorded in the graduated cylinder. calculate by using formula given below:

$$D_b = M / V_b$$

Where, M = It denoted as powder Mass and V_b = It denoted as powder bulk volume.

b. density of a Tapped powder: A known amount of 25 grams of API is delivered to the master cylinder, weighed and delivered to the compression unit. The first results have been recorded. The units are between 10,500 and 1,250. The bulk density was determined by calculating the ratio of the bulk density to the mass of the powder and assumed the same density. Calculate using the equation following.

$$D_t = M / V_t$$

Where, M It denoted as powder Mass and V_t = It denoted as powder Tapped volume

c. Angle of repose: The nozzle is perpendicular to the horizontal plane. The background is closed because the camera API is full. To moisten the dough, fold the paper over it and gently form a cone-shaped mound. Measure your waist height with a scale. The circle represents the size of the vertical bar and its diameter is measured in 4 degrees. To determine the radius, calculate the average diameter. The angle of repose is calculated according to the formula:

$$\text{Tan } \theta = h/r$$

Therefore $\theta = \text{Tan}^{-1} h/r$. Where,$\theta$ = Angle of repose,h = height of the cone and r =Radius of the cone base.

d. index of Compressibility: Tapped density of a labetalol was measure by setting of 10 taps, 500 taps and 1250 taps at neck of cylinder by a separate device. The results obtain must not be less than 2%. Calculated using the following formula:

$$\text{Compressibility index (\%)} = [(D_t - Db) \text{ X } 100] / D_t$$

Where, D_t is the tapped density and D_b is the bulk density

e. Hausner ratio: Hausner ratio represents the density of tapped powder and density of a bulk powder.

$$\text{Hausner ratio} = D_t/D_b$$

Where, D_t is the tapped density and D_b is the bulk density.

3.6. Evaluation parameters of Post compression:

A variety of tests are used to evaluate the properties of manufactured tablets, including studies of hardness, thickness, viscosity change, weight change, selectivity, and drug release using in vitro dissolution models.

a. General appearance: The fast dissolving tablets, morphological characterization which includes size, shape, colour, presence or absence of odour, taste surface texture was determined.

b. variation of Weight: To determine weight change, 20 slabs were collected during construction, a random sample was taken from each lot, and each sample was weighed on an electronic scale to determine the average weight of the samples. Find the average of the area and the weight. All boards must be the same weight and shape. Weight changes must be within established parameters.

c. hardness: Electrolab digital meter is used to measure the hardness of prepared labetalol tablets.

d. Thickness: By using vernier caliprse the thickness of the tablets selected randomly from the prepared

e. Test of Friability for tablet: The test of friability for tablet was performed using a Roche friabilitor tester. A 6.5 g tablet was weighed and tested for abrasion and impact using a plastic crushing chamber at 25 rpm, with 6 inches space between each impact paddle. After cycles 100, the tablets were reweighed. The percentage of difference is calculated as follows:

$$\text{\% Friability} = \text{Initial weight} - \text{Final weight} / \text{Initial weight} * 100$$

% Friability of the tablets not more than 1% w/w was considered acceptable.

f. Assay: labetalol hydrochloride tablets was precisely weighed which the equivalent to labetalol hydrochloride 100 mg standard, transfer to a 250 ml volumetric flask, add 30 ml of prepared diluent (ACN: water 50:50), to diluted and the flask is sonicated for 30mins to dissolve and mix with diluent. Fill the dilution to the indicated line with continuous stirring and add 0.45 mg of labetalol HCL. The solution is filtered by passing it through a nylon

membrane. Transfer an amount of 5 ml of the solution to a 100 ml bottle and dilute to the required amount with the appropriate diluent. The absorbance of the standard labetalol solution and the prepared labetalol sample was measured using a UV spectrophotometer.

g. In-Vitro Dissolution Study: The In-vitro dissolution study for the Labetalol HCl extended release tablets were carried out in USP XXXIX type-II dissolution test apparatus (Paddle type) using 900 ml of phosphate-buffered medium (pH 6.8) as dissolution medium at 50 rpm and temperature 37±0.5°C for 12 hours. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 219 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

3.7. Kinetic modeling of drug release:

The dissolution profile of the optimized formulation was fitted in 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.

4. Results:

4.1. UV spectrometry:

For the selection of analytical wavelength, standard solution of Labetalo Hcl was scanned in the spectrum mode from 200 nm to 400 nm separately. From the spectra of drug, λmax of Labetalo Hcl, 219 nm was selected for the analysis of samples. Sample was prepared by Aliquots of standard stock solution were diluted with methanol solvent and the same buffer solution as the blank.

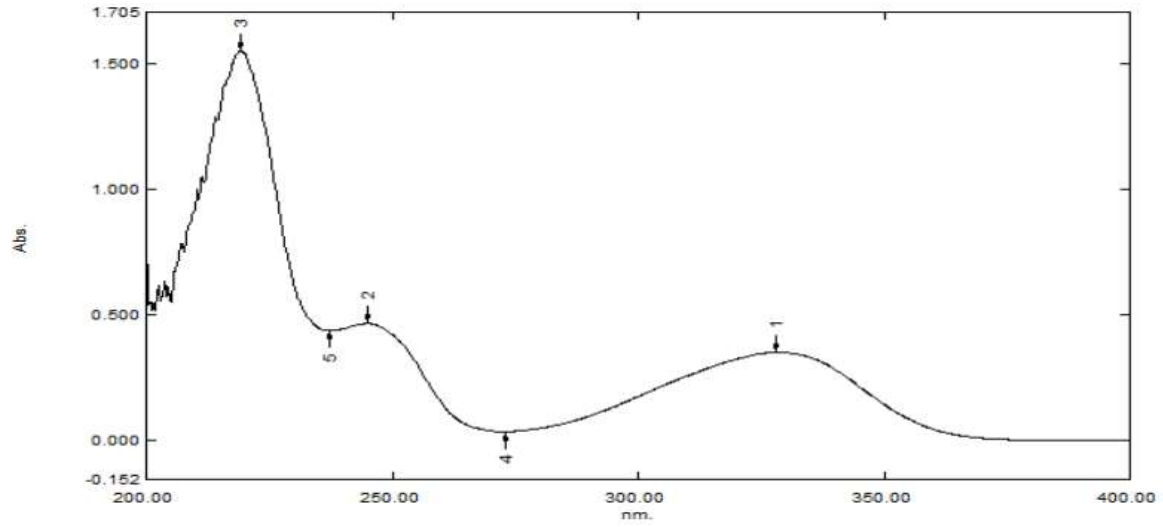

Fig.1. Spectrum Peak of Labetalol HCL

Discussion: The maximum wavelength of Labetalo Hcl solutions at a concentration of 100 µg/mL was determined using the comprehensive inspection mode of the UV-visible spectrophotometer, taking into account the required level of accuracy. The λ-max of Labetalo Hcl maximum absorption is optimized as 219nm

4.2. FTIR:

FTIR spectroscopy was performed to confirm pure drug samples by FTIR spectra. The existence of electronic and chemical interactions between Labetalo Hcl and polymers was clearly ruled out by FTIR spectra. This structure retains its medicinal properties. The absence of new peaks is a clear indication that there are no new active groups. As a result, we can say that there is no interaction between the components found.

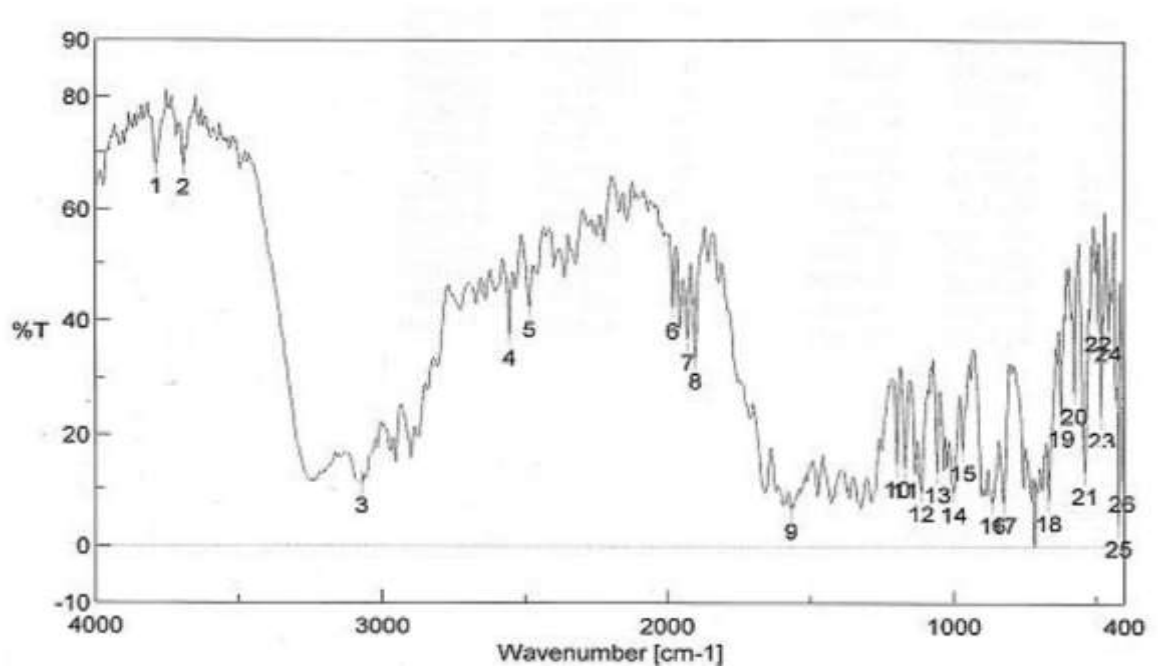

Fig. 2. FTIR spectra of Labetalol Hcl pure drug

Discussion: The findings support the safety of the drug and suggest that the method of drug administration should be further investigated.

4.3. Formulation of Extended release tablets of Labetalol hydrochloride

Labetalol hydrochloride with all available information proved to be a suitable candidate for development of sustained release formulation. The present investigation was to fabricate and evaluate the sustain release formulation Labetalol hydrochloride extended matrix tablet. The tablets were prepared by using combined polymers i.e. Eudragit RSPO or Lubritab by wet granulation technique. In each batches 10 tablets were prepared.

4.3.1. Pre-formulation parameters of tablet were determined:

Before compression the formulated blend was subjected for various evaluation parameters. The powder blend was evaluated by the measurement of bulk density, tapped density, angle of repose, compressibility index and hausner's ratio.

Table.2. pre-compression parameters results of Labetalol Hcl tablets

Formulation code (n=3)	**Bulk Density (gm/ml) ±SD**	**Tapped Density (gm/ml) ±SD**	**Carr's Index (%) ±SD**	**Hausner's ratio ±SD**	**Angle of repose(º) ±SD**
F1	0.47±0.02	0.56±0.02	16.0±0.36	1.19±0.01	35.60±0.51
F2	0.48±0.01	0.62±0.01	22.5±0.62	1.29±0.03	36.72±0.60
F3	0.52±0.02	0.65±0.02	20.0±0.40	1.25±0.02	36.09±0.23
F4	0.47±0.02	0.58±0.03	18.96±0.24	1.23±0.02	34.95±0.18
F5	**0.56±0.02**	**0.67±0.01**	**16.41±0.22**	**1.19±0.02**	**35.82±0.45**
F6	0.46±0.03	0.60±0.02	23.33±0.55	1.30±0.01	36.09±0.56
F7	0.54±0.02	0.67±0.03	19.40±0.16	1.24±0.03	34.76±0.47
F8	0.46±0.03	0.60±0.02	23.33±0.55	1.30±0.01	36.09±0.56

Discussion: The results obtained by evaluating the powder blends of drug and excipients are shown in table-2.Bulk density and tapped density were found in the range of 0.46-0.56 g/cc and 0.56-0.67 gm/cc respectively. The Carr's index was within between 16.0 – 23.33 indicating that all batches of powder blends were having good compressibility .The haursner's ratio was within between 1.19-1.30 indicating that all batches of powder blends were having good compressibility. Value of angle of repose was found in the range of 34.76-36.72 showing that blend of powder mass was good flowing.

4.3.2. Post-compression parameters of tablet were determined:

The different parameters of the dosage were examined after the compression like the weight of tablets, firmness, and thickness of tablets, adaptability file and consistency. It is imperative that all contracts meet the established limits.

Table.3.Post compression parameters results of Labetalol Hcl tablets

Formulation code	Hardness (N) ±SD, n=5	Friability(%) ±SD, n=5	Thickness (mm) ±SD, n=5	Weight variation (mg) ±SD, n=20	Assay (%) ±SD,n=6
F1	112.9±0.15	0.07±0.02	5.24±0.07	361.2±0.15	98.9±0.11
F2	124.1±0.25	0.12±0.05	4.97±0.02	360.3±0.15	98.8±0.25
F3	118.6±0.20	0.07±0.06	5.00±0.03	297.5±0.15	99.7±0.69
F4	**107.3±0.32**	**0.20±0.03**	**4.97±0.01**	**296.4±0.15**	**98.3±0.52**
F5	121.2±0.23	0.13±0.12	5.10±0.02	264.5±0.15	100.36±0.71
F6	118.8±0.21	0.04±0.15	5.12±0.03	267.6±0.15	100.89±0.26
F7	122.9±0.25	0.13±0.09	5.05±0.04	232.8±0.15	100.05±0.25
F8	119.9±0.25	0.12±0.09	5.04±0.04	232.8±0.15	100.05±0.25

Discussion: The average weight in all the formulation was found to be 232.8mg to 361.2mg. 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 98.31% and 100.89% of labetalol hydrochloride which was within the acceptable limit.

4.3.3. In-Vitro Studies:

To investigate the drug release rate of prepared labetalol Hcl formulations with different concentrations of polymers was evaluated in dissolution model of In-vitro studies up to the time 12 hours. The results of performed study were analyzed to optimize the best formulation.

Table.4.Dissolution data of formulation F1 to F8

% Drug release (±SD) n=6									
Dissolution	**Time (hrs)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Water 900ml 50rpm	1	18.3	20.3	18.4	21.3	22.2	36.2	**32.3**	42.5
	2	26.2	29.6	25.8	33.7	33.4	58.2	**53.3**	68.9
	4	36.5	41.5	38.8	51.3	50.9	74.2	**75.4**	91.9
	6	44.5	51.2	47.7	60.9	59.5	93.3	**84.9**	98.7
	8	49.3	56.0	56.1	68.5	75.4	107.9	**99.8**	106.7
	10	54.3	62.3	60.2	71.7	84.0	109.1	**103.8**	107.5
	12	56.5	65.6	67.3	79.1	91.8	105.4	**106.2**	100.8

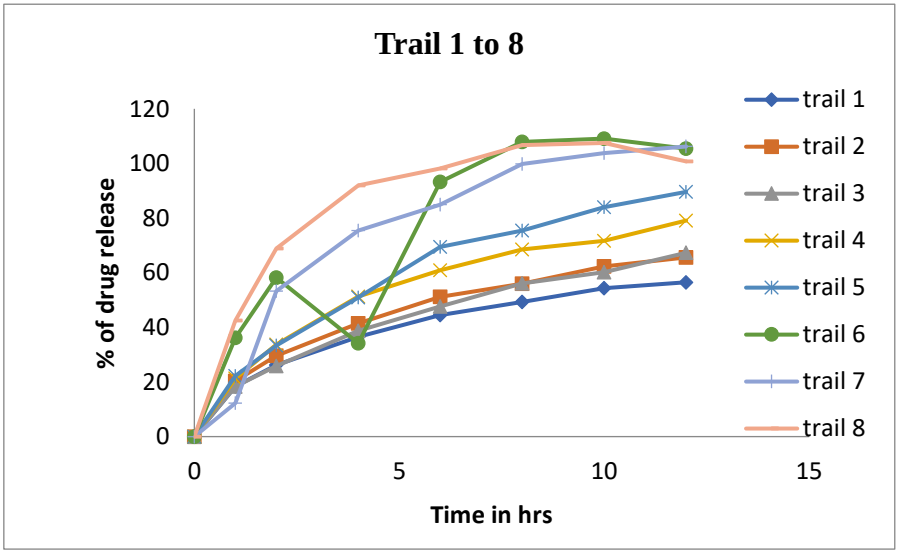

Fig.3.Dissolution data of formulation F1 to F8

Discussion: From all the formulations F7 showed faster drug release and F1 showed slow drug release when compared to other formulations. Hence F7 was considered to be the best formulation based on its drug release (106.2%) characteristics.

4.3.4. analysis of Drug release in-vitro model:

Based on the data obtained in in-vitro model for rate of drug release of labetalol Hcl. And F7 formulation was optimized as best formulation and to confirm it is processed with various models of mathematics for biological studies.

Table.5.R^2 value of various kinetic models

Kinetic model		**Result**
Zero order	R^2	0.940
First order	R^2	0.988
Higuchi	R^2	0.986
Korsmeyer-Peppas	R^2	0.981
	N	0.5

Table.6. Drug Release Kinetic Profile for F7

Labetalol HCl tablets 200mg									
Time (Hr)	**cumulative % drug released**	**% drug remaining**	**Square root time**	**log Cumu % drug remaining**	**Log time**	**log Cumu % drug released**	**% Drug released**	**Cube Root of % drug Remaining(Wt)**	**Wo-Wt**
0	0.0	100	0.000	2.000	0.000	0.000	100.000	4.642	0
1	**22.20**	77.8	1.000	1.891	0.000	1.346	22.200	4.269	0.373
2	**33.40**	66.6	1.414	1.823	0.301	1.524	11.200	4.053	0.588
4	**50.90**	49.1	2.000	1.691	0.602	1.707	17.500	3.662	0.980
6	**59.50**	40.5	2.449	1.607	0.778	1.775	8.600	3.434	1.207
8	**75.40**	24.6	2.828	1.391	0.903	1.877	15.900	2.908	1.733
10	**84.00**	16	3.162	1.204	1.000	1.924	8.600	2.520	2.122
12	**89.60**	10.4	3.464	1.017	1.079	1.952	5.600	2.183	2.459

Discussion: 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-7 highest "R2 " value was obtained for Hixson Crowell, and In Case of F- 1 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.

5. Conclusion:

Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration accurate dosage, self-medication, pain evasion and most importantly the patient compliance. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect.

Labetalol was freely water soluble drugs found to be suitable for formulating as extended release matrix tablets with polymers Eudragit RSPO or Lubritab by wet granulation process.

The results obtained by evaluating the powder blends of drug and excipients are shown in table-2.Bulk density and tapped density were found in the range of 0.46-0.56 g/cc and 0.56-0.67 gm/cc respectively. The Carr's index was within between 16.0 – 23.33 indicating that all batches of powder blends were having good compressibility .The haursner's ratio was within between 1.19-1.30 indicating that all batches of powder blends were having good compressibility. Value of angle of repose was found in the range of 34.76-36.72 showing that blend of powder mass was good flowing.

The physical parameters evaluated for the matrix tablet formulations such as weight uniformity, hardness, friability and drug content were uniform and were within the IP limits. The average weight in all the formulation was found to be 232.8mg to 361.2mg. 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 98.31% and 100.89% of labetalol hydrochloride which was within the acceptable limit.

From all the formulations F7 showed faster drug release and F1 showed slow drug release when compared to other formulations. Hence F7 was considered to be the best formulation based on its drug release characteristics 106.2% for duration of 12 Hours.

In kinetic study, the best fit model was selected on the basis of R2 values. Thus, Higuchi model and korsmeyerpeppas model were followed by formulation N value between 0.5-0.85 which showed that anomalous (non-Fickian) diffusion.

No significant changes were observed in the physical characteristics and in the drug release profiles of selected matrix tablet formulations of Labetalol after storing them at accelerated storage conditions.

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