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FORMULATION AND EVALUATION OF ONDANSETRON HCL TRANSDERMAL PATCHES

1Meenakshi Cheera, 2M.Sunitha Reddy, 3S.Muhammed Fazal Ul Haq

1M.Pharmacy, 2Associate professor, 3Assistant Professor

JNTUH

ABSTRACT

Extended release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. Labetalol used for the treatment of hypertension. The extended release matrix tablets of Labetalol HCl utilize release retarding ability of Eudragit RSPO and Lubritab in different ratios polymers to extend the release of drug over 12 hrs period thereby improve its bioavailability. The tablets were prepared by using wet granulation method.. Extended release matrix tablet of Labetalol HCl were formulated by using different ratios (1:0.5, 1:0.3, 1:0.2, 1:0.1) of polymers. The formulated granules blends were evaluated for angle of repose, tapped density, bulk density and compressibility index. The formulated tablets were subjected to thickness, weight variation test, hardness test, friability test and assay and all parameters are within the limits. *In-vitro* dissolution studies were carried out by using USP dissolution apparatus Type 2 (paddle type),

first 2 hrs in water as a media at 50 rpm for a total period of 12 hrs. Based on the dissolution data comparision with innovator product, among 8 formulations the F7 formulation was found to be optimized formulation. The drug release of formulation F7 followed first order and higuchi kinetics and the mechanism was found to be Fickian diffusion.

Keywords: **:** Labetalol HCl, Hydroxy Eudragit RSPO, Lubritab, Wet granulation, Extended release and evaluation.

INTRODUCTION

ORAL DRUG DELIVERY SYSTEMS:

Oral drug delivery system is the largest and oldest segment of the total drug delivery system. It is the fastest growing and most preferred route for drug administration. Oral drug delivery system has been know for decades as the most widely used route of administration among all the routes that have being explored for the systematic delivery of drug via; various pharmaceutical products of different dosage forms.

Recently several technical advancements have resulted in development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting a drug to a tissue.

Drug delivery systems

- Conventional drug delivery systems
- Modified drug delivery systems.

Advantages of oral drug dosage forms:

- The oral medication is gradually considred as the initial possibility of investigation in the discovery and development of new drug moiety and pharmaceutical formulation due to
- Superior flexibility in dosage form design
- Patient acceptance

Disadvantages of Oral drug delivery system:

- Limited solubility of drug
- Poor preparation across the gastrointestinal tract

Extended release dosage forms

A dosage form that allows at least twofold reduction in dosing frequency as compared to that drug presented as immediate release form. Ex: Controlled release, Sustained release

- Controlled release: It includes any drug delivery system from which the drug is delivered at predetermined rate over a long period.
- Sustained release: It includes any drug delivery system that achieves slow release of drugs over extended period of time not particularly at predetermined rate.

DEFINITION

Transdermal therapeutic systems are defined as self contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. The first Transdermal drug delivery (TDD) system, Transdermal-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

MATERIALS AND METHOD MATERIALS

LIST OF MATERIALS

S.No	Ingredients	Functional category	Mfg by
1.	Labetalol HCl	API	Teva
2.	Eudragit RSPO	ER polymer/ Release retardant	Evonik
3.	Lubritab	ER polymer/ Release retardant	JRS Pharma
4.	Magnesium stearate	Lubricant	Polymer additives Inc
5.	Lactose monohydrate	Diluent	DFE pharma
6.	Purified water	Granulating fluid	RA Chem Pharma

LIST OF INSTRUMENTS

Equipment	Make
Weighing balance	Sartorious
Rapid mixer granulator	Saral engineering company
Tablet compression machine 8 stage	Rimek Karnavati
Rapid dryer	Retsch
Hardness and thickness tester	Pharma G tablet tester
Friability tester	Electrolab
Tapped density tester	Electrolab
Dissolution apparatus	Electrolab

Methods:

Preformulation studies:

- Preformulation studies are conducted to characterize the API & Excipient physical and chemical properties for designing of dosage form.
- In which, the investigation of physical and chemical properties of drug substance alone and when combined with excipients.
- The main objective of preformulation is to get adequate information useful for the developing the formulation which is stable and bio available

Preformulation study can divide in to three sub classes.

1. API characterization,
2. Analytical methods,
3. Compatibility study.

API characterization:

Physical appearance:

The appearance of API was done by visual observation.

Colour of the drug sample:

The drug sample was viewed visually for the determination of its colour using white and dark backgrounds and then the results were compared with pharmacopoeias.

Odour and taste of the drug sample:

The odour and taste of the drug sample results were compared with pharmacopoeias.

Solubility:

Solubility profiles of Labetalol HCl were done by solubility equilibrium method. It is done by stirring an excess of drug in the water and other solvents like methanol, ethanol, isopropyl alcohol. It is also done in various concentrations of p^H buffers.

Melting point:

Melting point of Labetalol HCl was found out using traditional melting point apparatus. Labetalol HCl was packed in the capillary tube which was placed in the holder provided in melting point apparatus. Melting range was found out from the reading which was observed visually.

Loss on drying:

Required quantity of drug was weighed and placed on the steel plate provided in the LOD tester and tested for LOD at 105ºC.

Bulk density:

The bulk density is defined as mass of powder divided by bulk volume. A sample powder of API (20 gm) was introduced in 50 ml graduated cylinder. The volume of material was noted on graduated cylinder.

The bulk density was calculated by the formula given below:

$$\mathbf{D_b = M / V_b}$$

Where,

M is the mass of powder.

V_b is the bulk volume of the powder.

Tapped density:

It was measured by transferring a known quantity (25 gm) of API into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 10, 500 and 1250 taps. The tapped density was determined as the ratio of mass of blend to the tapped volume.

The tapped density was calculated by following formula

$$D_t = M / V_t$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder

Angle of repose:

A funnel was kept vertically in stand at a specified height above a paper placed on the horizontal surface. The bottom was closed and the required quantity of API was filled in funnel. The funnel was opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured using the scale. A border heap was marked circularly and its diameter was measured at four points .The average diameter was calculated and radius was found out from it. The angle of repose was calculated using the formula

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

Therefore $\theta = Tan^{-1}\ h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Acceptance limits for angle of repose

S.No	Angle of repose(degrees)	Flow property
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair
4	41-45	Passable
5	46-55	Poor
6	56-65	Very poor
7	>66	Very very poor

Compressibility index:

It was measured by tapped density apparatus for 10, 500 and 1250 taps for which the difference should not be more than 2%.

It was determined by using the formula

Compressibility index (%) = [(D_t-Db) X 100] / D_t

Where,

D_t is the tapped density

D_b is the bulk density

Acceptance limits for compressibility index

S.No	Compressibility index (%)	Flow characteristics
1	<10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Very very poor

Hausners ratio:

The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausners ratio = D_t/D_b

Where,

D_t is the tapped density.

D_b is the bulk density.

Acceptance limits for Hausners ratio

S.No	Hausners ratio	Flow characteristics
1	1.00 -1.11	Excellent
2	1.12 -1.18	Good
3	1.19 -1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very poor
7	>1.60	Very very poor

Analytical methods:

Determination of ƛmax:

The prepared solution of Labetalol HCl was scanned for maximum absorbance in UV double beam spectrophotometer (shimadzu) in the range of 200-400 nm, by using water as a blank. The lambda max of the drug was found to be 302 nm

Drug excipient compatibility:

Formulation Development and Evaluation:

1. Sifting:

Sift weighed quantity of Labetalol HCl, polymer (Lubritab/ Eudragit RSPO) and Lactose monohydrate through #40 mesh and collect in double lined polyethylene bag.

2. Dry mixing:

The sifted materials were transferred to RMG for dry mixing for 10 min at 100 rpm.

3. Granulation: Required quantity of binder solution was added. Parameters like amount of binder solution, impeller speed, chopper speed, kneading time and air pressure were optimized during initial trials.

Optimization parameters during granulation

Formulation code	Amount of binder solution(ml)	Impeller speed(rpm)	Chopper speed(rpm)	Air pressure(kg/cm^2)	Kneading time (sec)	Binder addition time(sec)
F1	140	120	NA	1.5	60	90
F2	140	120	NA	1.5	60	90
F3	140	120	NA	1.5	60	90
F4	140	120	NA	1.5	60	90
F5	140	120	NA	1.5	60	90
F6	140	120	NA	1.5	60	90
F7	140	120	NA	1.5	60	90
F8	140	120	NA	1.5	60	90

4. Drying:

The wet mass obtained after granulation was air dried in rapid driers for 10 min. Later it was subjected to temperature drying in rapid driers till LOD value of NMT 2% was reached. Loss on drying of granules was determined by LOD apparatus at 105ºC.

Optimization parameters during drying

Formulation code	Temperature (ºC)	Air flow	Time (min)
F1	55	20	60
F2	55	20	60
F3	55	20	60
F4	55	20	60
F5	55	20	60
F6	55	20	60
F7	55	20	60
F8	55	20	60

5. Sizing and milling: The dried granules are sifted through #20 mesh and the #20 mesh retains were subjected to dry milling through 1.5 mm screen at high speed, knife in forward direction and the milled granules were passed using #20 mesh.

6. Lubrication: Sift accurately weighed magnesium stearate through #40 mesh, which is added to step no 5 and blend for 5 min at 12 rpm in double cone blender.

7. Compression:

Lubricated blend was compressed

Process parameters during compression

Process parameter	Data
Punch shape	Round
Punch size(mm)	9.8
Compression speed(rpm)	15

Evaluation parameters:

Pre compression parameters:

Prior to the compression of tablets, the blend was subjected to the following parameters.

Bulk density:

The bulk density is defined as mass of powder divided by bulk volume. It is measured by transferring a known quantity (20 gm) of blend into a 50 ml graduated cylinder. The volume of material was noted on graduated cylinder.

The bulk density was calculated by the formula given below

$$D_b = M / V_b$$

Where,

M is the mass of powder.

V_b is the bulk volume of the powder.

Tapped density:

It was measured by transferring a known quantity (25 gm) of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus

was set for 10, 500 and 1250 taps. The tapped density was determined as the ratio of mass of blend to the tapped volume.

The tapped density was calculated by following formula

$$\mathbf{D_t = M / V_t}$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

Angle of repose:

A funnel was kept vertically in stand at a specified height above a paper placed on the horizontal surface. The bottom was closed and the required quantity of blend was filled in funnel. The funnel was opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured using the scale. A border heap was marked circularly and its diameter was measured at four points .The average diameter was calculated and radius was found out from it. The angle of repose was calculated using the formula

$$\mathbf{\tan \theta = h/r}$$

Therefore $\theta = \tan^{-1} h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility index:

It was measured by tapped density apparatus for 10, 500 and 1250 taps for which the difference should not be more than 2%.

It was determined by using the formula

Compressibility index (%) = $[(D_t-D_b) X 100] / D_t$

Where,

D_t is the tapped density

Db is the bulk density

Hausners ratio:

The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausners ratio = D_t/D_b

Where,

D_t is the tapped density.

D_b is the bulk density.

Post compression parameters:

The prepared tablets were evaluated for tests like hardness, thickness, friability, weight variation, assay and *in vitro* dissolution studies.

Tablet hardness:

The crushing strength of the tablet was measured using Electrolab digital tablet hardness tester.

Thickness:

The tablets were randomly selected from each formulation and their thickness was measured by using vernier calipers.

Friability:

Friability test was done by Roche friabilator. 6.5 gm of tablets were weighed and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that resolve at 25 rpm dropping the tablets at distance of 6 inch with each revolution. Operated for 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated as

% Friability = Initial weight – Final weight / Initial weight *100

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

Assay:

Preparation of standard solution:

Accurately weigh and transfer 40 mg of Labetalol HCl into a 50 ml of volumetric flask, add 30 ml of diluent(50:50 ACN:Water) sonicate to dissolve and dilute to volume with diluent and mix. Transfer 5.0 ml of the above solution into a 100 ml volumetric flask and dilute to volume with diluent.

Preparation of sample solution:

Accurately weigh and transfer the crushed powder of labetalol HCl tablets equivalent to about 100 mg of labetalol HCl into a 250 ml volumetric flask, add 30 ml of diluent(50:50 ACN:Water), sonicate for 30 min with intermittent shaking and dilute to volume with diluent

and filter the solution through 0.45µ nylon membrane filter. Transfer 5 ml of this solution into 100 ml volumetric flask and dilute to the volume with diluent.

Procedure:

The above prepared standard and sample solutions were tested for its absorbance by UV spectrophotometry

Calculations:

Content of Labetalol HCl:

AT/AS * WS/100 * 4/50 *100/WT * 50/5 * P/100 * AW = ...mg/tab

% of labeled amount = content of labetalol HCl / label claim *100

Weight variation:

For each batch 20 tablets were collected randomly during compression and weight of individual tablets was carried out using electronic balance and calculate the average weight. Compare the individual tablet weight to the average.

It is desirable that all the tablets of a particular formulation should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits.

Acceptance criteria for tablet weight variation (IP)

Average weight of tablet (mg)	Maximum % difference allowed
80 or less than	10
80-250	7.5
More than 250	5

Acceptance criteria for tablet weight variation (USP)

Average weight of tablet (mg)	Maximum % difference allowed
130 or less than	10
130-324	7.5
More than 324	5

***In-vitro* drug release studies (UV spectrophotometry):**

Spectrophotometry conditions:

Wave length : 200-400 nm

Detector : UV

Dissolution parameters:

Medium : water

Apparatus : USP Type Π (paddle type)

RPM : 50

Temperature : 37 ± 0.5ºC

Sampling intervals : 1, 2, 3, 4, 5, 6, 7, 8, 10, 12hrs

Preparation of standard stock solution: Weigh accurately 55.0 mg of Labetalol HCl working standard into 100 ml volumetric flask add 70 ml of diluent, sonicate to dissolve and make up the volume to 100 ml with diluent and mix well.

Preparation of standard solution: Transfer 5.0 ml of the standard stock solution into a 50 ml volumetric flask and dilute to volume with diluent.

Preparation of sample solution:

Dissolution procedure:

The samples were taken with filter from the basket after every individual time interval and checked for the absorbance in UV

Preparation of 200 mg sample solution:

10ml sample was withdrawn from the dissolution basket in test tube with the help of filter and then from that 5ml of sample was taken into 20ml volumetric flask and make up the volume with diluent and checked for the absorbance by uv.

Calculation:

For 200 mg

AT/AS * WS/100 * 1/20 * 900/1 * 25/3 * P/100 * 100/label claim in mg

Where,

AT = Area of Labetalol HCl in sample solution

AS = Average area of Labetalol HCl in standard solution

WS = Weight of Labetalol HCl working standard (mg)

P = Purity of Labetalol HCl working standard used

Kinetic analysis of *in-vitro* release data:

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data was fitted to Zero order, First order, Higuchi's matrix model and Korsmeyer-Peppas model. The model with the highest correlation coefficient value (R^2) was considered as the best fit model. The release data were also kinetically analysed using the Korsmeyer-Peppas model and the release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation:

$$\frac{M_t}{M_\infty} = kt^n$$

Where M_t/M_∞ is the fraction of drug released at time t and k is a constant incorporating the structural and geometric characteristics of the release device. When n = 0.5, Case I or Fickian diffusion is indicated, 0.5<n<1 for anomalous (non- Fickian) diffusion, n = 1 for Case Π transport (Zero order release) and n>1 indicates Super case Π transport.

Results

Preformulation studies:

API characterization: Following properties of the active ingredient Lamotrigine were evaluated during preformulation study.

Characterization of drug properties

Property	Inference
Organoleptic characteristics	White coloured crystalline powder, bitter in taste and odourless
Bulk Density (g/ml)	0.42
Tapped Density (g/ml)	0.51
Melting Point (ºC)	134
LOD (%w/w)	0.72
Solubility	soluble in water and soluble in ethanol

Drug and excipient compatibility study:

Composition	Inference
API+ Lubritab	No change
API+ Eudragit RSPO	No change
API+ Lactose monohydrate	No change
API+ Magnesium stearate	No change
API	No change

Precompression parameters:

Precompression parameters were done prior to the compression of tablets.

Pre compression parameters

Formulation code	Bulk Density (gm/ml) ±SD n=3	Tapped Density (gm/ml) ±SD n=3	Carr's Index (%) ±SD n=3	Hausner's ratio ±SD n=3	Angle of repose(º) ±SD n=3
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

Post compression parameters:

Post compression parameters like weight variation, hardness, thickness, friability and assay were studied. All the formulations were within the limits.

Post compression parameters

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

***In-vitro* drug release studies:**

In order to achieve the objective of fabricating an extended release matrix tablet formulation of Labetalol HCl where its dissolution profile was extended till 12 hrs in a predictable and reproducible manner, the dissolution study of different batches was performed and results were analysed.

DESCRIPTION

F1 - First formulation was taken on the basis of literature. This batch was formulated by using Lubritab polymer using wet granulation method. Lubritab was used as an extended release polymer to prevent the release of drug. On dissolution the drug release was less than the USP Specification.

F2 – Second formulation was taken on the basis of literature. This batch was formulated same the concentration of Eudragit RSPO using wet granulation method. Eudragit RSPO was used as an extended release polymer to prevent the release of drug. On dissolution the drug release was less than the USP Specification.

F3 - Third formulation was taken on the basis of F1. This batch was formulated with decrease in the concentration of Lubritab using wet granulation method. Lubritab was used as an extended release polymer to prevent the release of drug. On dissolution the drug release was less than the USP Specification.

F4 - This batch was formulated by using Eudragit RSPO polymer using wet granulation method. Eudragit RSPO was used as an extended release enteric polymer to prevent the release of drug. On dissolution the drug release was less than the USP Specification.

F5 - Fifth formulation was taken on the basis of F3. This batch was formulated with decrease in the concentration of Lubritab using wet granulation method. Lubritab was used as an extended release polymer to prevent the release of drug. On dissolution the end release was equal to the USP Specification..

F6 – Sixth formulation was taken on the basis of F4. This batch was formulated with decrease in the concentration of Eudragit RSPO using wet granulation method. Eudragit RSPO was used as an extended release polymer to prevent the release of drug. On dissolution the end release was equal to the USP Specification

F7 - This batch was formulated by using Lubritab polymer using wet granulation method. Lubritab was used as an extended release polymer to prevent the release of drug. On dissolution the drug release was matches with the USP Specification.

F8 - formulation was taken on the basis of F6. This batch was formulated with decrease in the concentration of Eudragit RSPO using wet granulation method. Eudragit RSPO was used as an extended release polymer to prevent the release of drug. On dissolution the end release was equal to the USP Specification

Dissolution data of formulation F1 to F4

		% Drug release (±SD) n=6			
Dissolution	**Time (hrs)**	**F1**	**F2**	**F3**	**F4**
Water 900ml 50rpm	1	18.3	20.3	18.4	21.3
	2	26.2	29.6	25.8	33.7
	4	36.5	41.5	38.8	51.3
	6	44.5	51.2	47.7	60.9
	8	49.3	56.0	56.1	68.5
	10	54.3	62.3	60.2	71.7
	12	56.5	65.6	67.3	79.1

Dissolution data of formulation F5 to F8

		% Drug release (±SD) n=6			
Dissolution	**Time (hrs)**	**F5**	**F6**	**F7**	**F8**
Water 900ml 50rpm	1	**22.2**	36.2	32.3	42.5
	2	**33.4**	58.2	53.3	68.9
	4	**50.9**	74.2	75.4	91.9
	6	**59.5**	93.3	84.9	98.7
	8	**75.4**	107.9	99.8	106.7
	10	**84.0**	109.1	103.8	107.5
	12	**91.8**	105.4	106.2	100.8

Drug kinetic studies:

Drug release kinetic profile for F5

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

Kinetic analysis of *in-vitro* release data:

The in vitro release studies data of optimized batch F5 was fitted into various mathematical models to determine the best fit model.

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

Discussion

- The pure drug was evaluated for properties such as organoleptic characteristics, bulk density, tapped density, solubility, loss on drying and melting point.
- The angle of repose was in the range of 34.76º to 36.72º shows that blend have good flow property.
- The bulk density and tapped density for the formulations were calculated. The value ranges from 0.46 to 0.56 and 0.56 to 0.67 gm/ml.
- The compressibility index of various formulations was calculated. The compressibility index of pre compressed blends was in the range of 16.00% to 23.33%.
- The hardness is done by using Digital tablet hardness tester and it is measured for all formulations and the results were in the range of 120.2 to 135.8 N. T
- Tablet thicknesses were found to be uniform in all formulations and were found to be in the range of 4.97 to 5.24 mm. Friability values were found to be less than 1% in all cases and considered to be within the specified limits. Assay values of all the batches were within the limits of 98-102%.
- The weight variation of all formulations was found between 399 to 403 mg.
- *In vitro* dissolution studies of innovator and formulations F1 to F8 were carried out in water by UV spectrophotometry method and percentage of drug release was calculated for all the formulations.

- The regression coefficient (r^2) value for zero order, first order, higuchi's and peppas plots for optimized formulation F7 was found to be 0.940, 0.988, 0.981, and 0.978 respectively.

- The best formulation shows high R^2 value for first order release (0.988) than zero order (0.940) hence drug release mechanism is first order i.e., concentration dependent.

- The optimized formulation shown n value 0.5. So drug diffusion is following fickian diffusion.

Conclusion:

The Labetalol HCl extended release tablets were prepared by wet granulation method. Among all formulations F5, F6, F7, F8 formulation showed the >85.5% drug release in 12 hrs which is comparable with the USP specification. Finally concluded that the formulation (F5) containing Lubritab (Hydrogenated vegetable oil) showed the better drug release compared to other formulations. The drug release followed first order and the higuchi kinetics and drug diffusion is following fickian diffusion.

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