Formulation And Evaluation of Landiolol Hydrochloride Immediate Release Tablet

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***Abstract*—Landiolol hydrochloride is a highly selective ultra-short acting beta-1 adrenergic receptor blocker, including some alpha-1 blocker effects. Thus, administered to patients who suffer with the conditions: congestive heart failure; hypertension; and in post-myocardial infarction, being such a high-line useful drug and also potent with dose as low as 3.25 mg being effective, a quick and effective delivery would be a crucial step in health management of patients with CHF and hypertension. Formulating and developing an Immediate-Release Tablet, which is as close in comparison to a standard marketed tablet is the aim of this study. The key factors in IR tablets are the dissolution profile and disintegration time. Super-disintegrates are polymers which aid in quickly disintegrating the tablets in body aiding in quicker release of drug. Polymers of different caliber were subjected to preformulation studies with drug to test the compatibility and among them Croscarmellose sodium, Microcrystalline cellulose and Povidone were included as the super-disintegrants. Ten different formulations were designed and developed, varying in composition of binders, diluents to develop a superior tablet formula, out of all the 10 formulations, F1 & F2 failed to meet pre compression evaluation studies and remaining 7 formulations were prepared using wet granulation process, showed fair amount of dissolution done as per USP standards in comparison to standard Landiolol HCL IR tablet Coreg-25. The disintegration and dissolution studies were carried in various buffers with 0.1N HCl being deemed the most suitable one, the assay was done using HPLC which led to the conclusion that F9 & F10, having larger amounts of super-disintegrants showed the best dissolution of 98.54% and 99.43% drug release within 45 mins. Both the formulations were subjected to stability studies under the ICH guidelines to further test the stability and were studied for 2 months showing no change in appearance, however the assay showed decrease in drug release to 98% but within the IP limits, showcasing that the formulated tablets were stable, effective and pharmaceutical equivalent to marketed product.**

***Index Terms*—Landiolol hydrochloride, Immediate-Release, Super-disintegrant, wet granulation, Assay, Dissolution, Stability studies.**

I. INTRODUCTION:

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

Oral drug delivery1-6:

The most extensively studied and sought-after pharmaceutical dosage form is oral medication administration. Oral medication delivery is the most suggested and advised method of drug delivery because to its naturalness, ease of delivery and passage, and potential financial benefits. The world's ongoing progress and the way the human body functions have also contributed to the creation of a highly undesirable patient noncompliance with pharmaceuticals. To address this, the pharmaceutical industry's breakthroughs have increased up to three times annually. Given the obvious1 economicalr and development constraints in research and development of a new chemical entity, pharma companies have shifted their focus on optimizing existing or incorporating newer technologies into drug delivery systems in aiding the better drug delivery, efficacy, safety and overall patient compliance2.

Release of the drug from the designed product as soon as possible is a trending feature desired in pharmaceutical products. Such Immediate Release (IR) products promote rapid onset of pharmacological action in body. However, upon complete absorption of the drug from the dosage form, plasma concentrations decline in accordance with the pharmacokinetic profiles of the compound. Conventional drug therapy mandates the administration of periodic doses of therapeutic agents, which are meticulously formulated to achieve maximal stability, potency, and bioavailability. In general, established methods of drug delivery are deemed effective for the majority of pharmacological agents4.

Oral drug delivery is recognized as the most advantageous and preferred route for administering therapeutic agents intended for systemic effects. Furthermore, oral formulations are often prioritized during the discovery and development of new drug entities, primarily due to their high level of patient compliance and convenience in administration.

The oral route of drug administration represents approximately 50 -60% of all dosage forms, indicating substantial acceptance among patients and healthcare providers. Solid dosage forms are especially popular due to their ease of administration, precise dosing, suitability for self- medication, pain avoidance, and crucially, high patient compliance. Tablets and capsules Dominate this category; however, a notable limitation is the difficulty some individuals have in swallowing these forms. In the United States, oral dosage forms are the primary method for drug therapy, with over 80% of medications formulated for systemic effects produced as oral preparations. Among these, tablets are frequently favoured by manufacturers due to their cost- effectiveness in production and packaging.

1.2.1 Advantages of oral drug delivery systems3:

- Compliance and Convenience:
- Economic Superiority:
- Formulation Versatility:
- Non-Invasion and Safety:
- High Acceptance by Patients:
- Local and Systemic Impacts:

1.2.2 Disadvantages:

1. Variable Bioavailability
2. Onset of Action
3. First-Pass Effect
4. Limited Absorption of Certain Drugs
5. Potential for Irritation and Side Effects
6. Patient-Related Limitations
7. Stability Concern
8. Drug-Drug and Drug-Food Interactions:

II. FORMULATION DEVELOPMENT

Different formulations of Landiolol HCL were developed based on pre-formulation studies conducted.

Table No 2.1: Compilation of Landiolol HCL tablets:(F1-F5)

S. No	INGREDIENTS	mg/tab				
		F-1	F-2	F-3	F-4	F-5
1	Landiolol HCL	10	10	10	10	10
2	Lactose anhydrous	70	75	75	80	65
3	Mannitol	9	6	_	_	10
4	Cross carmellose sodium	9	12	6	6	6
5	Copovidone (Plasdone K-30)	_	_	5	5	5
6	Purified water	Q. S	Q. S	Q. S	Q. S	Q. S
7	Microcrystalline cellulose powder (AVICEL PH 103)	_	_	10	10	10
8	Magnesium stearate	1	1	2	2	2
9	Opadry pink (y-L-24802)	3	3	3	3	3
10	Total					

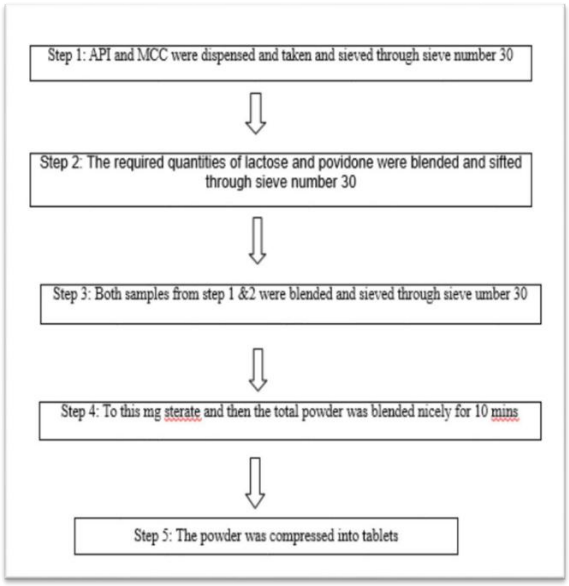
Table No-2.2: Compilation of Landiolol HCL tablets(F6-F10):

S. No	INGREDIENTS	mg/tab				
		F6	F7	F8	F9	F10

1	Landiolol HCL	10	10	10	10	10
2	Lactose anhydrous	60	58	55	51.5	51.5
3	Mannitol	25	22	20	15	15
4	Cross carmellose sodium	6	6	6	9	9
5	Copovidone (Plasdone K-30)	5	5	4	3	3
6	Purified water	Q. S	Q. S	Q. S	Q. S	Q. S
7	Microcrystalline cellulose powder (AVICEL PH 103)	10	15	15	20	20
8	Magnesium stearate	2	2	2	2.5	2.5
9	Opadry pink (y-L-24802)	2	2	2	2	2
10	Total	125	125	125	125	125

III. DIRECT COMPRESSION INTO TABLETS

- F1: The excipients and API were mixed, blended and granulated into granules; this batch had low amounts of disintegrants and more amounts of diluent and binder which resulted in poor flow property exhibition by the granules. Hence the amount of binder and filler were reduced in subsequent batch.
- F2: similar quantities of excipients used except filler quantity being reduced, still the flow properties weren't satisfactory, hence further changes in following batches were done.



- In F3: Flow properties were not satisfactory and also sticking problem also observed, so magnesium state concentration was increased in the further.
- In F4: Flow properties were satisfactory, the sticking problem was resolved but, dissolution time was still over par, compared to core tablets, hence conc. of disintegrants was increased in subsequent batches.
- In F5: Release profiles of initial points were very less, so maize starch concentration was increased in next trail.
- In F6: No significant change in release was observed, so binder concentration decreased from 5 mg to 3.0 mg.
- In F7: Slight increase in dissolution was observed, so disintegration concentration was increased in next trail.
- In F8: Dissolution of the tablets was not passed with in the limit; further slight increased the disintegration concentration increased in next trail
- In F9: Dissolution parameters of the tablets within the limits&
- In F10: Repeatability of formula next trail has taken for reproducibility.

IV. BRIEF MANUFACTURING PROCESS

- Landiolol HCL, lactose anhydrous, maize starch, and cross-carmellose sodium were sifted and added to a High Shear Mixer Granulator (HSMG).
- The granulating mix were subjected to dry mixing at low speed for 15-20 minutes, then this dry mix was added to HSMG without interrupting the process.
- The speed of granulation was increased gradually, along with consistent scrapping of any of the mucilage being stuck to the walls of the granulator.
- Along with addition of water for mucilage formation, the mixing and granulation was employed till a homogenous mixture was obtained.
- The wet mass was then sifted in sifting mill and size reduced to form wet granules of desired size.
- The wet granule mass was then transferred onto

tray, for tray drying.

- The granules were dried at 60°C -70°C. for 5 minutes until, moisture content was found to be within limits (4-6%)

4.1. Procedure For Sifting & Milling:

- The multi-mill was equipped with a 1.0 mm screen and a 30 # sieve.
- The cleaned HDPE container was positioned near the sifter and multi-mill's discharge end and a sieve number 30 was used to sieve the dried grains.
- Using a multi-mill, the granules were milled through a 1.0 mm screen into twin polythene-lined HDPE drums with knives traveling forward at a medium pace.
- Milling and sifting were carried out until all of the granules had passed through sieve-#30.
- The amount of milled material in the first sample was examined.
- The granules were weighed and their net wt. noted and the sifted grains were loaded into a double cone blender
- The blender was turned on in inch mode, and any material leaks were examined.
- The granules were blend thoroughly for 20 minutes. The time was noted.
- Unload small quantities of mixed material into a bag, add Mg. Stearate, and mix for 5 minutes.

4.2 Procedure For Compression:

- Observations were made for upper and lower punches and dies.
- The machine was started in inch mode and tested for noise.
- Proceeding the safety check, the machine was run until 5 rounds of 10 tablets in in each formulation were obtained.
- Tablets from the first two rounds were gathered and disposed of by submerging them in water to check the integrity.
- 10 Tablets (For 16 stations.) and checked them individually for any defects on upper and lower surface before continuing compression, proceed for coating.
- Individually checked wt. variation and thickness of 20 Tablets.
- The tablets were subjected to in-process quality control tests.
- The tablets were collected for analysis.
- The tablets were collected in double polythene lined HDPE Containers.

4.3 Procedure For Coating

a. Operated the Set upped conventional coating pan
b. Compressed tablets were loaded into the coating pan and rotate the coating pan for few mins for pre heating of the tablets.
   - The tablets were coated with the following parameters.`Inlet air temperature: 65 –75 º c
   - Outlet temperature: 45-50 º c
   - Atomization air pressure: 4-7 Pa
   - Spray gun Distance (Moving): 20—25 cm
   - Pan RPM: 7—8
c. Coating parameters were recorded in the table.
d. Tablets were preheated till the outlet temperature reaches to 40-43º C.
e. After completion of coating, Tablets were dried in the pan for 2-5 mins. At an outlet temperature not exceeding 45º c.
f. Coated tablets were unloaded into the double polythene lined HDPE container

Table-4,1: Tablet Compression Parameters:

PARAMETER	SETTING
Tablet wt.	125 mg
Hardness	6.0 kP
Thickness Limit	3.3 ± 0.2 mm

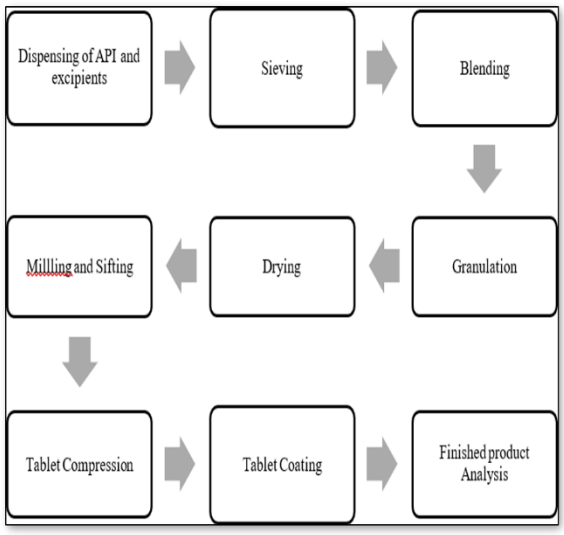


Figure-4.2: Flow-Chart Representating Preparation of Landiolol Hydrocholoride Tablets

V. ANALYTICAL METHODOLOGY:

5.1. Scanning Of Landiolol Hcl

A methanolic solution of 10 mg pure Landiolol HCL was diluted to get a conc. of 10 µg/mL. The solution was scanned over the wavelength range of 220 nm to 300 nm to obtain the absorption maximum, or λmax. That was 242 nm. It was used to further determine analyses of the drug solution. The absorbance of the final standard solution was determined at 242 nm.

5.1. Preparation of 0.1N HCl Solution:

- 8.33 mL of conc. HCl (approximately 37% w/w, 12 N) was measured using a calibrated pipette or burette.
- A 1L Vol. flask was filled with about 500 mL of purified water.
- The 8.33 mL of conc. HCl was added to the water in the flask, with gentle mixing along the addition.
- After adding the conc. HCl, more purified water was added to make up volume to 1L.

5.2. Landiolol Hcl Stock Solutions Preparation

A 10 mg quantity of pure Landiolol HCL was dissolved in a standard flask of 10 mL using distilled water. This stock solution was diluted up to 10 mL using

0.1 N HCl. From the stock, 1 mL was transferred to a 10 mL Vol. flask and then filled up to 10 mL, such that the concentration becomes 100 µg/mL of Landiolol HCL. Aliquots of solution in vol. of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 mL of the latter solution were diluted to a final volume of 10 mL in each of a series of Vol. flasks with 0.1 N HCl to obtain the final standard concentrations as shown below: 2, 4, 6, 8, 10, and 12 µg/mL.

5.3. Drawing The Caliberation Curve for Landiolol Hcl:

UV spectroscopy was opted for determining the wavelength maxima(λmax).

- An aliquot of 10 µg/ml was used to determine wavelength maxima in the range of 00-400 using beer-lamberts law, which was found to be 242 nm.
- Then a blank sample of 0.1N HCl was placed as control and the absorbance for each serial dilution was observed at the λmax (242nm).
- The absorbances were noted.
- The concentrations were plotted on the x-axis and the corresponding absorbance on the best-fit line was drawn through the points to obtain the calibration curve.
- The regression equation ($y = mx + c$) and the correlation coefficient (R^2) were obtained to assess the linearity of the calibration curve.

5.4. Preformulation Study

Preformulation study were conducted as part of an investigation to assess the Physico- chemical properties of a drug substance and compatibility with excipients.

It's a predominant measure in the development and formulation of tablet dosage form as it gives us the compatibility data and assessment of how the excipients interact with the drug and how much of the excipient: drug ratio is good enough to deliver an optimal formulation.

5.4.1. Objective of Preformulation study: -

Assessment of the drug and excipient compatibility.

Understanding drug: excipient interaction and developing the formulation in accordance to the observations.

Optimizing the ingredients mixing to obtain a quality dosage form.

5.4.2. Class: There are two sub-classes in pre-formulation study:

- API characterization,
- Compatibility study

5.4.3. Active pharmaceutical ingredient (API) characterization: -

Organoleptic evaluation: -Identification of any characteristic properties which can help in assessing the API's quality:

- Color
- Odor and taste

5.5. Characterization Of Granules Formulated:

Bulk Density:

The bulk density of a material varies largely with the formulation, milling, or type of crystallization applied. In the measurement of bulk density, a big funnel transfers granule from a pre-sieved group into a graduated cylinder after which wt. and volume measurements are taken.

$$\text{Bulk density} = \frac{\text{weight of granules}}{\text{Bulk volume of granules}}$$

Tapped density:
A graduated cylinder filled with known mass grains is placed onto a mechanical tapping device to ascertain the taped density. The device runs for a predetermined number of taps until the powder bed's volume reaches a minimum. Tapped density is computed using the granule mass and the reduced volume.

$$\text{Tapped density} = \frac{\textit{weight of granules}}{\textit{tapped volume of granules}}$$

Carr's index:
Carr's index calculates the value of the bulk density and tapped density. The formula of Carr's index

$$\text{CI} = \frac{\textit{Tapped density} - \textit{Bulk density}}{\textit{Tapped Density}} \; x\; 100$$

Hausner's Ratio:
Hausner ratio is a measurement which indicates the flow characteristics of powder. In that, the ratio of tapped density to bulk density defines the parameter. It can indicate how cohesiveness will be in powder because poor flowability normally corresponds with higher values of this ratio. The formula is:

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk density}$$

Table-4.1: Flow property relationship with Huasner's Ratio and Compressibility index

Compressibility Index (%)	Flow Character	Hauser's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Angle of repose:
The There are several angles of friction and response that indicate how stress is transferred through a bead and how it reacts to applied forces. Pouring the powder into a conical heap on a level, level surface and measuring the angle between the heap's slope and the horizontal plane yields the angle of repose, a crucial indicator of powder flowability. This perspective sheds light on the powder's internal friction and flow characteristics.

$$\text{Tan}\theta = \text{height of the heap/radius of the heap}$$

Table no-4.2.: Flow Properties Corresponding to Angle of Repose I.P Limits:

Angle of repose (degrees)	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

Sieve analysis:
Determining the size of the Landiolol HCL particles present is the primary goal of sieve analysis. Several standard sieves were layered one on top of the other, with the larger pore sieves (less sieve number) at the top and the smaller pore sieves (more sieve number) at the bottom. The Astm-seive analytical machine does it.
Procedure:

- The sieves were numbered 20, 30, 40, 60, 100, 120, 140, and 200, respectively, in sequence of decreasing pore diameter (increasing sieve number).
- After precisely weighing 30 grams of the medication, it was moved to sieve 60 and left on top.
- For five to ten minutes, the sieves were shaken.
- The drug that was retained on each sieve was then removed, weighed independently, and the
- Total percentage retained was used to express the amount retain.

5.6. Drug - Excipient Compatibility studies:
An essential precondition for formulation is the drug's and formulation components' compatibility. Therefore, under experimental settings, it is vital to establish that

the medicine does not react with the polymers and excipients, affecting the product's shelf life or causing any other undesirable effects on the formulation.

- Procedure:
- The drug is blended with excipients in varying ratios. The resulting mixtures are then placed in 5 mL glass vials, which are white in color, and sealed appropriately to ensure proper storage.
- These vials are exposed to:
  - Room temperature
  - 2 – 8° C
  - 40˚C / 75% RH
- Three vials are filled with 15 grams of the prepared combination.
- Samples were taken out for study of the following parameter after physical apearance observations were conducted at zero, two, and four weeks:
- They were evaluated for the following parameters:
  - Content of moisture
  - Evaluation of Assay
  - Related Substances
  - Appearance

VI. ANALYSIS OF INNOVATOR PRODUCT (LANDIOLOL HCL)

Numerous physical characteristics and the in-vitro dissolution profile of the innovator product were analyzed.

For the tablet(parameter):

- Shape
- A test for thickness
- hardness tests.
- A test for reliability.
- The test of wt. variation.

In-vitro dissolution studies

Table No-4.3: Reference Product (Eu Market)

Attribute	Details
Generic Name	Landiolol Hydrochloride
Brand Name (EU RLD)	Rapibloc (powder for solution for infusion)
Manufacturer	AOP Orphan Pharmaceuticals (EU marketing authorization holder)
Strength	6 mg/ml (after reconstitution)
Dosage Form	Powder for solution for infusion (lyophilized, immediate use post-reconstitution)
Product Description & Embossing	White to almost white powder or cake in vials; no specific embossing noted (vials typically labeled with strength and batch details). Supplied in colorless glass vials with bromobutyl rubber stopper.

Table No-4.4 Reference product characteristics: -

VII. EVALUTION OF TABLETS

- Physical appearance: The compressed tablets are assessed on a scale of physical appearance features such as shape, smoothness, chipping, cracks, surface roughness, color, embossing, and debossing.
- Thickness: The thickness of 20 pre-weighed tablets from each batch is measured using a digital vernier caliper in millimeters. Tablet thickness is within ±5% of standard deviation.
- Wt. variation: Twenty tablets are taken from each batch, and individual wt.s is determined and average is calculated. The tablets will comply with USP specifications if no more than two tablets have wt.s that deviate from the average by more than the percentage limit set. No tablet will exceed twice the percentage variation that is allowed

- IP LIMITS:

Table No-4.5: IP Limits of % Weight Difference in tablets

WEIGHT VARIATION TOLERANCES FOR UNCOATED TABLETS

Sr. No	Average wt. of tablet(mg)	Max. % difference allowed
1	130 or Less	10%
2	130-324	7.5%
3	More than 324	5%

- Hardness test: A hardness tester was used to measure the crushing load, or the force needed to shatter the tablet radially. Ten tablets were tested for hardness, and the average was determined. It is provided in KP.
- Percentage friability: The tablets were abrasively and shock-tested during friability testing. It provides a measure of the tablets' resistance to abrasion and chipping during shipping and transit.

METHOD – Ten tablets with a wt. greater than 650 mg were chosen for the purpose and the pre-wt. taken. As

much quantity of the tablets, which weighed below 650 mg, was used as in that way cumulative wt. amounted to 6.5 g. Those tablets are put into a Roche Friabilator which rotate thisfor 100 revolutions at 25 rpm. This tablet after de-dusting was weighed again. Friability percentage is not to be more than 1% w/w for the tablet tested.

- The % friability is expressed as the loss of wt. and is calculated by formula

$$\%friability = (wo - w_f) / w_o \times 100$$

Were,
Wo – Initial wt. of tablets
Wf – Final wt. of tablets

- Disintegration time:

The time it takes for a tablet to degrade and fragment into tiny pieces is known as the disintegration time. The disintegration test is carried out in a device with a basket- rack assembly that holds six glass tubes measuring 7.75 cm in length and 2.15 mm in diameter. A 10-mesh sieve is positioned at the bottom of the apparatus.
The disintegration apparatus's basket oscillates 28–32 times per minute in 900 mL of medium that is kept at 37°C. The disintegration time was the amount of time that passed before the tablet fragments completely passed through the 10-mesh sieve after one tablet was placed in each tube.

- Assay By Hplc:

The chromatographic conditions can be carried out using:

Table No-4.6: Parameters employed in HPLC

COLOUMN	4.6 mm x 250-mm column packed with C18, 5 µ.
Flow rate	1.5 ml per minute.
Detector	UV-detector at 242 nm.
Load	20µl
Temperature	400C
Run Time	About 20 minutes.

- Mobile phase: A 70:30 combination of filtered and degassed methanol and 0.01 N Na2HPO4.
- Standard Preparation: a 100 ml vol. flask containing precisely 25 mg of Landiolol HCL was dissolved and diluted to volume using mobile phase.
- Sample preparation: 20 tablets were weighed, crushed, and precisely transferred to a 100 ml vol. flask containing 25 mg of Landiolol HCL. The volume was then diluted with mobile phase.
- Method: The std and test preparations were separately injected into the liquid chromatograph, and the peak regions were noted.
- System suitability: As instructed by procedure, chromatograph the std preparation and record the peak responses. The relative standard deviation of replicate injections is not greater than 2.0, and the tailing factor is not greater than
- Calculation: Calculated the amount of Landiolol HCL present in mg per average wt. of tablet using the formula

$$\frac{At}{As} \times \frac{Sw}{Tw} \times \frac{P}{100} \times \frac{324.40}{405.31} \times Av.wt$$

Were,
At = sample preparation area

As = std. preparation area

Sw = Wt. of standard Landiolol HCL in mg.

Tw = sample wt. in mg

Av.wt = Avg.wt of tablet in mg.

P = Standard Landiolol HCL purity.

Dissolution By Hplc:

Table No-4.7: Parameters employed in Dissolution

APPARARATUS	USP Apparatus II
RPM	100
TEMPERATURE	37 ± 0.5 º C
MEDIUM	0.1N HCl
VOLUME	800 mL
TIME	45 minutes

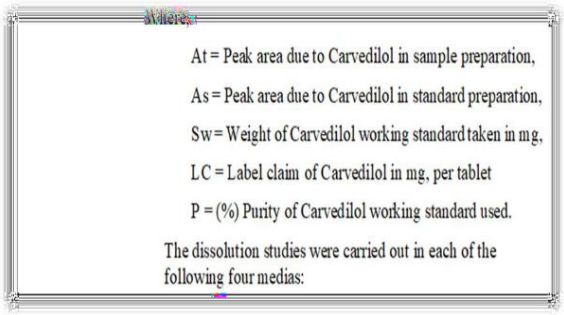
VIII. THE CHROMATOGRAPHIC CONDITIONS CAN BE CARRIED OUT USING

Table No-4.8: Parameters employed in HPLC

COLOUMN	C18- 250 X 4.6 mm, 5 µ
Flow rate	1.5 ml/minute.
Detector	UV detector at 242 nm.
Load	20µl
Temperature	25ºC ± 2 ºC
Run Time	20 minutes

- Media: To create the dissolving medium, 1180 ml of 1 M HCl solution and 820 mL of 1 M NaOH were combined, and the remaining volume was filled with water to create 10,000 mL.
- Solution A: The necessary 6.12 g of KH_2PO_4 solubilized in 1000 mL of water. 1.5 mL was then put inside with the aid of triethylamine. A pH of 2.5 was achieved by using orthophosphoric acid.
- Mobile phase: A 700:300 combination of Solution A and acetonitrile.
- Typical setup: Fill a 100 mL Vol. flask with 25 mg of the reference standard, then top it off with dissolving media to reach volume. A 10 mL aliquot of this solution should be diluted in a 100 mL Vol. flask and make up to volume with dissolution media.
- Preparation: Add 800 mL of the previously adjusted medium at 37°C ± 0.5°C to the dissolution baskets containing six tablets, one at a time. After removing any air bubbles that remained on the tablet's surface, the device was turned on. At specific intervals, samples were aspirated from a position that was at least 1 centimeter from the vessel wall and halfway between the medium's surface and the revolving blade's leading edge. After discarding the first 5 mL, the material was filtered through a 0.45 µm membrane filter.
- Method: The liquid chromatograph was injected with separate injections of the standard preparation and the sample preparation. The major peaks' regions were identified.
- System suitability: The analyte peak tailing factor-based column efficiency cannot be more than 2.0. The chromatogram derived from the standard preparation serves as evidence for it. Additionally, replicate injections must have a relative Std.Deviation ≤ 2.0%. Calculation: Using the appropriate calculation, the percentage of Landiolol HCL dissolved from each tablet was determined based on the label claim.

$$\frac{At}{As} x \frac{Sw}{100} x \frac{800}{LC} x 0.1 x P$$



The dissolution studies were caied out in the following four medias

- 1M HCl: 1M NaOH
- Acidic media using 0.1 N HCl.
- Using Buffer pH-4.5.
- Using Buffer pH-6.8.

- Preparation of media solutions: For preparation of media, I used the standard/ pharmacopeial methods.

A brief procedure for preparation of media:

- 1M HCl: 1M NaOH: Mix 820 ml of 1M NaOH with 1180 ml of 1M HCl to create a 1M HCl: 1M NaOH solution. Then, dilute the mixture with water to make 10,000 ml.
- 0.1N HCl: Use Milli-Q water and to it add 8.8 ml of AR-grade hydrochloric acid to 1000 ml.
- Buffer pH-4.5: Dissolve 2.989 grams of sodium acetate in 500 milliliters of water, combine 1.61 milliliters of acetic acid with 400 milliliters of water, and dilute to 1000 milliliters.
- Buffer pH-6.8 Preparation: Weighed potassium dihydrogen phosphate is added to about 900 mL of the water; the mixture was dissolved and make up to the final volume of 1000 mL in a Vol. flask using water.

In vitro drug release studies:

TOLERENCE: ≥ 85% of the labeled amount of Carvedilol is dissolved in 45 min %

To determine whether the formulation can provide immediate drug delivery, the immediate release tablets are put through 45 minutes of in vitro drug release experiments in pH 0.1N Hcl. Using a predetermined volume of dissolving media kept at 37±10C, drug release tests were conducted in an eight-stage dissolution test device. The tablets are rotated at 100 rpm while being stored in the cylindrical basket. At each time interval (10, 20, 30, and 45 minutes), 10

milliliters of the sample were removed from the dissolution medium, and 5 milliliters of new medium were added. After filtering the material, the filtrate was extracted.

In vitro dissolution kinetic studies

All drug release data were analyzed using a variety of kinetics, including zero-order kinetics (cumulative % drug released vs. time) and first-order kinetics (log % remaining vs. time). The figures show zero-order release kinetics as opposed to first-order release kinetics. The in vitro dissolution properties, including dissolution rate constants (K), correlation coefficients (R), half-life or time for 50% drug release (t50), and dissolving efficiency, were established and presented in later chapters.

The slopes of the linear plots were used to compute the rates of dissolution. For four hours, the in vitro dissolution was carried out. Plotting the slopes versus age over time is done. So: The slope of the log percent drug remaining vs. time pl was used to compute k1.

First – order release kinetics log Q1 = log Qo + k1t 2.303

- Dissolution efficiency:

When represented as a percentage of the area of the trapezoid described by 100% dissolution at the same time, DE is the area under the dissolution curve up to time "t." Depending on the time period selected, this can have a range of values. For instance, the drug's dissolution from a certain formulation after 45 minutes is indicated by the index DE30, which can only be compared to DE30 of other formulations

$$DE = t\ d\ y.dt\ Yidd.t$$

IX. DISSOLUTION STUDY:

Table No-4.9 Parameters Employed for Dissolution

APPARARATUS	USP Apparatus II
RPM	100
TEMPERATURE	37 ± 0.5 ° C
MEDIUM	0.1N HCl
VOLUME	800 mL
TIME	45 minutes

- Stability Study:

Determining the dosage form's durability is crucial for all pharmacological dosage forms. The product will be stored at both normal and elevated temperatures, with the proper adjustments made, to ensure that it will continue to supply the drug for absorption at the same rate as when it was first produced. The design of the formal stability studies for the drug product should be based on formal stability studies of the drug substance and knowledge of its characteristics and behavior. Specifications, which include a list of tests, references to analytical techniques, and recommended acceptance criteria, are covered by ICH guidelines. They also discuss the concept of different acceptable release conditions and shelf-life requirements.

- Storage Conditions:

A pharmaceutical product should generally be evaluated under storage conditions that test its stability and, if applicable, its vulnerability to moisture or solvent loss. The long-term testing should be carried out for a sufficient amount of time to cover the recommended shelf life, and it should be done for at least three batches at the time of submission or for a minimum of 12 months of study.

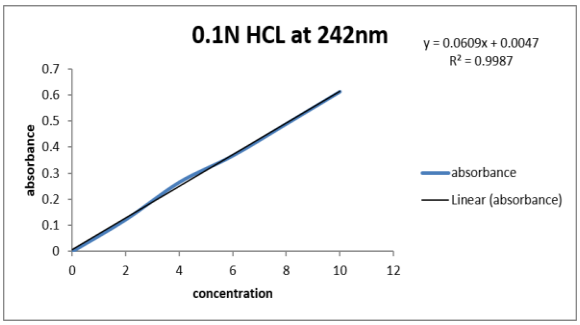
Table No-4.10: Conditions for stability according to ICH-guidelines:

Study	Condition	Time Period
Long Term	25 ± 2º C, 60 ± 5% RH (OR) 30 ± 2º C, 75 ± 5% RH	12 months
Intermediate Term	30 ± 2º C, 65 ± 5% RH	6 months
Accelerated Term	40 2º C, 75 ± 5% RH	3 months

X. RESULTS

Calibration curve of landiolol HCL in 0.1 N HCL solutions:

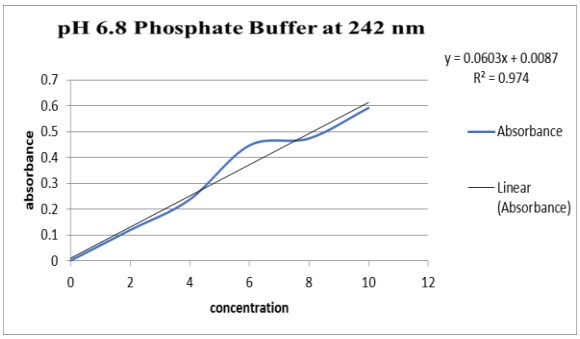
Absorption	Concentration
0	0
2	0.122
4	0.265
6	0.367
8	0.495
10	0.612



The calibration curve of Landiolol HCl in 0.1 N HCl was constructed at 242 nm using concentrations ranging from 0–10 µg/mL. A linear relationship was observed between concentration and absorbance. The regression equation was y = 0.0609x + 0.0047 with a correlation coefficient R^2 = 0.9987, indicating excellent linearity and compliance with Beer–Lambert's law. Therefore, the method was found suitable for quantitative estimation of Landiolol HCl in dissolution studies.

The calibration curve of Landiolol HCl in pH 6.8 phosphate buffer:

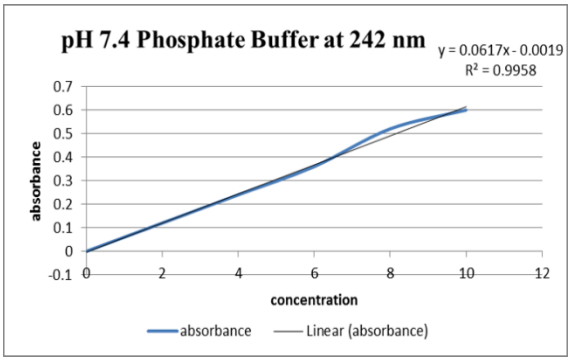
Absorption	Concentration
0	0
2	0.118
4	0.236
6	0.445
8	0.472
10	0.59



The calibration curve of Landiolol HCl in pH 6.8 phosphate buffer was prepared at 242 nm over the concentration range of 0–10 µg/mL. The absorbance increased proportionally with concentration, demonstrating good linearity. The regression equation obtained was y = 0.0503x + 0.0087 with a correlation coefficient R^2 = 0.974, confirming the suitability of the analytical method for estimation of Landiolol HCl in pH 6.8 phosphate buffer.

The calibration curve of Landiolol HCl in pH 7.4 phosphate buffer:

Absorption	Concentration
0	0
2	0.120
4	0.240
6	0.360
8	0.520
10	0.600



The calibration curve of Landiolol HCl in pH 7.4 phosphate buffer was prepared at 242 nm using concentrations ranging from 0–10 µg/mL. The absorbance values increased proportionally with increasing concentration, indicating good linearity within the selected concentration range. The regression equation obtained was y = 0.0617x − 0.0019 with a correlation coefficient R^2 = 0.9958, demonstrating excellent compliance with Beer–Lambert's law. The high correlation coefficient confirms the accuracy and reliability of the analytical method for the quantitative estimation of Landiolol HCl in pH 7.4 phosphate buffer. Therefore, the developed method was found to be suitable for dissolution and drug release studies.

Conclusion for Standard Graphs:

Calibration curves of Landiolol HCl were successfully developed in 0.1 N HCl, pH 6.8 phosphate buffers, and pH 7.4 phosphate buffer at 242 nm. All calibration curves exhibited good linearity with correlation coefficients close to unity, confirming adherence to Beer–Lambert's law. The developed analytical methods were found to be suitable for the quantitative

estimation of Landiolol HCl during dissolution studies.

Ftir Studies

Fourier Transform Infrared (FTIR) spectroscopy was performed to investigate the compatibility between Landiolol Hydrochloride and the excipients used in the formulation. The FTIR spectrum of the drug exhibited characteristic absorption peaks corresponding to its functional groups. The major peaks observed in the spectrum were in the region of 3100–2500 cm^{-1}, indicating the presence of characteristic stretching vibrations associated with the drug molecule. The FTIR spectrum of the optimized formulation retained all the characteristic peaks of the pure drug without any significant shift, disappearance, or formation of new peaks.

The preservation of the characteristic absorption bands confirms that there was no significant chemical interaction between Landiolol Hydrochloride and the selected excipients during the formulation process. Therefore, the drug was found to be compatible with all formulation components. The results indicate that the excipients used in the formulation did not affect the chemical stability of the drug and were suitable for the development of immediate-release tablets.

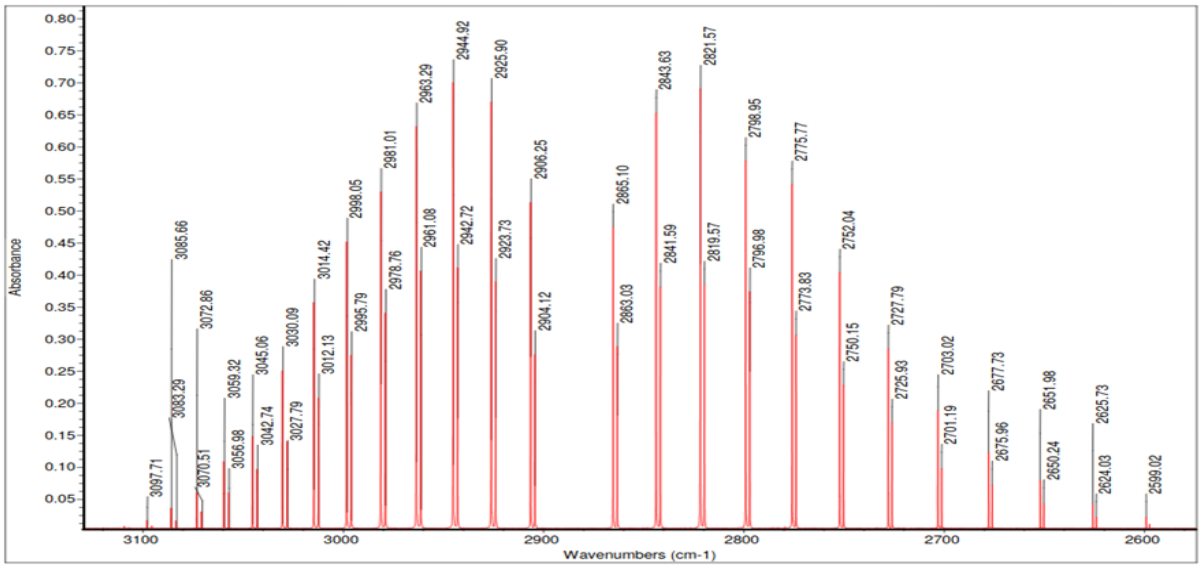


Figure No 5.27: - FTIR Spectrum of Optimized Formulation (F10)

FTIR analysis confirmed the compatibility of Landiolol Hydrochloride with the selected excipients. No significant changes in the characteristic absorption peaks were observed, indicating the absence of drug–excipient interactions and confirming the stability of the drug in the optimized formulation.

The FTIR spectrum showed retention of characteristic functional group peaks, confirming drug–excipient compatibility and formulation stability.

XI. RELEASE KINETIC GRAPH OF OPTIMISED FORMULATION

Time	Zero Order (% Released)	First Order (Log % Unreleased)	Higuchi (√Time)	Hixson-Crowell (Cube Root % Remaining)
0	0	2	0	4.642
10	68.31	1.5009	3.162	3.165
20	95.02	0.6972	4.472	1.708
30	95.48	0.6551	5.477	1.654
45	96.41	0.5551	6.708	1.531

Zero Order:
The Optimaised Formulation Showed Near Zero – Order Release Kinetics Indicating Controlled and Unifom Drug Release

First Order:
The Formulation Followed First –Order Kinetics Indicating Concentration-Dependent Drug Release

Higuchi Model:
Higuchi Model Suggested Diffusion Controlled Release Mechanism.
Hixson Crowell Model:
Hixson crowell model indicated changes in tablet surface area and diameter during dissolution.

Preformulation Parameters:
The goal of the current study was to create immediate-release tablets of Landiolol HCL as. Preformulation investigations of the drug and excipients, formulation and processing development, and tablet evaluation using the improved formulation are all part of the study. Lastly, in vitro techniques were used to assess instant release tablets.
Results and discussion of the above studies are presented below:

Table No-5.1: Preformulation studies

S.No.	Characteristics	Results
1.	Organoleptic Evaluation	White crystalline powder
2.	Solubility Analysis	Sparingly soluble in water Soluble in methanol
3.	Bulk density	0.5214 gm/ml
4.	Tap density	0.773 gm/ml
5.	Compressibility index	32.13 %
6.	Hausner's ratio	01.472
7.	Melting point	184 ^{0}C
8.	Molecular weight	405.35

For bulk density / flow properties:
The bulk density and tapped density values indicated acceptable packing ability of the powder blend. the angle of repose values was found within acceptable limits, suggesting good flow properties suitable for tablet compression.

Table No-5.2: Sieve Analysis Report

Sieve no	Empty sieve(gm)	Sample sieve(gm)	Difference (gm)	%Retained	%Cumulative Retained
#20	321.5	321.5	0	0	0
#30	328.6	326.9	0.3	0.3	0.3
#40	299.1	300.0	1.1	1.1	1.1
#60	287.2	297.4	10.2	10.2	11.4
#100	255.0	275.0	20.0	20.0	31.4
#140	274.0	299.0	25.0	25.0	56.4
#200	270.0	303.2	33.2	33.2	89.6
Receiver	348.8	359.0	10.2	10.2	99.8

*Wt. of sample=100gm
According to sieve analysis, a significant amount of powder was retained on sieve number 200, indicating that the drug's flow characteristics were inadequate. Because flow characteristics and particle size are inversely correlated, Landiolol HCL's tiny particle size adds to its poor flowability.

Table No.-5.3: Blend Properties of Different Formulations

Batch	Angle of Repose(º)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's ratio
F1	400 421 ± 0.42	0.53±0.02	0.73±0.03	30.66±0.54	1.43±0.03

F 2	370 231±0.38	0.42±0.01	0.75±0.02	36.48±0.63	1.55±0.04
F 3	370 241±0.35	0.71±0.03	0.79±0.03	15.39±0.41	1.18±0.02
F 4	240 261±0.31	0.63±0.02	0.71±0.02	15.29±0.36	1.47±0.03
F 5	260 381±0.33	0.64±0.02	0.72±0.03	15.09±0.39	1.30±0.02
F 6	280 341±0.36	0.56±0.02	0.74±0.03	13.31±0.35	1.28±0.02
F7	250271±0.30	0.65±0.03	0.73±0.02	15.55±0.37	1.34±0.03
F8	260 611±0.34	0.65±0.02	0.73±0.03	15.29±0.37	1.35±0.02
F9	260 451±0.32	0.65±0.02	0.78±0.03	14.47±0.36	1.17±0.02
F10	260 521±0.35	0.63±0.02	0.74±0.03	14.86±0.38	1.20±0.02

5.2 Post Compression Parameters:

Table No.-5.4: Physico-Chemical Parameters of the Formulated Tablets: F1-F5

S.No	Physical parameter	F 1	F 2	F 3	F 4	F 5
1	Wt. variation	1.66±0.05	1.51±0.04	1.29±0.03	1.35±0.04	1.34±0.05
2	Hardness(kP)	7.8±0.3	7.4±0.2	7.1±0.2	6.8±0.3	7.4±0.2
3	Thickness(mm)	3.49±0.04	3.46±0.03	3.37±0.03	3.25±0.04	3.31±0.03
4	Friability (%)	0.89±0.05	0.82±0.04	0.38±0.02	0.57±0.03	0.46±0.02
5	Disintegration time	6m19s±8s	6m13s±7s	5m11s±6s	3m15s±5s	2m20s±5s
6.	Assay	98.1±0.4	99.2±0.3	98.8±0.3	98.7±0.4	99.2±0.3

Table No.-5.5: Physico-Chemical Parameters of The Formulated Tablets: F6-F10

S. No	Physical parameter	F 6	F 7	F 8	F 9	F 10
1	Wt. variation	1.32±0.04	1.58±0.05	1.54±0.04	1.43±0.03	1.28±0.03
2	Hardness(kP)	6.8±0.2	6.5±0.3	6.8±0.2	6.4±0.2	6.1±0.2
3	Thickness(mm)	3.33±0.03	3.27±0.04	3.29±0.03	3.31±0.03	3.30±0.02
4	Friability %	0.55±0.03	0.45±0.02	0.49±0.03	0.12±0.01	0.18±0.01
5	Dissintegration time	2m38s±5s	2m25s±4s	2m22s±4s	2min±3sec	2min±3sec
6.	Assay	99.1±0.3	99.2±0.4	97.3±0.5	99.05±0.3	99.25±0.4

Dissolution Studies:

Table No-5.6: Parameters Employed for Dissolution

Appararatus	Usp Apparatus Ii
Rpm	100
Temperature	37 ± 0.5 º C
Medium	0.1n Hcl
Volume	800 Ml
Time	45 Minutes

Table No-5.7: Dissolution Profile for Landiolol Hcl Ir Tablets: (Innovator)

S.NO	Time in minutes	% Drug dissolved	log% Drug Undissolved
1	0	0	2
2	10	50.50	1.694605
3	20	81.45	1.245513
4	30	91.28	0.94939
5	45	99.87	0.69897

Figure 5.12: first order kinetics of F9 v M

Table No-5.15: Dissolution Profile Of F-10

S.NO	Time in minutes	% Drug dissolved in time (mins) in0.1 N HCL	log% Drug Un dissolved
1	0	0	2
2	10	55.3	1.650308
3	20	85.4	1.164353
4	30	92.8	0.857332
5	45	99.5	0.52288

Dissolution Studies:

The amt. of drug released from the product is indicated by the dissolution. Here, it provides insightful information on the process's ingredients and the results of modifications.

Acidic Stage:

Table No-5.25 Paramters Employed in Dissolution

Appararatus	USP Apparatus II
Rpm	100
Temperature	37 ± 0.5 º C
Medium	0.1N HCl
Volume	800 mL
Time	45 minutes

The drug release percentage of the tablets in Formulation 9 was initially determined to be 96.38.%; however, after one month, it dropped to 94.87% and 93.78%; after two months, at 400C/75%RH and 250C/75%RH, respectively, it was determined to be 94.35% and 93.36%.

The drug release percentage of the tablets in Formulation 10 was initially determined to be 98.90%; however, after one month, it dropped to 96.23% and 95.14%%; after two months, at 400C/75%RH and 250C/75%RH, respectively, it was found to be 95.98% and 95.39%.

XII. DISCUSSION

The purpose of this investigation was to prepare and formulate immediate-release Landiolol HCL tablets and evaluate in comparison with the innovator product, which is said to have long extended biological half-life. Such a product is administered as a treatment for congestive heart failure and hypertension. Compatibility studies involving drug-excipient interaction using a mixture were carried out. Findings are depicted in Table 5. Findings indicate no alteration at a variety of ratios at 40°C/75% RH, indicating compatibility of drug and excipients in use in the formulation. Table 11 presents the parameters: bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose for the blends. It is evident that formulations F1 and F2 exhibited bulk and tapped densities well outside the range of acceptable values of 0.52 to 0.68 g/cc, pointing to poor flow properties. These formulations were thus deemed unsuitable for direct compression and were not subjected to in vitro release testing. Formulations F3-F10 had undergone further in vitro release studies with bulk densities in the range of 0.75 to 0.76 g/cc which was within acceptable limits.

XIII. CONCLUSION

The study aimed to formulate and validate Landiolol HCL IR tablets versus the innovator product. For this purpose, both wet granulation and direct compression methods were used in preparing Landiolol HCL film-coated tablets.

Ten formulations were developed comprising lactose and starch as diluents, copovidone as a binder, and varying amounts of croscarmellose-sodium as a super disintegrant, with Opadry pink used for the film coating. The core tablets were prepared using wet granulation and direct compression techniques.

The following conclusions were drawn from the Results:

- Using a physical mixture, compatibility tests between the API and excipients were carried out, and the results demonstrated that the formulation's ingredients and the drug are compatible.
- Analysis of the pre-compression and post-compressional parameter values of the blends revealed that F1 and F2 had inadequate results. As a result, no further in vitro release testing was performed on these formulations. Results from Formulations F3 through F10 were within the permissible range.

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