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SOLUBILITY ENHANCEMENT OF LABETALOL HYDROCHLORIDE BY USING LIQUISOLID TECHNIQUE FOR MANAGEMENT OF HYPERTENSION

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ABSTRACT: Background: Hypertension is the most common disorder affecting different age groups of people. The increased blood pressure creates discomfort in the patients; these cardiovascular diseases are risky which can lead to “mortality and morbidity”. Labetalol hydrochloride is an anti-hypertensive drug used to treat high blood pressure and Angina. These compounds possess less water solubility and low bioavailability (25%). **Objective:** The current study is aimed to develop Labetalol hydrochloride Liquisolid Tablets to enhance its solubility. **Results:** The *in-vitro* dissolution studies showed enhanced drug release at 98.43% with Avicel PH102 as carrier and 96.54% with Fujicalin as the carrier. Hence F3 with 98.43% drug release was considered the optimized formulation. The optimized formulation batch F3 was subjected to stability studies as per the ICH guidelines. There was no significant change observed. **Conclusion:** It can be concluded that labetalol hydrochloride was successfully incorporated as a liquisolid tablet by the direct compression method. The direct compression method employed was easy and can be widely used’. The powder blend of F3 containing avicel pH 102 as a carrier material showed excellent flow ability, liquid retention potential compared to the Fujicalin as a carrier. Hence F3 is considered optimized. The *in-vitro* drug release confirmed the enhanced drug release from the liquisolid tablets. The stability studies revealed the formulation was stable.

INTRODUCTION: Hypertension is the most frequent condition that affects people of different ages. Hypertension is defined as a rise in blood pressure in the systemic arteries. The systolic blood pressure should not exceed 120 mm Hg, and the diastolic blood pressure should not exceed 80 mm Hg, which is considered normal.

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Patients have shortness of breath and chest pain as a result of high blood pressure, which can be alleviated by using anti-hypertensive drugs. Cardiovascular diseases are hazardous and can cause "mortality and morbidity. Anti-hypertensives are a type of medication that helps to "reduce blood pressure" by keeping the systolic to diastolic ratio at 120/80 mm Hg [1, 2].

Labetalol hydrochloride, an anti-hypertensive medication used to "reduce blood pressure," belongs to the β+α adrenergic blockers class of anti-hypertensives [3, 4]. This molecule has limited water solubility and bioavailability (25 %).

The half-life of Labetalol hydrochloride is 6 hours, and has a water solubility of 0.00578 mg/ml and a bioavailability of 25% [5]. To circumvent these restrictions, the Labetalol Liquisolid approach was considered.

The "Liquisolid approach" was chosen because the addition of carrier and coating ingredients improves the wetting capabilities and increases the surface area of the powder.

The "liquisolid technique" is a "new approach" that is commonly utilized in a tablet formulation to improve medication dissolving and boost the "flow property" of the powder blend. This technology is regarded "most perceivable" because it turns the liquid suspension/liquid drug into a free-flowing powder by adding various carrier and coating materials to the liquid suspension [6].

The type of carrier to be utilized in the formulation is determined by the amount of liquid retained in the carrier and coating. The higher the powder's liquid retention capacity, the more liquid can be added to dissolve the medicine. As a result, it is crucial in the formulation of tablets [7].

The super disintegrant is also included since it aids in the disintegration of the tablets. The importance of the "Liquisolid approach" is that it is a low-cost, simple, and cost-effective method that may be used commercially. The significance of "Liquisolid technique" is low cost, simple and economical method that can be easily applied commercially. It uses fewer excipients and is less technical than other approaches like solid dispersion and microencapsulation for enhancing dissolution. Granulation techniques can be avoided and compressed directly. This study aims to create and analyze Liquisolid tablets of Labetalol hydrochloride [8, 9, 10].

MATERIALS AND METHODS:

Materials: Labetalol hydrochloride gifted by S.G Pharma Pvt Ltd. Mumbai, Propylene Glycol purchased from Gatteforse France, Avicel pH 102 purchased from LOBA Chemi Pvt Ltd, Aerosil 200 procured from HiMediat Laboratories Pvt Ltd, Mumbai, Fujicalin (Dibasic Calcium Phosphate), Sodium Starch Glycolate (SSG), Talc procured M/s Hi-Media Laboratories Pvt. Ltd. and PVP K30 from M/s Balaji Drugs.

Preformulation Studies:

Organoleptic Properties: The API was taken in a petridish and observed for colour, odour, powder property and taste.

Melting Point: The small amount of Labetalol Hydrochloride was taken in a glass capillary tube sealed at one end, tied to a thermometer, and placed in Theil's tube apparatus containing liquid paraffin, and the melting point of the drug was observed by heating the paraffin using Bunsen flame [11].

Lambda Max (λ max): The lambda max of the drug was determined using UV Spectroscopy. The 10mg of the drug was dissolved in 10ml of pH 1.2 buffer solution in a volumetric flask to obtain 1000mcg/ml. Further, the secondary dilution was made up by taking out aliquots of 1ml and adding to 10ml of pH 1.2 buffer solution and then scanned in a range of 200 to 400nm and lambda max.

Standard Calibration Curve: The calibration curve of Labetalol hydrochloride was carried out in acidic pH 1.2. The primary stock solution of 100 mg of Labetalol hydrochloride was dissolved in 100ml of pH 1.2 buffer solution to get the concentration of 1000 µg/ml and sonicated for 5 min. 10ml aliquots was withdrawn from the primary stock solution and dissolved in 100ml of pH 1.2 in 100ml volumetric flask. Further aliquots of 1ml, 2ml, 4ml, 6ml, 8ml and 10ml was withdrawn and added to 10ml volumetric flask to obtain 10, 20, 40, 60, 80, 100 µg/ml. Absorbance was noted at 302nm [12, 13].

Solubility Analysis: The saturation solubility studies of the drug were carried out for 48hrs in various non-volatile solvents to check the highest solubility of the drug in the different solvents. The excess drug was dissolved in Propyleneglycol, polyethylene glycol 400, Tween 80, Glycerine, Liquid paraffin and was kept on a magnetic stirrer for 48 hrs and filtered through a vacuum filter. The absorbance was noted at 302nm spectrophotometrically in pH 1.2 buffer solution [11, 14].

Characterization:

Differential Scanning Colorimetry (DSC): Differential scanning calorimetry (DSC) analysis was performed on a DSC 60 detector (Shimadzu Co., Japan). Approximately 4mg of Labetalol

hydrochloride was weighed in an aluminium pan and sealed hermetically. DSC scan was recorded from 30 °C to 200 °C at a heating rate of 10°C/min under a nitrogen purge, using an empty pan as reference.

Compatibility Studies:

FT-IR: The FT-IR spectrum of the pure drug, drug, and excipients and the optimized formulation was carried out by the Potassium bromide method to note the changes in purity of the drug.

Method of Preparation for Liquisolid Tablets: The drug (Labetalol HCL) was dissolved in a non-volatile solvent (Propyeneglycol) and stirred to form a drug suspension.

The drug suspension or the liquid medication was mixed with calculated quantities of carrier particles (Avicel pH102 and Fuji Calin). The wet powder mixture is obtained, which is further coated with coating material. The coating material such as Aerosil 200 was incorporated and mixed thoroughly until a free-flowing powder mixture was obtained. The incorporation of the carrier and coating materials was done in ratios. The disintegrant (SSG), glidant (Talc), and binder (PVP K 30) was added to the freely flowable powder blend to obtain the liquisolid compact system **Table 1**. This powder mixture / liquisolid system was directly compressed in a rotary compression machine with 12 mm die size [15, 16, 17, 18].

TABLE 1: COMPOSITION OF LIQUISOLID TABLETS

Formulation	F1	F2	F3	F4	F5	F6
Drug (mg)	25	25	25	25	25	25
W (mg)	153	153	153	153	153	153
R (Q/q)	3	1	1.6	1	3	1.6
L_f	1.02	1.53	1.224	1.53	1.02	1.224
Avicel PH102 (Q) (mg)	150	100	125	-	-	-
Fujicalin (Q) (mg)	-	-	-	100	150	125
Aerosil 200 (q) (mg)	50	100	75	100	50	75
PVP K30 (mg)	5	5	5	10	10	10
Unit dose (mg)	401.8	401.9	402.4	407.6	406.7	406.8

W= weight of liquid medication R= carrier (Q)/ coating (q) Lf= Loading factor (W/Q) Each formulation contains 5%w/w of disintegrant Sodium Starch Glycholate.

RESULTS AND DISCUSSION: The evaluation of Labetalol hydrochloride liquisolid Powder is carried out for the following parameters.

Precompression Parameters:

Angle of Repose: The maximum angle between the surface of a pile of powder and the horizontal plane is termed as angle of repose. The powder was allowed to flow from a height through the funnel. The height of pile and radius of base was noted and calculated by the formula [19, 20].

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

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

Where, h = Height of the heap, r = Radius of the heap.

Bulk Density: An accurately weighed powder was poured in the measuring cylinder and the powder's initial volume or bulk volume was noted [17].

BD (Bulk density) = weight of powder / Bulk volume

Tapped density: The Accurately weighed powder added to the measuring cylinder was tapped until no change in the volume of the powder was observed. The tapped density is calculated by using the formula [14].

TBD (Tapped bulk density) = weight of powder / Tapped volume of powder

Carr's Compressibility Index and Hausner's Ratio: The powder's tendency to be compressed into a tablet is termed the carr's index and hausner's ratio. The powder property should possess good flowability. It is calculated by using the formula **Table 2** [12].

Carr's Index % = Tapped density – Bulk density × 100 / Tapped density

$$\text{Hausner's Ratio} = D_t / D_b$$

Where, D_t = Tapped density of the powder. D_b = bulk density of the powder."

TABLE 2: SCALE OF FLOWABILITY

Flow characters	Hausners Ratio	Carr's Compressibility index
Excellent	1.00 - 1.1	≤10
Good	1.12- 1.18	11- 15
Fair	1.19 -1.25	16-20
Passsable	1.26 -1.34	21-25

Post Compression Parameters [21, 22]: The formulated tablets are evaluated for different parameters as follows:

Shape and Colour of Tablet: The coated tablet is visually observed for its colour and shape by placing the tablet under light.

Thickness: The uniformity of the tablet thickness is measured individually using verniercallipers. The thickness in millimeters is noted along with standard deviation calculation.

Hardness: The tablet hardness is calculated using a Monsento hardness tester. The mechanical force is applied on the tablet using Monsento hardness tester to determine the strength of tablet and results noted in kg/cm^2 and standard deviation [18].

Friability: The 10 tablets were weighed accurately, placed in a Roche Friabilator, and subjected to 25 rotations per min for 100 revolutions and final weight was noted.

The tablets were subjected to shock and abrasion in order to withstand the physical damage. The initial and final weight of the tablet was noted and calculated using the formula

$$\text{Friability} = W_{initial} - W_{final} / W_{initial} \times 100$$

Weight Variation: The 10 tablets were weighed individually on a weighing machine, and the tablets' average was calculated. The individual and average weight of the tablets was compared, and % deviation was calculated using the formula **Table 3**.

$$\% \text{ Deviation} = \text{Individual weight} - \text{Average weight} / \text{Individual weight} \times 100$$

TABLE 3: PERCENTAGE DEVIATION CRITERIA

Average weight of tablet Limit	Average weight of tablet Limit
80 mg or less	±10 %
More than 80 mg or less than 250 mg	±7.5%
More than 250 mg	±5%

Drug Content Uniformity: The 5 tablets were weighed accurately and crushed in a mortar and pestle. The equivalent quantity of powdered tablet was weighed and added to a volumetric flask consisting of pH 6.8 as the solvent. The volumetric flask was sonicated for 10mins and filtered through whattman filter paper. The absorbance was noted spectrophotometrically at a detection wavelength 304nm and readings were noted in triplicates.

Disintegration Time: The time taken for the tablets to disintegrate was noted by placing 6 tablets in the disintegration test apparatus consisting of pH 1.2 buffer solution as the medium. The time taken for the tablets to disintegrate was noted. The procedure was carried out as per the IP specifications.

***In-vitro* Drug Release:** The *in-vitro* drug release of the liquisolid compact tablets was carried out to calculate the amount of drug dissolved in the alkaline pH. The solvent used was pH 6.8 phosphate buffer at a temperature of 37±0. 5°C. The "USP type 2 paddle dissolution apparatus" was used with a rotating speed of 50 rotations per min.

The solvent was withdrawn for every 5, 10, 15, 30, 45, and 60 min time interval and the absorbance was noted spectrophotometrically and standard deviation calculated. The formulation consisted of two carrier materials, *i.e.,* Avicel PH102 and Aerosil 200; hence comparison study between the formulations having two different carrier materials was done. The two optimized formulations were compared for drug release.

Dissolution Apparatus: USP type II paddle apparatus.

Dissolution Medium: Phosphate buffer pH 6.8.

Volume of Buffer in Basket: 900ml.

Rotation Speed: 50rpm.

Temperature: 37±0.50°C

Number of Trials: 3

Stability Studies: The "short-term stability studies" for Labetalol hydrochloride liquisolid tablets were carried out at room temperature for a period of 60 days. The ability of the tablets to withstand factors like temperature, light, and humidity under a specified period of time.

The changes for the "physical, "chemical, and "therapeutic efficiency "of the tablets were evaluated. The optimized formulation was evaluated for disintegration time, drug content, and friability tests. The tests were carried out as per ICH guidelines.

RESULTS AND DISCUSSION:

Preformulation Studies:

Organoleptic Properties: The API was taken in a petridish and observed. The white in colour powder was amorphous in nature and had a pleasant odour.

Melting Point: The Melting point of the API was calculated using a theils tube. The observed results were obtained at 188 °C. The results obtained were as per mentioned in IP.

Lambda Max: The detection wavelength of the drug was calculated spectrophotometrically. The pH 1.2 buffer solution solvent was the solvent. The detection wavelength was obtained at 100 µg/ml at 302 nm **Fig. 1**.

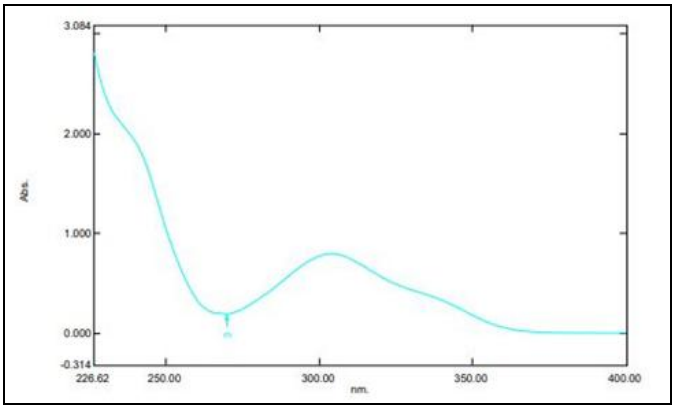


FIG. 1: LABETALOL HCL SPECTRUM PEAK

Standard Calibration Curve: The drug's concentration was determined using UV spectrophotometer at 302 nm in a concentration range 10 µg/ml to 100 µg/ml **Table 4**.

The correlation coefficient obtained 0.996, and linear regression obtained y= 0.008x+0.004. The Linear graph of concentration versus absorbance was obtained **Fig. 2**.

TABLE 4: STANDARD CALIBRATION CURVE

S. no.	Concentration	Absorbance
1	10	0.136
2	20	0.217
3	40	0.374
4	60	0.548
5	80	0.742
6	100	0.894
R2	0.996	

Solvent used: pH 1.2 buffer solution, Detection wavelength: 302 nm Linearity: 10-100 µg/ml.

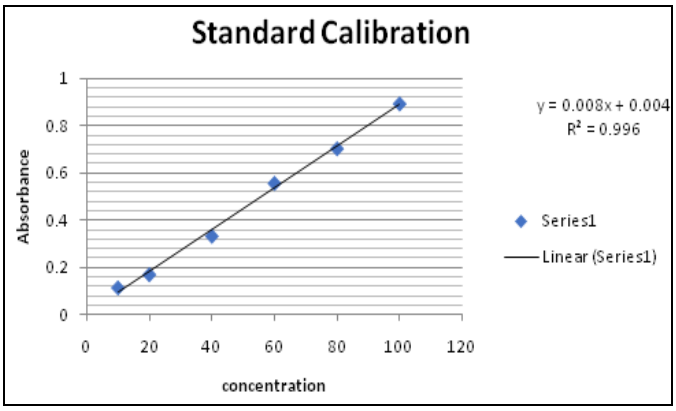


FIG. 2: CALIBRATION CURVE PLOT

Solubility studies: The excess quantity of the drug was dissolved in non-volatile solvents (e.g., "Propylene glycol, polyethylene glycol400, Tween 80, Glycerine, Liquid paraffin") and kept on the magnetic stirrer for 48 h **Table 5**. The solution was filtered through whattman filter, and the absorbance was noted spectrophotometrically. The drug showed the highest solubility in propylene glycol. Hence it was used as a solvent in the formulation of liquisolid tablets.

TABLE 5: SOLUBILITY STUDIES IN NON-VOLATILE SOLVENTS

Sl. no.	Non-volatile solvents	Solubility mg/ml
1	Polyethylene glycol 400	63.2
2	Propylene glycol	163.25
3	Tween 80	41.5
4	Glycerine	62
5	Liquid paraffin	4.6

Characterization:

DSC: The Melting point of the pure drug, optimized formulation, and excipients were calculated by Differential Scanning Calorimetry. The melting point of the pure drug showed a sharp endothermic peak at 189.46 C. The peak obtained in the optimized formulation is 189.68 **Fig. 3**. No significant change was observed in the pure drug's melting point and the optimized formulation.

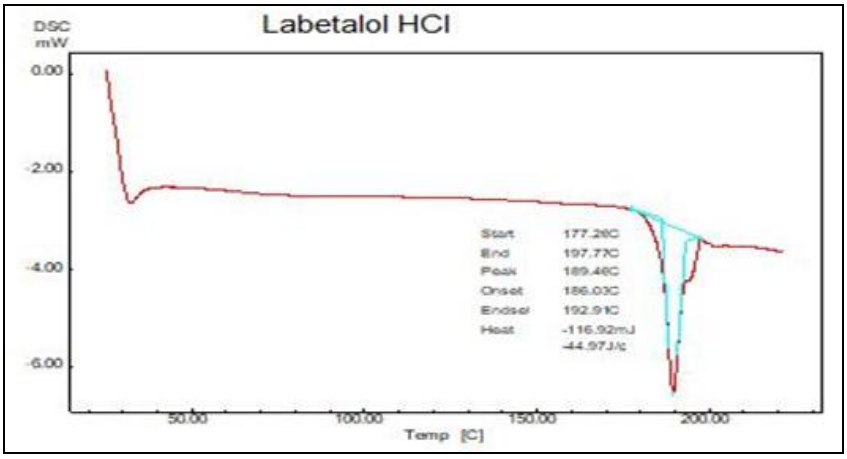
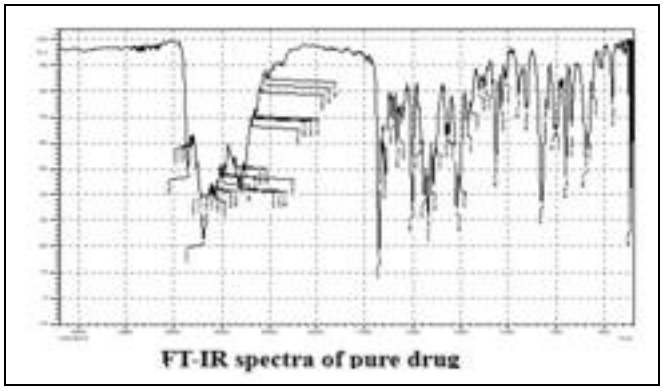
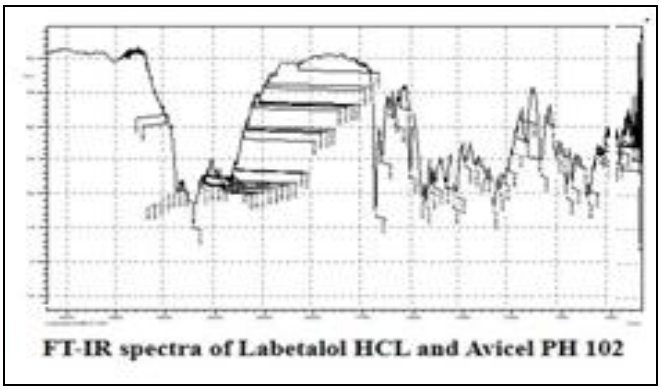
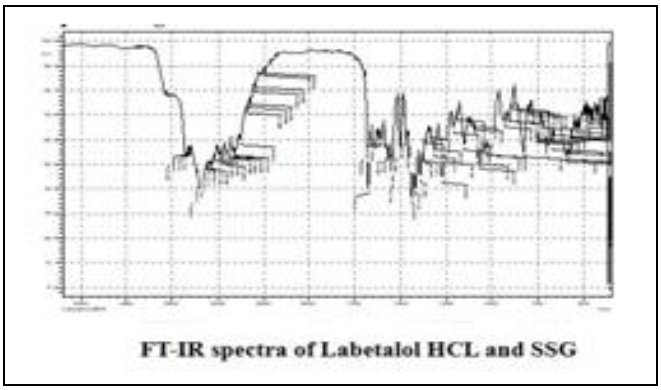


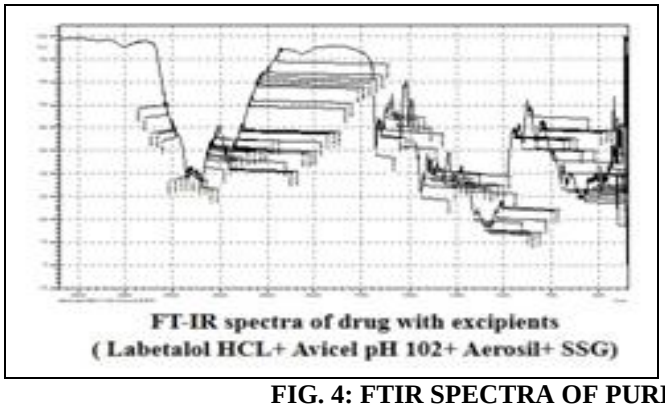
FIG. 3: ENDOTHERMIC PEAK OBSERVED AT 189.46 C

FT-IR Spectroscopy: The FT-IR spectroscopy was analyzed for interactions of the chemical bonds present in the drug and excipients. The pure drug showed peaks for functional groups O-H, C-H, N-H. The peaks obtained were in their limits for the pure drug as well as the physical mixture of drug with excipients **Fig. 4**.









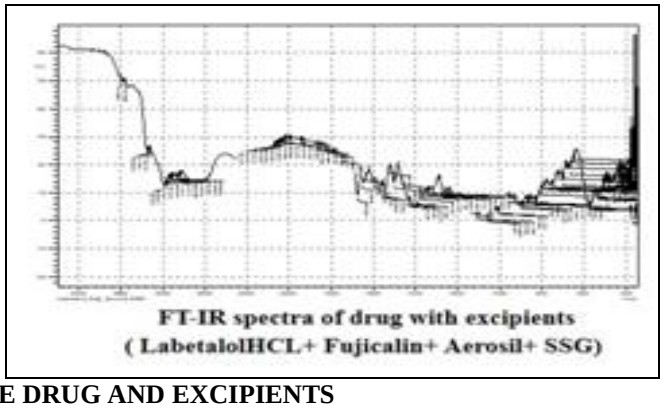


FIG. 4: FTIR SPECTRA OF PURE DRUG AND EXCIPIENTS

Determination of Flowable Liquid Retention potential (ϕ): The amount of liquid (non-volatile solvent) retained in the carrier and coating material is termed flowable liquid retention potential. The (ϕ) values for carrier and coating were determined using the formula. The obtained values are shown in **Table 6**.

Ø value = weight of liquid solvent / weight of carrier/coating

TABLE 6: FLOWABLE LIQUID RETENTION POTENTIAL (Φ) VALUES

Carrier	Ø Ca
Avicel pH 102	0.16
Fujicalin (Dibasic Calcium Phosphate)	0.04
Coating	**Ø Co**
Aerosil 200	3.31

The Ø values for carrier material Avicel PH 102 was 0.16 and coating material Aerosil 200 was 3.31 in propylene glycol non-volatile solvent was obtained from the literature review. The ØCa for fujicalin (dibasic calcium phosphate) in propylene glycol as a solvent was determined by angle of slide using the formula

ØCa = 200 / 5000 = 0.04

Evaluation of Liquisolid Tablets:

Precompression Studies: The pre-compression studies is carried out to evaluate the flow properties of the powder blend prior to compression. The evaluation parameters consist of angle of repose, bulk density, tapped density, Hausner's ratio, carrs index. The angle of repose obtained in the range 21.8 to 33.42, Bulk density 0.218 to 0.42, tapped density 0.19 to 0.49, Hausner's ratio 1.07 to 1.25, Carrs index 8.1 to 20.01 **Table 7.**

TABLE 7: PRECOMPRESSION PARAMETERS

	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.299±0.01	0.341±0.02	12.05±0.27	1.07±0.01	33.42±0.02
F2	0.278±0.1	0.314±0.22	11.73±0.32	1.12±0.01	21.80±0.2
F3	0.405±0.02	0.489±0.01	10.1±0.05	1.20±0.03	26.56±0.05
F4	0.181±0.12	0.197±0.03	8.17±0.21	1.08±0.01	29.68±0.02
F5	0.428±0.03	0.493±0.12	13.1±0.04	1.15±0.031	33.42±0.1
F6	0.3±0.05	0.375±0.45	20±0.13	1.25±0.06	26.56±0.04

Evaluation for Post Compression Parameters: The prepared liquisolid tablets are evaluated for weight, Hardness, thickness, disintegration, friability, and drug content. The results obtained are as shown in **Table 8**

TABLE 8: POST COMPRESSION PARAMETERS

	Weight variation	Hardness (kgs)	Friability (%)	Thickness (mm)	Drug content	Disintegration time (min)
F1	399.41±2.0	3.06±0.23	0.53±0.06	4.86±0.11	94.23±0.4	1.9±0.32
F2	400.21±5.0	3.46±0.15	0.67±0.03	5.03±0.15	90.27±0.2	2.0±0.2
F3	401.076±2.7	4.03±0.16	0.76±0.06	5.06±0.11	97.72±0.4	1.73±0.2
F4	406.51±2.5	3.7±0.2	0.61±0.08	4.86±0.11	95.27±0.2	1.76±0.15
F5	405.581±3.4	4.0±0.2	0.79±0.03	4.9±0.1	91.9±0.06	2.1±0.24
F6	407.28±2.9	3.53±0.11	0.92±0.08	4.7±0.15	94.40±0.4	2.3±0.09

Weight Variation: The Total weight of the tablet of F1 to F6 formulation ranges from 399.41 to 407.28.

The observed results conclude that no significant changes were observed in the tablet weights. The Hardness calculated using Monsento hardness tester.

The F3 formulation has 4.03 Kgs of Hardness, considered excellent Hardness (**Fig. 5.**

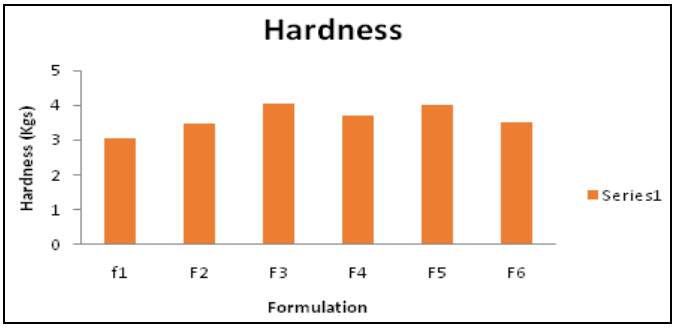


FIG. 5: COMPARISON GRAPH FOR HARDNESS OF TABLETS

The thickness calculated using Vernier callipers. The F3 formulation has 5.06 mm of thickness. The % friability of the tablets ranges within 1%. Hence all the formulations pass the friability test **Fig. 7**.

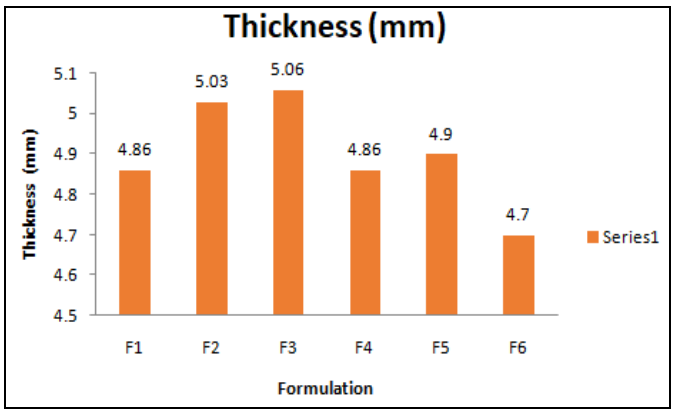


FIG. 6: COMPARISON GRAPH FOR THICKNESS OF TABLETS

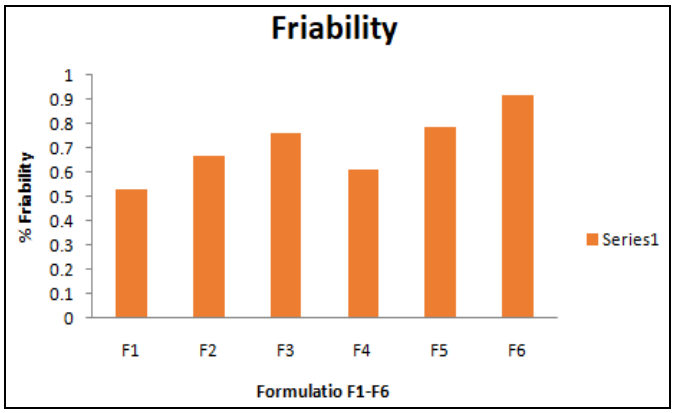


FIG. 7: COMPARISON GRAPH FOR % FRIABILITY OF TABLETS

The time is taken for the tablets to disintegrate ranges from 1.73 to 2.3 min. The F3 formulation takes the least time to disintegrate **Fig. 8**. The drug content for F1 to F6 formulation was carried out using pH 6.8, and absorbance was noted spectrophotometrically. The F3 formulation showed the highest percentage, 97.72%, compared to the other formulations **Fig. 9**.

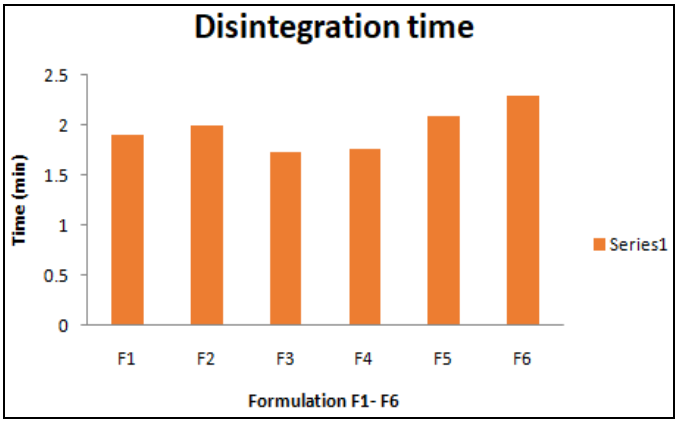


FIG. 8: COMPARISON GRAPH FOR DISINTEGRATION TIME OF TABLETS

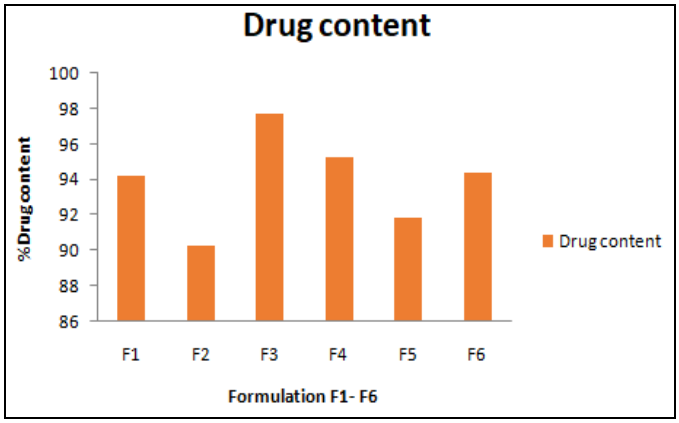


FIG. 9: COMPARISON GRAPH FOR HARDNESS OF TABLETS

***In-vitro* Drug Release:** The *In-vitro* drug release studies of the Liquisolid tablets of Labetalol hydrochloride were carried out in pH 6.8 Phosphate buffer in USP 2 paddle-type dissolution apparatus. The temperature conditions set at 37 C. The Pure drug possesses a pH dependency in pH 1 to 4. Hence the enhanced dissolution profile of the drug was noted in pH 6.8 for 60 min. The % Cumulative Drug release of F1 to F6 formulations ranges from 88.7% to 98.43 % **Table 9**. Formulations F3 and F4 show excellent drug release profiles **Fig. 10.** Data expressed are average of n=3±SD (Standard deviation)

TABLE 9: *IN-VITRO* DRUG RELEASE PROFILE OF F1 TO F6 FORMULATIONS

Time (Minutes)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	6.4	6.04	6.61	6.88	6.48	7.06
10	16.94	15.35	16.56	16.54	18.22	20.27
15	27.92	26.05	29.34	29.42	34.21	35.82
30	47.17	43.29	50.18	49.2	51.35	52.44
45	69.6	64.7	71.45	69.41	71.27	72.23
60	93.84	88.42	98.43	96.54	94.07	95.78

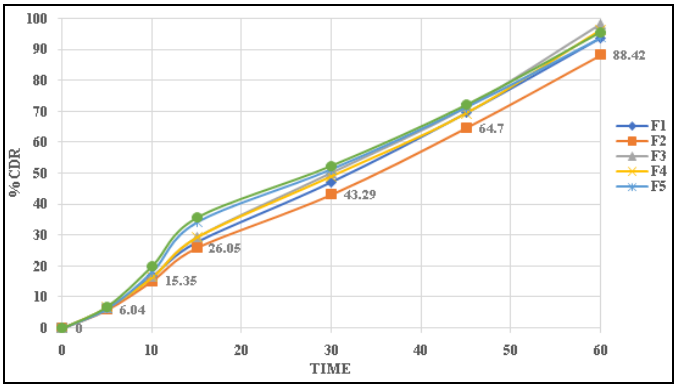


FIG. 10: COMPARISON OF *IN-VITRO* DRUG RELEASE PROFILE FOR F1 TO F6 FORMULATIONS

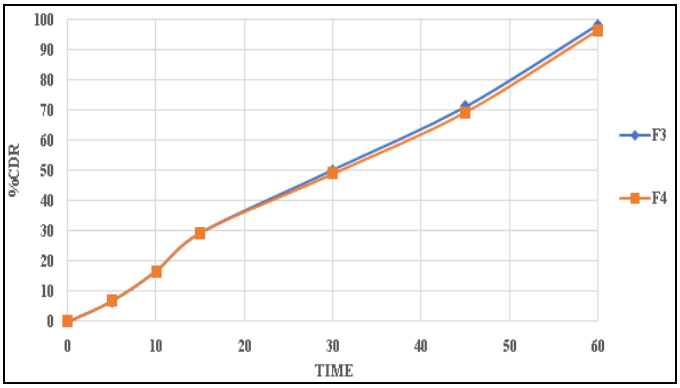


FIG. 11: COMPARISON OF IN-VITRO DRUG RELEASE PROFILE FOR F3 AND F4 FORMULATIONS

Drug Release Profile F3 and F4: The *in-vitro* drug release profile for formulations F3 and F4 where in the F3 consists of Avicel pH 102 as a carrier and F4 consists of fujicalin as the carrier material.

The comparison study between the formulation consisting of different carrier materials was done and results noted as shown in the figure. The F3 shows the highest drug release **Fig. 11**.

Stability Studies: The Short-term stability studies were carried out as per the ICH guidelines over 60 days. The tablets were subjected to a friability test, a Disintegration test, and Drug content. No significant difference was noted in the results obtained within the range compared to the initial results. Hence the Optimized formulation was stable **Table 10**.

TABLE 10: STABILITY STUDIES OF F3 OPTIMIZED FORMULATION

Data Lables	Initial	30 days	60 days
Friability	0.76±0.06	0.77±0.01	0.81±0.02
Disintegration time	1.73±0.2	1.75±0.02	1.76±0.02
Drug content	97.72 ±0.4	96.4±0.5	95.9±0.6

CONCLUSION: It can be concluded that Labetalol hydrochloride was successfully incorporated as a liquisolid tablet by the direct compression method. The direct compression method employed was easy and can be widely used. The powder blend of F3 containing Avicel pH 102 as a carrier material showed excellent flow ability, liquid retention potential compared to the Fujicalin as a carrier. Hence F3 is considered optimized. The drug was compatible with the excipients since no interactions were observed in DSC and FTIR studies. The In-vitro drug release confirmed the enhanced drug release from the liquisolid tablets. The stability studies revealed the formulation was stable.

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