Characterization and Optimization of Liquisolid Compact for Enhancement of Dissolution rate and Solubility of Bilastine

Utkarsh Rupavatiya[1]*, Mrs. Velenti Chauhan[2]
Bhagwan Mahavir College of Pharmacy
Bhagwan Mahavir University
BMEF Campus, Nr. Aakash E-Space, Bharthana, Vesu, Surat 395017

ABSTRACT

This study aimed to improve the dissolution rate of bilastine, a poorly soluble drug used to treat allergic rhinitis, allergic rhinoconjunctivitis, asthma and urticaria, by utilizing the liquisolid technique. Liquisolid compacts were prepared using Propylene glycol as a non-volatile solvent, Avicel PH102 as a carrier, and Lactose as the coating material. Various concentrations of bilastine in the non-volatile vehicle and different excipient ratios were tested. The prepared liquisolid powders exhibited good flow properties. The powders were then mixed with a superdisintegrant and compressed into tablets. These tablets underwent evaluation for hardness, friability, content uniformity, disintegration time, and dissolution rate. The results showed that the formulated liquisolid compacts had acceptable flowability and compressibility. They also demonstrated significantly improved drug release compared to the directly compressed formulation. Among the different tablet formulations, F12 exhibited the highest dissolution rate, attributed to enhanced wetting properties and increased drug surface exposure. FTIR analysis indicated no drug-excipient interaction, ensuring compatibility. DSC analysis revealed that bilastine was molecularly dispersed and in an amorphous form in the final formulation. Powder X-ray diffraction patterns confirmed the absence of characteristic drug peaks, indicating complete conversion to an amorphous or solubilized state. Particle size analysis shows that particle size increase therefore flow property and compressibility was improve. This study demonstrated that the liquisolid technique effectively enhanced the dissolution rate of bilastine. These findings suggest that the liquisolid approach is a promising strategy for improving the solubility and dissolution properties of poorly soluble drugs like bilastine in pharmaceutical formulations.

I. INTRODUCTION

Drugs belonging to biopharmaceutics classification system (BCS) class II encounter the problem of low solubility, dissolution rate which leads to poor bioavailability.[1]Liquisolid compacts are a successful procedure for improving the bioavailability of BCS class II drugs, alongside methods like micronization, lyophilization, solid dispersion, co-solvancy, and complexing agents.[2]Liquisolid technology converts liquid drugs into a dry, non-sticky powder by mixing them with carriers and coating agents.[3]The dissolution profile of the drugs was found to increase from liquisolid method due to the increased wetting properties and surface area. The technique is limited to low dose drugs with poor water solubility.[4]Liquisolid compacts require a carrier with high adsorption properties and a porous surface for liquid medication, commonly used as microcrystalline cellulose (Avicel PH 20, 102, 200).[5]Coating material like silica covers powder surface, enhancing flowability and uniformity. Disintegrants like starch glycolate and crosspovidone increase drug release rate, while non-volatile solvents like polyethene glycol and glycerin provide binding action.[6]

The liquid-solid systems are versatile in the fact that it can be used for poorly soluble drugs.Improves the bioavailability of water-insoluble drug candidates, which are given by oral route (E. g. Risperidone, Griseofulvin, Carvidelol).[7]When compared to soft gelatin capsules, the manufacturing expenditure is low.The drug can be formulated as a tablet or a capsule or as an encapsulated liquisolid microsystem, where the drug is presented in solubilized state which leads to enhanced wetting phenomena and improvement in drug release profiles.Instant release or continual release dosage forms can be formulated into

liquisolid compact depending on the character of carriers used.Improved drug release can be achieved by using hydrophobic carriers (Eudragit RL) for sustained release and surface active agents (polysorbate 80) for enhanced wettability and dissolution profile.[8]The technique can be scaled up to manufacturability.When compared to conventional tablets the extent of absorption can be enhanced up to 15%.The manufacturing efficiency can be improved.[9]

Bilastine, a piperidine derivative, is a highly effective, long-acting, non-sedating H1-antihistamine.[10]Bilastine is an antihistamine used to treat allergy symptoms like stuffy nose, itchy eyes, sneezing, and chronic urticaria. Its antihistaminic effect can be felt within an hour and lasts 24 hours.[11]However, bilastine has low bioavailability (60.67%) due to incomplete absorption and interactions with high/low fatty meals.The "liquisolid" method is a new technique for enhancing the dissolution of water-insoluble drugs. It increases wetting and surface area, improving dissolution properties and bioavailability. The addition of a superdisintegrant accelerates drug release.[12]

II.   MATERIALS AND METHODOLOGY
2.1 MATERIALS
Bilastine was received as a gift sample from Ajanta Pharmaceutical, Aurangabad. Propylene glycol, Avicel PH102, Lactose, Cross Povidone, Magnesium Stearate, Talc were obtained from Chemdyes Corporation, Rajkot.

2.2 METHODOLOGY
2.2.1 Pre-formulation study of Drug and Excipients
The pre-formulation study of drug and excipients were subjected as per the methods suggested in the Indian Pharmacopoeia like organoleptic characteristics, melting point determination, UV Spectroscopy, FTIR, solubility study.

2.2.1.1Identification of pure drug and drug-excipients compatibility study by Fourier Transform Infrared Spectroscopy (FT-IR)[13]
To investigate drug compatibility, FTIR spectra for the drug are recorded using an FTIR with KBr. This will provide crucial drug information. By scanning the sample with FTIR spectrophotometer in the wave number range of 4000-400 cm^{-1} and comparing the results to the reference spectra of Bilastine, the identification of pure Bilastine was investigated.

To investigate the compatibility of the drug and all the excipients, FTIR spectra for the drug and all excipients were obtained using an FTIR spectrophotometer with KBr. This will provide important details regarding the interactions between the Excipient and the Drug.

2.2.1.2 Solubility study[14]
The solubility of Bilastine in various non-volatile solvents including Polyethylene glycol 200, 400, 600, Propylene glycol, Tween 20, 80, Span 20, and Span 80. The drug was mixed in these solvents, shaken, and centrifuged for 48 hours. The filtered supernatant was then diluted with methanol and spectrophotometrically analysed for drug content. The solubility value was calculated using a methanol calibration curve.

2.2.2 Flowable liquid-retention potential (φ-value) of the excipients (Avicel PH102 and Lactose)[15]
2.2.2.1 Determination of the angle of slide
The angle of slide carrier and coating material (10 gm of Avicel PH102 and Lactose) is measured as follows:
The angle of the slide is determined by weighing the carrier material and placing it on a polished metal plate. The plate is raised until it becomes angular to the horizontal, with an optimum angle of 33°.

2.2.2.2 Determination of flowable liquid-retention potential (φ-value)
The Φ-value is a measure of a powder material's ability to retain a specific amount of liquid while maintaining good flow properties, referring to the maximum weight of liquid that can be retained per unit weight for an acceptable liquid/powder admixture.
The Φ values are calculated according to the equation,

$$\Phi \text{ value} = \frac{\text{Wt. of the liquid}}{\text{Wt. of solid}}$$

The Φ-values are plotted graphically against the corresponding angles of slide (h). The Φ-value corresponding to an angle of slide of 33° represented the flowable liquid-retention potential of excipients.[16,17]

2.2.3 Development of Liquisolid Compacts[18]

Several Bilastine liquisolid compacts formulation are prepared in the ratio of (1:1, 1:2 and 1:3) Drug:liquid vehicle. Each formulation contains Avicel PH102 as carrier and lactose as coating material, at carrier/coat ratio (R value) of 5, 10, 15 and 20. The appropriate amounts coating material, used for each formulation depend upon Lf of that formulation. The ΦCa and ΦCo values for liquid vehicle are used to calculate Lf [Eq-(1)] of that respective liquid vehicle. Once the liquid load factor (Lf) and amount of liquid medication (W) are determined amount of carrier (Q) and coating (q) can be calculated by rearranging Eq-(2) and (3).

$$Lf = \Phi Ca + \Phi Co \times 1/R \quad (1)$$
$$Lf = W/Q \quad (2)$$
$$R = Q/q \quad (3)$$

The drug-vehicle liquid system is produced by mixing Bilastine (20 mg) in non-volatile liquid vehicle using a mortar and pestle. To this liquid medication, the calculated amount of the carrier (Avicel PH102) is added by continuous mixing for a period of 10 to 20 minutes in a mortar. Then the coating material (Lactose) is carefully added and mixed until mortar contents start to look like dry powder.

2.2.4 Optimization by using 3^2 full factorial experimental design

3^2 full factorial statistical design was employed to evaluated main effects and interaction effects of independent variables on the various properties of Bilastine Liquisolid Compacts in order to optimize the formulation. The non-linear quadratic model generated by the design is as follows:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y_i is dependent variable, b_0 is arithmetic mean response of 9 runs and b_i is the estimated coefficient for factor X_i. The main effects (X_1 and X_2) signify average result of altering one factor at a time from its lowest to highest value. The interaction terms (X_1X_2) prompt change in responses when two factors are simultaneously altered. The polynomial terms (X_1^2 and X_2^2) are added to investigate non-linearity of the model.

A two-factor, three-level 3^2 full factorial design was generated by an experimental design-expert software version 10(Software from Stat Ease, Inc) and based on preliminary trials, independent variables (factors) were determined.

Table 2.1 Selection of dependent and independent variables

Translation of coded value in actual units			
Independent variables	**Variable level**		
	Low (-1)	Medium (0)	High (+1)
Ratio of Drug:Non-Volatile Solvent (X_1)	1	2	3
R Value(X_2)	10	15	20
Dependent Variables			
1	Solubility(Y_1)		
2	%CDR at 30 min (Y_2)		

2.2.5 Evaluation of Liquisolid Compacts
2.2.5.1 Bulk density[19]

Bulk density of Liquisolid compact was determined by pouring gently 5.00 gm through a glass funnel into 20 ml graduated cylinder. The volumes occupied by the samples were recorded.

Bulk density(gm/ml)=

$$\frac{\text{Wt. of sample}}{\text{Volume occupied by the sample}}$$

2.2.5.2 Tapped density[20]

Tapped density was determined using a graduated cylinder and mechanical tapping device, with a weighed powder sample added using a funnel. The initial volume was noted, and the

sample is then tapped (50, 100, 150, 250 tapping) until no further reduction in volume is noted.

Tapped density(gm/ml) =

$$\frac{\text{Wt. of sample}}{\text{Tapped volume}}$$

2.2.5.3 Compressibility Index and Hausner's ratio[21]

In recent years the carr's index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the carr's index and the Hausner's ratio were determined by bulk density and the tapped density of a powder.

Carr's index =

$$\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio = $\dfrac{\text{Tapped Density}}{\text{Bulk Density}}$

2.2.5.5 Flow property

Table 2.2 The relation between angle of repose and flow property

Angle of repose(θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2.2.5.6 Solubility study
Solubility study of all batches are performed as per the procedure already discussed in Pre-formulation study.

2.2.5.7 In vitro drug release studies
In vitro release studies is performed by using dissolution apparatus in 900 ml of 0.1 N HCl maintained at 37° C ± 0.5° C and rotation speed of 50 rpm. Samples (5 ml) are withdrawn at suitable time intervals (10, 20, 30 minutes) and filtered through whatman filter paper. Sink conditions are maintained throughout the study. The withdrawn samples are analyzed by UV visible spectrophotometer at λmax of 282 nm.

2.2.6 Conversion of Liquisolid compacts into Tablets
In the last stage of preparation, The optimized Liquisolid Compacts, equivalent to 60 mg of Bilastine were taking with pharmaceutical excipients like 2% (w/w) Crospovidone as Super disintegrant, 1% (w/w) Magnesium Stearate as Lubricant, 1% (w/w) Talc as Glidant and Residue amount of Avicel PH102 as Diluent. Mixed whole ingredients for five minute and directly compress into tablet by using tablet punching machine using 6 mm punch for total weight 120 mg of each tablet.

2.2.7 Evaluation of Liquisolid Tablets
The prepared liquisolid tablets were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like general

2.2.5.4 Angle of repose[22]
The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated by using the equation.

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

Where, h and r are the height of pile and radius of the pile.

appearance, thickness, diameter, hardness, weight variation, friability test, disintegration test, drug content, in vitro drug release studies.

2.2.7.1 Friability test[23]
The test assesses tablets' abrasion resistance in packing, handling, and transport. Friability, a measure of poor cohesion, is used. 20 tablets are placed in a circular plastic chamber, rotated at 25 rpm, and dropped 15 cm apart. The difference is weighed and expressed as percentage.

%Friability = $\dfrac{W2 - W1}{W1} \times 100$

Where,
W1 = weight of tablets before test, W2 = weight of tablets after test

2.2.7.2 Disintegration test[24]
Disintegration is the state where no tablet remains on the screen of an apparatus. Liquisolid tablets are disintegrated using a disintegration test apparatus. Tablets are introduced into tubes, and the disintegration time is recorded by moving the basket rack in distilled water.

Disintegration time (As per IP Limitation)
a) Uncoated tablets: 5- 30 minutes
b) Coated tablets: 1-2 hours

2.2.7.3 Drug content[25]

The Tablet is dissolved in methanol, then the volume is made upto 100ml with distilled water. From the above solution, 10 ml is taken and diluted with distilled water. The absorbance of resulting solution (10 μg/ml) is measured at 282 nm using spectrophotometer and the drug content is calculated from the standard curve using the formula,

$$\text{Drug content} = \frac{\text{Sample absorbance} \times 100}{\text{Standard absorbance}}$$

2.2.7.4 In vitro drug release studies[26]

The study uses a dissolution apparatus in 900 ml of 0.1 N HCl, maintained at 37°C ± 0.5°C and 50 rpm. Samples are withdrawn at specific intervals, filtered through whatman paper, and analyzed using a UV visible spectrophotometer at 282 nm.

2.2.8 Comparison with marketed product[27]

The in vitro release of best formulation is compared with marketed tablets are prepared by mixing all tablet excipients, except non-volatile liquid vehicle.

2.2.9Characterization of Liquisolid Compacts
2.2.9.1 Fourier-Transform Infrared Spectroscopy (FT-IR)
Liquisolid compacts is subjected to FTIR procedure already discussed in Preformulation study.

2.2.9.2 Differential Scanning Calorimetry (DSC)[28]

DSC was performed using Differential scanning calorimeter, in order to thermotropic properties and thermal behaviour of pure drug& liquisolid compacts. About 5 mgsample were sealed in the aluminium pans and heated at 10°C/min, covering a temperature of 30-300°C.

2.2.9.3 Powder X-Ray Diffraction Studies (XRD)[29]

Powder X-ray diffraction pattern of Bilastine, Avicel PH102, Lactose and liquisolid compacts are studied using X-ray diffractometer with CuKα radiation. Voltage and current are set 40 kV and 30 mA. All pattern scanned over range 3-50° 2θ angle with a scan speed of 2°/min.

2.2.9.4Particle size analysis

The size of pure drug particles and optimized Liquisolid compacts was measure by Malvern instrument Mastersizer 3000.Which give the information about the size of particles and Liquisolid compacts to check their flow property.

2.2.10Stability Study[30]

The accelerated stability study was carried out of optimized formulation. The tablet sample was wrapped in the laminated aluminium foil and stored in the stability chamber at 40° C ± 2°C and relative humidity(RH) 75% ± 5%. Sampling was done as a predetermined time interval of 0, 15 and 30 days. The tablets were evaluated for different physicochemical parameter.

III. RESULT AND DISCUSSION
3.1 Pre-formulation study of Drug and Excipients
3.1.1Organoleptic characteristics
The Drug's organoleptic characteristics were noticed, and they are consistent with the standard data.

Table 3.1 Organoleptic characteristics of drug

Sr. No.	Organoleptic characteristics	Observation	Inference
1.	Colour	White Powder	Complies with standard data which confirms identity of drug sample.
2.	Odour	Odourless	
3.	State	Solid	

3.1.2 Melting Point Determination
The detected melting point was compared to the standard Bilastine melting point value, which measures the identity and purity of the Drug sample.

Table 3.2 Melting point of Bilastine

Drug	Standard Value	Observed Value (Mean ± S.D.) (n=3)	Inference
Bilastine	194- 197 °C	195.33 °C ± 0.57°C	Complies with standard data which confirms identity of drug sample.

3.1.3 Fourier Transform Infrared Spectroscopy (FT-IR)
3.1.3.1 Identification of pure drug by FT-IR Spectroscopy

FTIR Spectrum of Bilastine pure drug was observed at wave numbers represents in Table 6.6, which was near to standard Bilastine peak value. The obtained FTIR Spectrum complies with standard frequency data which further confirms identity of pure drug.
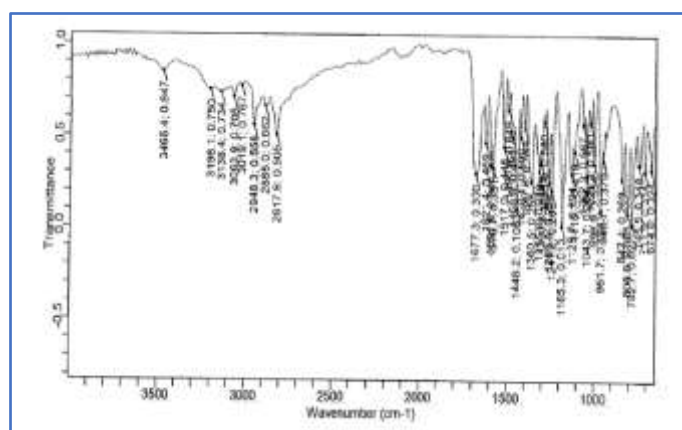

Figure 3.1 FTIR Spectrum of Bilastine Pure Drug

Table 3.3 Characteristic FTIR peaks for Bilastine Pure Drug

Functional group	Standard frequency range(cm^{-1})	Observed frequency(cm^{-1})
O-H stretching	3300-2500	3198.1
C-H stretching	3100-3000	3019.1
C=O stretching	1685-1666	1677.3
C=N stretching	1690-1430	1446.2

3.1.3.2 Drug - excipients compatibility studies by FT-IR Spectroscopy

IR spectra of Bilastine with excipients are shown in following Figure 6.9-6.11. All Spectrums are shows that there were no significant changes in major peaks of Bilastine in sample with excipients when compared to spectra of pure drug, that indicating absence of any interaction of drug with excipients.
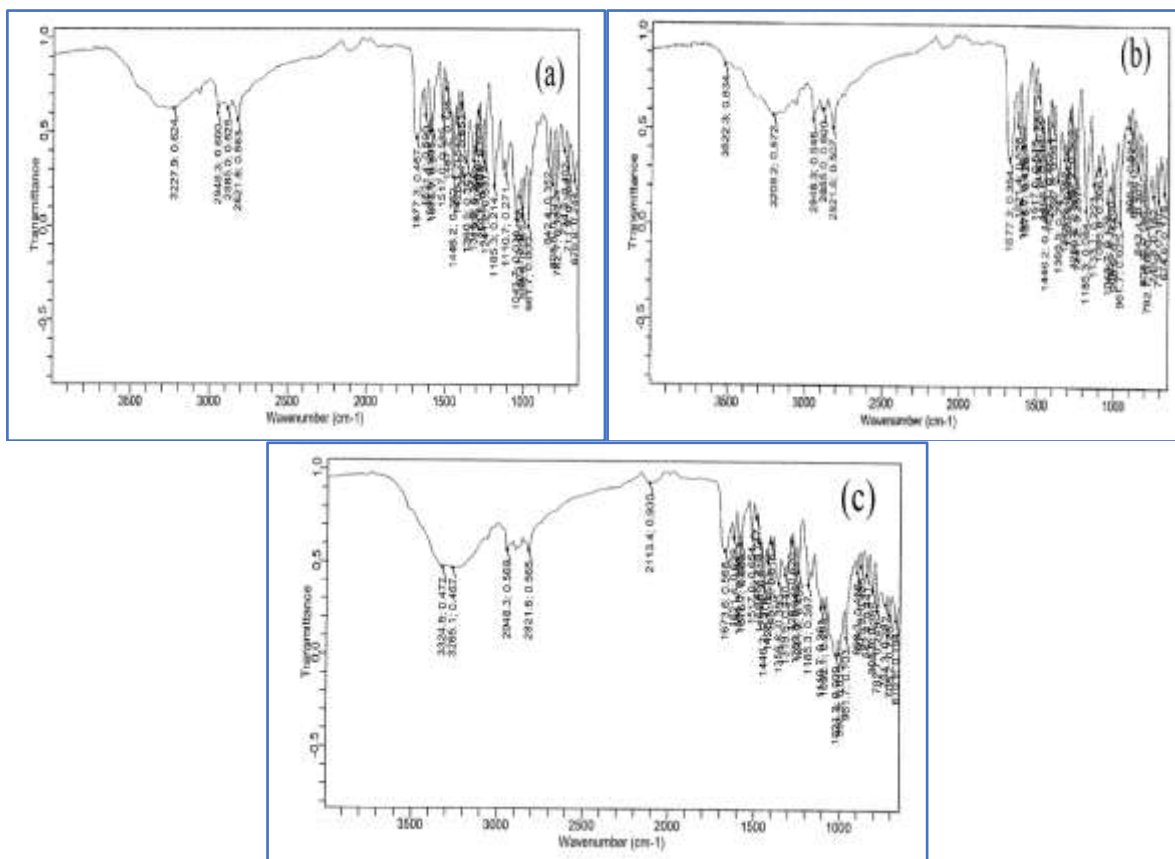
Figure 3.2 FTIR Spectrum of Bilastine with (a)Avicel PH102 (b)Lactose (c)all excipients

3.1.4 Solubility study

In addition, selection of Non-volatile Solvent, it should be immiscible with poor solvent and have low toxicity compare to other solvents. Therefore Propylene Glycol was selected as Non-volatile Solvent for Liquisolid Compacts of Bilastine.
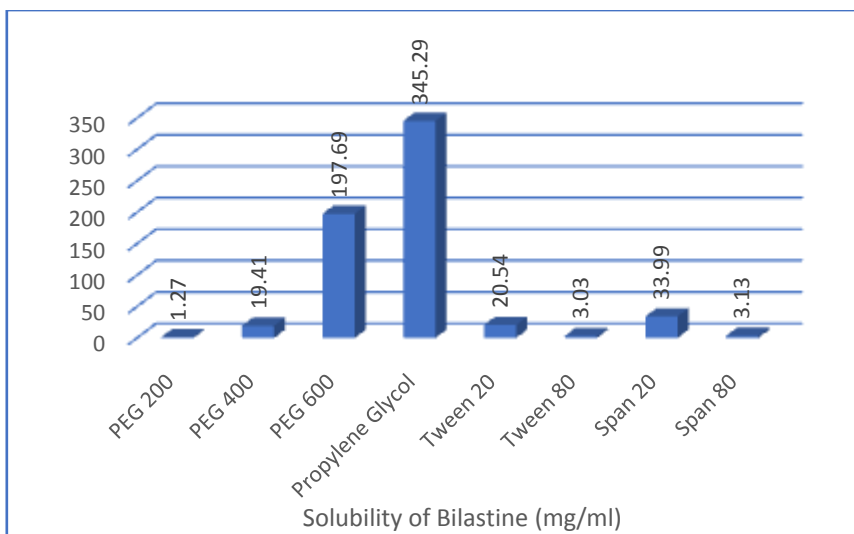

Figure 3.3Solubility study of Bilastine in different non-volatile solvents

3.2 Preparation and Evaluation of preliminary trial batch of Liquisolid Compacts

Based on preliminary trials, independent variables were determined as Ratio of Drug:Non-

volatile solvent (X1) between in range 1:1 to 1:3 and R value (X2) between 10 to 20.

Table 3.4 Φ–values for carrier material and coating material

Non-volatile Solvent	Φ–values for carrier material (Avicel PH 102)	Φ–values for coating material (Lactose)
Propylene Glycol	0.16	3.34

Table 3.5 Composition of preliminary trial batch of Liquisolid Compacts

Formulation Code	Ratio	Non-volatile Solvent	R Value	API (mg)	Non-volatile Solvent (mg)	Lf Liquid load factor	Avicel PH102 Q (mg)	Lactose q (mg)
F1	1:1	Propylene Glycol	5	20	20	0.828	48.309	9.662
F2	1:1	Propylene Glycol	10	20	20	0.494	80.972	8.097
F3	1:1	Propylene Glycol	15	20	20	0.383	104.439	6.963
F4	1:1	Propylene Glycol	20	20	20	0.327	122.324	6.116
F5	1:2	Propylene Glycol	5	20	40	0.828	72.464	14.493
F6	1:2	Propylene Glycol	10	20	40	0.494	121.457	12.146
F7	1:2	Propylene Glycol	15	20	40	0.383	156.658	10.444
F8	1:2	Propylene Glycol	20	20	40	0.327	183.486	9.174
F9	1:3	Propylene Glycol	5	20	60	0.828	96.618	19.324
F10	1:3	Propylene Glycol	10	20	60	0.494	161.943	16.194
F11	1:3	Propylene Glycol	15	20	60	0.383	208.877	13.925
F12	1:3	Propylene Glycol	20	20	60	0.327	244.648	12.232
F13	1:3	Propylene Glycol	25	20	60	0.294	272.109	13.605

Table 3.6 Evaluation of preliminary trial batch of Liquisolid Compacts

Formulation Code	Bulk density (gm/ml ± S.D.) (n=3)	Tapped density (gm/ml ± S.D.) (n=3)	Carr's index(% ±S.D.) (n=3)	Hausner's Ratio (Ratio ± S.D.) (n=3)	Angle of repose (θ)	Solubility (mg/ml)	% CDR at 30 min. (%)
F0(API)	0.297 ± 0.0012	0.347 ± 0.0016	14.39 ± 0.455	1.168 ± 0.006	31.09 ± 0.062	0.95	11.89
F1	0.402 ± 0.0030	0.443 ± 0.0057	9.31 ± 1.189	1.103 ± 0.014	28.34 ± 0.041	6.79	44.31

F2	0.407 ± 0.0016	0.459 ± 0.0042	11.46 ± 1.126	1.129 ± 0.015	27.97 ± 0.161	8.96	56.96
F3	0.421 ± 0.0064	0.467 ± 0.0031	9.71 ± 1.402	1.130 ± 0.032	27.90 ± 0.041	10.35	60.38
F4	0.427 ± 0.0086	0.473 ± 0.0031	9.71 ± 2.184	1.108 ± 0.027	28.09 ± 0.097	21.89	62.58
F5	0.431 ± 0.0076	0.489 ± 0.0050	11.79 ± 1.526	1.134 ± 0.019	27.77 ± 0.097	9.62	58.92
F6	0.432 ± 0.0041	0.484 ± 0.0025	10.74 ± 0.709	1.12 ± 0.009	27.33 ± 0.000	10.25	61.53
F7	0.429 ± 0.0042	0.490 ± 0.0038	12.44 ± 0.843	1.139 ± 0.014	26.7 ± 0.035	12.38	69.53
F8	0.434 ± 0.0031	0.492 ± 0.0035	11.66 ± 0.068	1.132 ± 0.001	26.47 ± 0.035	29.68	71.52
F9	0.427 ± 0.0035	0.491 ± 0.0026	13.03 ± 1.172	1.15 ± 0.016	26.37 ± 0.121	20.82	72.75
F10	0.439 ± 0.0055	0.494 ± 0.0035	11.13 ± 1.052	1.125 ± 0.013	26.38 ± 0.064	23.67	75.73
F11	0.448 ± 0.0057	0.499 ± 0.0046	10.29 ± 0.319	1.114 ± 0.004	25.52 ± 0.105	25.67	87.63
F12	0.456 ± 0.0025	0.501 ± 0.0047	9.25 ± 0.894	1.102 ± 0.011	24.43 ± 0.071	38.96	88.09
F13	0.443 ± 0.0048	0.461 ± 0.0037	14.67 ± 0.276	1.137 ± 0.003	27.86 ± 0.107	24.43	76.84

3.4 Statistical analysis of 3^2 full factorial design

Table 3.7 Coded & Actual value with observed responses of 3^2 full factorial design layout

Experimental Batch code	Coded value (X_1)	Actual value (X_1)	Coded value (X_2)	Actual value (X_2)	Solubility (mg/ml) (Y_1)	%CDR at 30 min (%) (Y_2)
LSC1	-1	1	-1	10	8.96	56.96
LSC2	0	2	-1	10	10.25	61.53
LSC3	1	3	-1	10	23.67	75.73
LSC4	-1	1	0	15	10.35	60.38
LSC5	0	2	0	15	12.38	69.53
LSC6	1	3	0	15	25.67	87.63
LSC7	-1	1	1	20	21.89	62.58
LSC8	0	2	1	20	29.68	71.52
LSC9	1	3	1	20	38.96	88.09

Table 3.8 Summary of results of multiple regression analysis for dependent variable

Dependent variables	Y_1 = Solubility		Y_2 = %CDR at 30 min	
	Coefficients	P value	Coefficients	P value
Intercept	13.37	0.0053	69.60	0.0027
X_1	7.85	0.0023	11.92	0.0005
X_2	7.94	0.0022	4.66	0.0072
X_1X_2	0.59	0.5929	1.68	0.1477
X_1^2	4.15	0.0593	4.37	0.0379
X_2^2	6.10	0.0223	-3.11	0.0851

Solubility (Y_1) = $13.37 + 7.85X_1 + 7.94X_2 + 0.59X_1X_2 + 4.15X_1^2 + 6.10X_2^2$

The observed value for solubility of all 9 batches varied from 8.96 - 38.96. Theresult indicates that Y_1 is affected by the independent variables selected for the study.The two independent variables, the X_1 (7.85) and X_2 (7.94) shows the main effect inaffecting Y_1. The X_1 and X_2 with P value <0.05 was found to be significant inaffecting Y_1. X_1 and X_2 both have positive value of co-efficient, showingsimilar effect which increases the solubility. Apart from the main effect, theinteraction effect of X_1X_2 shows a positive co-efficient value (0.59) whichindicate a positive effect on Y_1 means it increases the solubility.

%CDR at 30 min (Y_2) = $69.60+11.92X_1+4.66X_2+1.68X_1X_2+4.37X_1^2-3.11X_2^2$

The observed value for cumulative % drug release at 30 min of all 9 batches variedfrom 56.96 – 88.09 %. The result indicates that Y_2 is affected by the independentvariables selected for the study. The two independent variables, the X_1 (11.92) andX_2 (4.66) shows the main effect in affecting Y_2. The X_1 with P value <0.05 wasfound to be significant in affecting Y_2 means it showing positive effect on Y_2 and $X_2$with P value <0.05 was found to be significant affecting Y_2 and it showing positiveeffect on Y_2. Apart from the main effect, the interaction effect of X_1X_2shows a positive co-efficient value (1.68) which indicate a positive effect on Y_2means it increases the cumulative % drug release at 30 min.

Table 3.9 Results of ANOVA for Dependent variable

Sources	Sum of Squares	Degrees of Freedom	Mean square	F Value	P Value
For Y_1 = Solubility					
Regression	858.40	5	171.68	43.86	0.0053
Residual	11.74	3	3.91		
Total	870.14	8			
For Y_2 = %CDR at 30 min					
Regression	1052.03	5	210.41	69.76	0.0027
Residual	9.05	3	3.02		
Total	1061.08	8			

Results of ANOVA for dependent variable are shown and The P value <0.05 shows that all the responses are significant and applied Non-linear quadratic response surface method is fitted to the model.

3.6.1 Effect of X_1 and X_2 on response Y_1

From the contour and 3D surface plots, it was observed that as the Ratio of Drug:Non-Volatile Solvent and R Value increases the solubility increases and also the interaction of both factors at higher level increased the solubility.
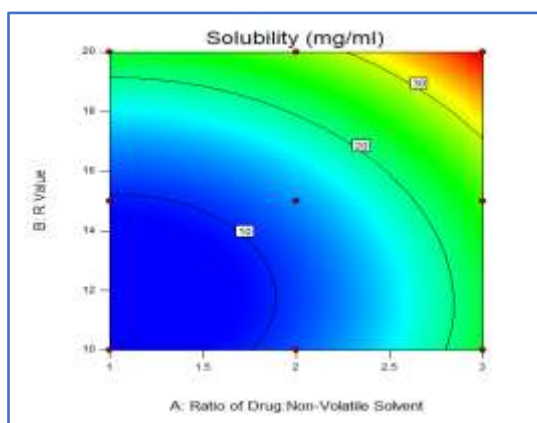

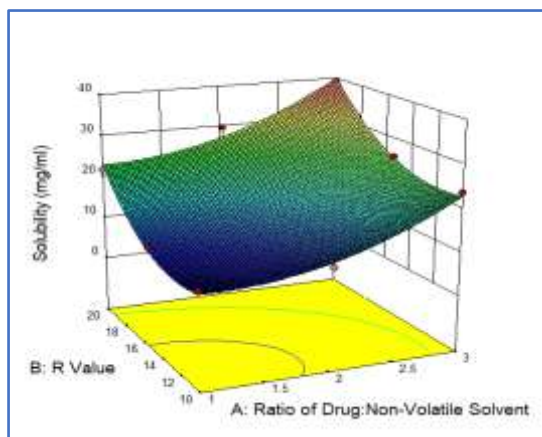**Figure 3.4 Two dimensional contour plots showing effect of X_1 and X_2 on Y_1**

Figure 3.5 Three dimensional surface plots showing effect of X_1 and X_2 on Y_1

3.6.2 Effects of X_1 and X_2 on response Y_2
From the contour and 3D surface plots, it was observed that as the Ratio of Drug:Non-Volatile Solvent and R Value increases the cumulative % drug release at 30 min increases and also the interaction of both factors at higher level increases the cumulative % drug release at 30 min.
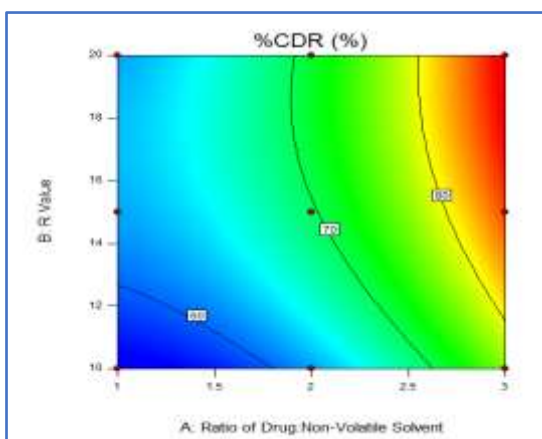

Figure 3.6 Two dimensional contour plots showing effect of X_1 and X_2 on Y_2
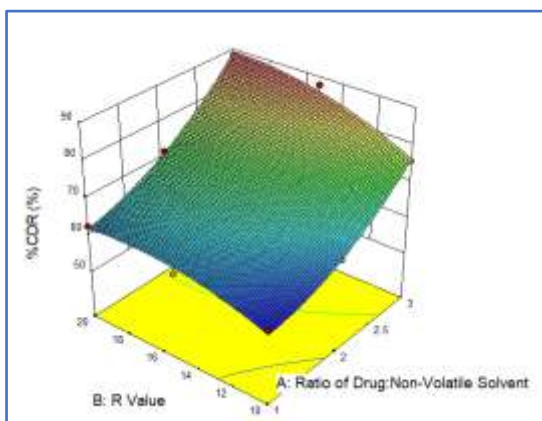
Figure 3.7 Three dimensional surface plots showing effect of X_1 and X_2 on Y_2

3.7 Validation and Optimization

The optimized batch was found from the Design Expert 10. It was arbitrarily decided to select final batch of Bilastine Liquisolid Compacts based upon the criteria 70-90 % for cumulative % drug release at 30 minutes and 30-40 mg/ml for solubility. The optimized batch was prepared, in which yellow region is the optimize region.
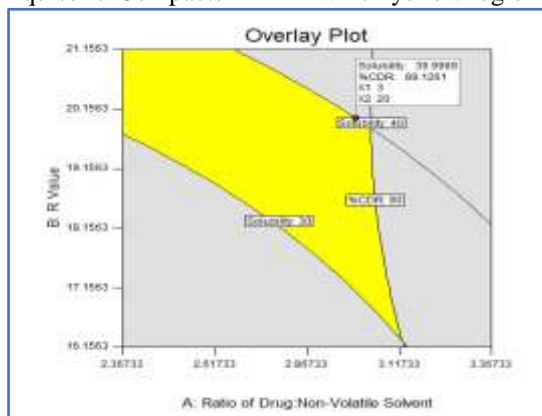

Figure 3.8 Overlay plot of optimized batch

3.8 Formulation and Evaluation of Optimized Batch of Bilastine Liquisolid Compacts

The results revealed that the flow property and compressibility of optimized Liquisolid Compacts of Bilastine was found to be excellent.

Table 3.10 Formula of Bilastine Liquisolid Compacts

Ingredients	Quantity(mg)
Bilastine	20 mg
Propylene Glycol	60 mg
Avicel PH102	244.648 mg
Lactose	12.232 mg

Table 3.11 Evaluation of Optimized Batch of Liquisolid Compacts

Test Parameter	Result
Bulk density (gm/ml ± S.D.) (n=3)	0.456 ± 0.0025
Tapped density (gm/ml ± S.D.) (n=3)	0.501 ± 0.0047
Carr's index(% ±S.D.) (n=3)	9.25 ± 0.894
Hausner's Ratio (Ratio ± S.D.) (n=3)	1.102 ± 0.011
Angle of repose (θ)	24.43 ± 0.071
Flow property	Excellent

3.10 Formulation and Evaluation of Bilastine Liquisolid Tablets

A result of general appearance, hardness, thickness, diameter, weight variation, drug content, %CDR at 30 min., solubility and disintegration time of tablet were found. Friability of tablet of Liquisolid Compacts of Bilastine was found to 0.48 % which is within the limit (< 1 %).

Table 3.12 Formula of Bilastine Liquisolid Tablets

Ingredients	Quantity(mg)
Bilastine Liquisolid Compacts	60 mg
Avicel PH102	55.2 mg
Cross Povidone	2.4 mg
Magnesium Stearate	1.2 mg
Talc	1.2 mg
Total Weight	120 mg

Table 3.13 Evaluation of Bilastine Liquisolid Tablets

Test Parameter	Result
General appearance	White to Beige
Thickness (mm± S.D.) (n=3)	2.69 ± 0.03
Diameter (mm± S.D.) (n=3)	6.00 ± 0.00
Hardness (kg/cm^2± S.D.) (n=3)	4.06 ± 0.24
Weight variation (%)	5.96
Friability (% ± S.D.) (n=3)	0.48 ± 0.02
Disintegration time (sec ± S.D.) (n=3)	49.32 ± 1.07
Drug content (% ± S.D.) (n=3)	99.10 ± 0.20
Solubility (mg/ml)	19.24
%CDR at 30 min. (%)	92.57

3.12 Comparison with marketed product
The tablet of optimized batch of Liquisolid compacts showed > 90% drug release in 30 min which was greater than the % drug release prepared conventional tablet of Bilastine while marketed tablet of Bilastine (Elbel 20) showed less tham < 55% drug release in 30 min.
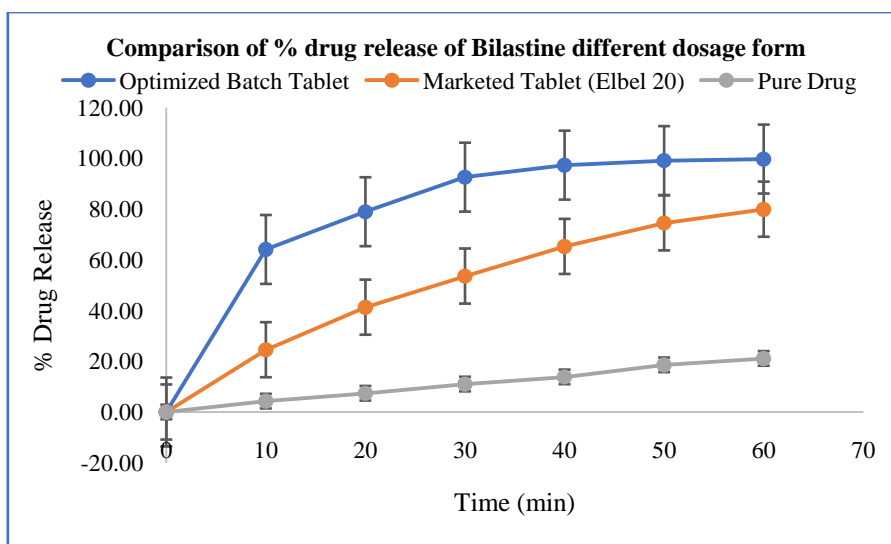
Figure 3.9 Comparison of % drug release of Bilastine different dosage form

3.13 Characterization of Liquisolid Compacts
3.13.1 Fourier-Transform Infrared Spectroscopy (FT-IR)
FTIR spectrum of optimized batch was determined. All the major peaks of drug are present, indicating there is no extensive degradation of drug & drug is present in formulation.
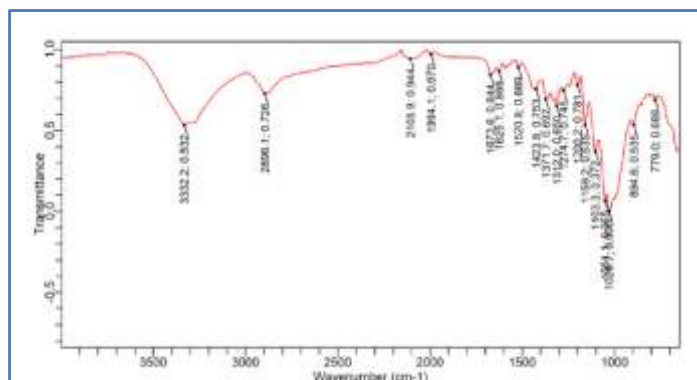
Figure 3.10 FTIR Spectrum of Bilastine Liquisolid Compacts

3.13.2 Differential Scanning Calorimetry (DSC)

The thermal behavior of pure Bilastine and Bilastine Liquisolid Compacts was determined using Differential scanning calorimetry. Pure Bilastine showed a sharp endothermic peak at 140.5 C, while the optimized batch of Bilastine Liquisolid Compacts with Propylene Glycol showed an endothermic peak at 44.3 C.
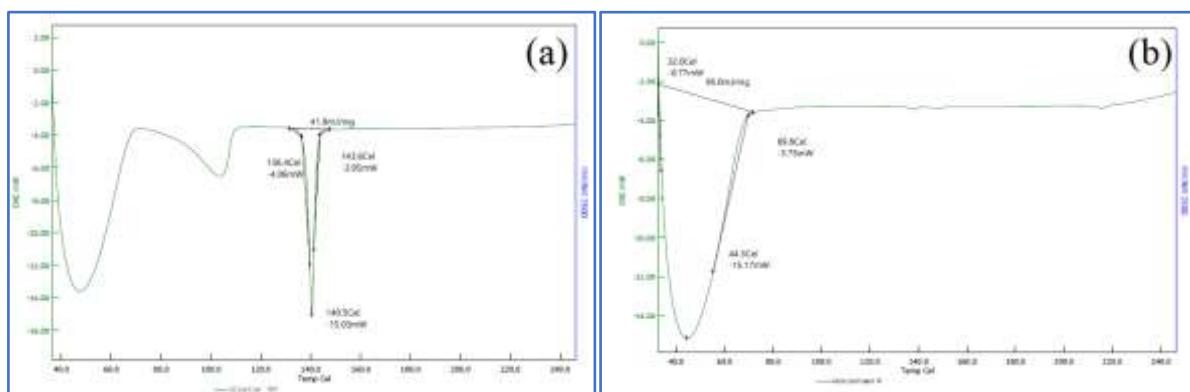

Figure 3.11 DSC Thermogram of (a)Pure Bilastine (b)Bilastine Liquisolid Compacts

3.13.3 Powder X-Ray Diffraction Studies (XRD)

Reduction of constructive reflection (specific intense peak) in the X-ray diffractogram of Liquisolid Compacts of Bilastine indicates that Bilastine has reduced crystallinity and might be partially converted into amorphous form.
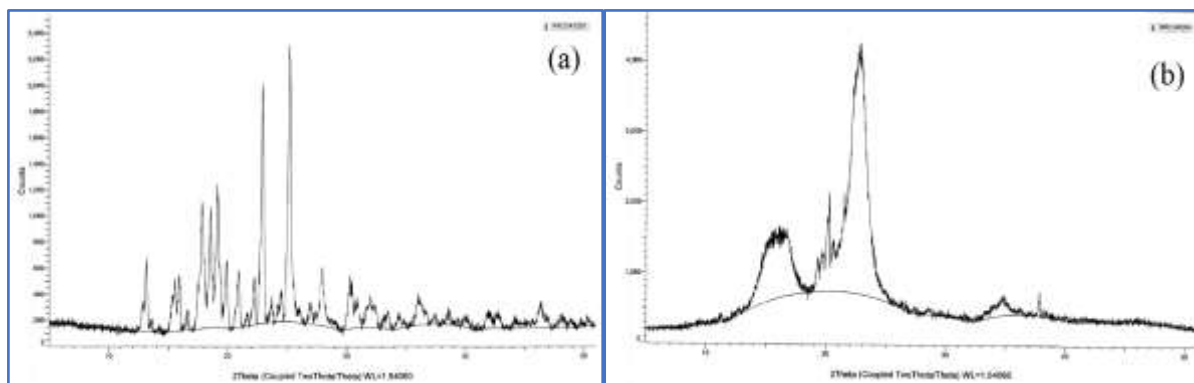

Figure 3.12 X-ray diffractogram of (a)Pure Bilastine (b)Bilastine Liquisolid Compacts

3.13.4 Particle size analysis

The size of pure drug particles and optimized Liquisolid Compacts was measured by Malvern instrument Mastersizer3000. In which the particle size of pure Bilastine drug was found to be 13.3 μm and Bilastine Liquisolid Compacts was found to be 162 μm. Data shows that particle size increase therefore flow property and compressibility was improve.
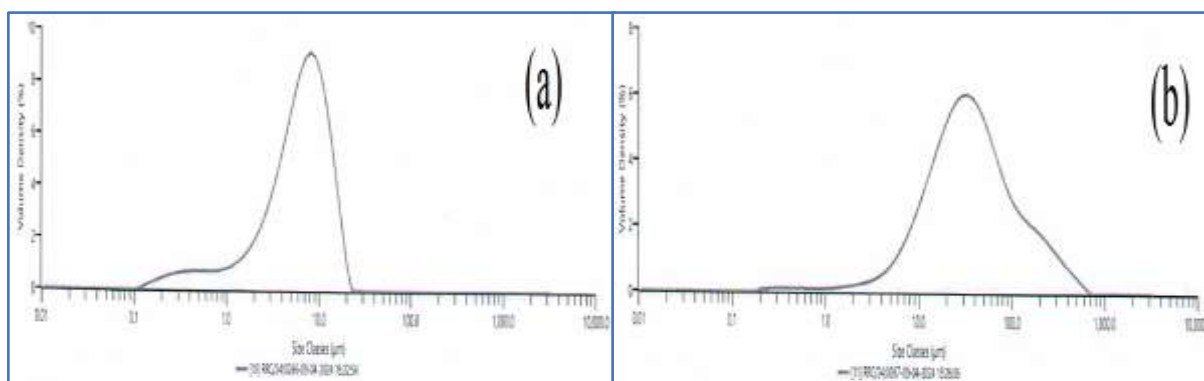

Figure 3.13 Particle size analysis of (a)Pure Bilastine (b)Bilastine Liquisolid Compacts

3.14 Stability Study

Accelerated stability study data of optimized batch is revealed that there were no significant change in physical parameters when stored at temperature and humidity condition of 40 ± 2 ℃ / 75 ± 5 % RH respectively and at room temperature for 30 days.

Table 3.14 Stability data of optimized batch of Liquisolid compacts

Condition	Angle of repose	% Drug content	Cumulative % drug release at 30 min	
Initial	24.43 ± 0.071	99.10 ± 0.20	**Time (min)**	**% CDR**
			0	0
			10	64.07
			20	78.94
			30	92.57
After 15 days				
40 ± 2℃/ 75 ± 5% RH	24.59 ± 0.075	98.75 ±0.02	0	0
			10	62.34
			20	76.61
			30	91.29
After 30 days				
40 ± 2℃/ 75 ± 5% RH	24.71 ± 0.040	98.08 ±0.16	0	0
			10	62.23
			20	76.48
			30	90.52

IV. CONCLUSION

The liquisolid compact technique can be effective way for dissolution rate improvement of water insoluble drug such as Bilastine. Propylene Glycol was used as a liquid vehicle. The liquid vehicle plays a contributing role in improving the dissolution profiles of a water insoluble drug in the liquisolid formulations, besides choosing a suitable liquid vehicle according to its solubility. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. Hence it can conclude that liquisolid compacts of Bilastine was prepared by using Propylene Glycol (1:1, 1:2, 1:3 ratio of drug and Propylene Glycol). Avicel PH102 as carrier used to give high absorption and Lactose as coating material used to cover the surface, to impact

flowability and provide greater release of drug among the formulation, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug Bilastine. This novel approach to the formulation may be helpful to improve oral bioavailability.This study demonstrated that the liquisolid technique effectively enhanced the dissolution rate of bilastine. These findings suggest that the liquisolid approach is a promising strategy for improving the solubility and dissolution properties of poorly soluble drugs like bilastine in pharmaceutical formulations.

Conflict of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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