

## Formulation development of Ezetimibe by using Soluplus and Co- Processed Acacia: tragacanth with Design Expert

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### ABSTRACT

Ezetimibe is an antihyperlipidemic drug that lowers cholesterol levels. The purpose of this study was to compare different amounts of solid dispersions and formulations using various carriers in order to improve the dissolution. The Design Expert software was used to perform Analysis of Variance (ANOVA), 3D surface plots, counter plots, optimization, and desirability for a two-level factorial. Sun pharma laboratories limited market product, Ezentia, was compared to the optimised formulation, F6. We compared amount of released that was considerably increased using the solid dispersion method. The dissolving characteristics of the improved formulation, F6, and the market tablet were found to be similar, with f1 and f2 values of 11.71 and 99.89. When the experimental data matched the expected values, the model predictability and validity were shown.

**Keywords:** Design Expert, Ezetimibe, formulation

### INTRODUCTION

The ezetimibe is a class II biopharmaceutical classification system medication with low solubility and high permeability. It is widely prescribed an antihyperlipidemic medication that aids in

cholesterol reduction. The ezetimibe's recent research formulations reported that *in-vitro* and *in-vivo* evaluation of solid lipid nanoparticles [1], improve the solubility and dissolution of two fixed dose combination formulations [2]. The water-soluble carriers have showed promise as a technique of improving bioavailability for

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most hydrophobic medicines by increasing dissolution rate observed [3]. The solubility of ezetimibe should be improved in the formulation since it melts quickly by sublimation technique were reported [4], Solid Lipid Nanoparticles (SLNs) were prepared using a high-speed homogenization technique with Glyceryl monostearate as the lipid carrier and Poloxamer 188 as the surfactant designed [5]. The ezetimibe was prepared with a surfactant, Pluronic 188 in various ratios for dissolution studies were shown significant drug released behavior [6,7]. The prepared kneading method with soluplus with good release, crospovidone was added as a disintegrant as reported [8]. By using Hydrophilic Matrix Polymers, metformin HCL and ezetimibe are utilized to treat type 2 diabetes mellitus [9]. The Solid Self-Emulsifying Drug Delivery System (SSEDDS) for ezetimibe to improve solubility and dissolution rate, reducing absorption variability and possibly increasing oral bioavailability of the poorly soluble medication [10]. The binary Ezetimibe (EZT) and Aspirin (ASA) pharmaceutical mixes to see if the presence of eutectic in this system affects EZT solubility shown beneficiary [11]. The researchers investigated ezetimibe-loaded

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solid Self-Nanoemulsifying Drug Delivery System (SNEDDS), Surface Modified Solid Dispersion (SMSD), and solvent evaporated solid dispersion to determine the optimal drug delivery technology with the highest oral bioavailability [12]. The tween 80, poly ethylene glycol 400 (PEG 400), and Propylene Glycol (PG) were used as non-volatile solvents to make Ezetimibe liquisolid compacts with acceptable flowability and compaction properties were reported [13]. The better control of dyslipidemia and hypertension, a gastro-bilayer floating matrix tablet with ezetimibe as an immediate layer and atenolol as a sustained release layer was developed [14]. Co-crystals have shown to be a viable tool for altering the physicochemical properties of Active Pharmaceutical Ingredients (APIs) through the use of a co-former to improve solubility and dissolution rate. A new method for the fabrication of amorphous Nano-Solid Dispersions (NSDs) of ezetimibe combination as poorly water-soluble drugs improves the in-vitro dissolution and in vivo performance of the poorly bioavailable drug Ezetimibe [15], increases its bioavailability [16], and improves the drug's performance in clinical trials [17]. The effect of HPC (hydroxypropyl

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cellulose) and Tween 80 on the physicochemical properties and oral bioavailability of ezetimibe-loaded solid dispersions reported [18] and the effect of HPC (hydroxypropyl cellulose) and Tween 80 on the physicochemical properties and oral bioavailability of ezetimibe-loaded solid dispersions [19]. To optimize diverse formulas, the factorial design and optimization allegedly utilised  $2^2$  and  $2^3$  factorial designs was reported [20-32] and developed many formulations are reported. The various approach by using Soluplus as carrier and additive used weakly water-soluble indomethacin, hot-melt extrusion processing could change the interactions between medicines, altering the microstructure and characteristics of supra molecular gels, mixtures that included amphiphilic polymers Soluplus, develop a topical nano micellar formulation of the immune suppressant drug everolimus using. The Soluplus®, a grafted copolymer of Polyvinyl Caprolactam-Polyvinyl Alcohol-Polyethylene Glycol (PVCL-PVA-PEG) for improved permeation through ocular epithelia with minimal or no irritation, resulting in increased ocular bioavailability reported [33-38]. The acacia and tragacanth are used to create a natural nanocarrier for the

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hydrophobic medication berberine that boosts its anti-inflammatory and antioxidant properties reported [39].

The goal of this study was to make ezetimibe solid dispersions by kneading, fusion method and solvent evaporation and to enhancement of dissolution rate. The using soluplus and hydrophilic compounds acacia and tragacanth co processed were combined with as per  $2^2$  level factorial designs. The investigation of tablet formulations with many parameters such as physical features, Fourier Transform Infrared spectroscopy (FTIR), and comparative examinations with commercially available tablets. The Design Expert software was used to do Analysis of Variance (ANOVA), 3D surface plots, counter plots, optimization, desirability, and optimization.

**MATERIALS AND METHODS**

Ezetimibe A gift sample by VKT company private limited, Srikakulam, Primellose a gift sample from IMDC Private limited, Mumbai, Soluplus, a gift sample from IMDC Private limited, Mumbai, Acacia purchased sample from Loba chemie pvt ltd Mumbai India, Gum tragacanth was purchased sample from Oxford Laboratory Mumbai, Talc purchased sample from Loba

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chemie pvt ltd Mumbai India, Magnesium stearate was purchased sample from Loba chemie pvt ltd Mumbai India.

***Solid dispersion by kneading method***

In the kneading procedure, mannitol (3gm) was wetted with enough water (5ml) in a mortar to make a paste, then the medicine was slowly added to the dough to make the drug: Ezetimibe: Mannitol (1:3). Kneading was done manually for 30 mints, with a small amount of water added as needed to keep the paste from becoming too thick. For one hour, the mixture was dried in a “50-60 ° C oven. After filtering through #20, the dried material was mashed with a mortar and pestle and designated as K1.

***Solid dispersion by fusion method***

“Mannitol was heated at 70 °C, for 15 min, molecular mobility of the drug and carrier molecules, which is greatest at the melting points of the two components of the dispersion, causes mixing that results in the formation of the molecular dispersion and the medication was dissolved in a molten polymer: Ezetimibe: Mannitol (1:2) in the fusion process (1:3). Cooled fast in an ice bath for up to 1 h by steady stirring for 10 to 15 min. This mixture was refrigerated for 12 h at 10-15 °C to solidify. The solid dispersion that resulted was scraped,

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crushed in the mortar, and sieved through 22#, resulting in F2. The material was preserved in a desiccator until they could continue their research.

***Solid dispersion by solvent evaporation method***

SD1 (1:0.5), SD2 (1:0.25), SD3 (1:0.75), SD4 (1:1), SD5 (1:2), accordingly, are the solid dispersion by Ezetimibe with soluplus comprising varied weight ratios. Place the drug in a mortar, add a few drops of dichloromethane, and thoroughly triturate. Later, the solvent was evaporated at room temperature, and the resulting residue was dried in a hot air oven for 1 hour at 60 ° C. The product was then stored in desiccators overnight, ground in a mortar, and passed through sieve no. # 22 until further research.

***Preparation of tablets***

The Tablets were made utilizing a wet granulation process and a 2<sup>3</sup> factorial design, as indicated in Table.1. The appropriate quantity of medication(10mg), soluplus (X1) higher (+) (4 mg) lower (-)(2.5 mg), acacia: tragacanth (X2) higher (+) (6 %) lower (4 %), Primellose(X3) higher(+) (4.5 %) lower (-) (2.5 %), lactose(156 to 171.5 mg ) were weighed accurately and mixed well, and water was

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added drop by drop to produce that damp mass. Wet granules were obtained by passing the bulk through filter #10. These granules are dried for 1 hour in a hot air oven at a temperature of 50 to 60 degrees Celsius. After passing through sieve no. 22#, dry granules with superdisintegrant, primellose, and Talc, as well as magnesium stearate. Using a single punch tablet compression machine, the blend equivalent to 200 mg of each tablet was compressed into a tablet.

### ***Evaluation of the tablets***

All tablets prepared were evaluated for active ingredient, Hardness, Friability, Disintegration time, Dissolution rate and Data analysis.

### ***Content of active ingredient***

The 5 tablets were weighed and pulverized precisely. In a boiling test tube, the tablet powder equivalent to 20 mg of ezetimibe was extracted with 6-10 ml of methanol. The methanolic extract was collected into a 100ml volumetric flask, diluted to 100 ml with pH 7.4 phosphate buffer and the drug content was determined using a UV spectrophotometric technique at 232 nm (ELICO Double beam SL 210).

### ***Formulation of Ezetimibe by using Soluplus Hardness***

Monsanto: Tablet Hardness Tester  
Monsanto Type hardness tester to determine the tablet's hardness. The tablet is sandwiched between the movable and stationary jaws. The screw knob is used to move the moving jaw and provide pressure on the tablet. The moment at which the tablet begins to fail. Scale is used to keep track of it. The hardness is measured in kilograms per square meter.

### ***Friability***

Friability was assessed using the Lab India Tablet Friability Tester (FT 1020), which involved taking 20 tablets and weighing them before placing them in the friabilator. For 4 min, rotate the drum at 25 rpm per min or 100 rpm. During this process, the tablet is dropped into plastic from a height of 6 inches and is subjected to mechanical shocks. The final weight of the tablets and the percent friability after 4 minutes.

### ***Disintegration time***

The Tablet Disintegrating Tester from Lab India was used to determine the disintegration time (DT 1000). One tablet is inserted in each tube, and the basket rack is positioned in a 1-L beaker of water as medium at 37 °C, with the tablets remaining 2.5 cm below the surface of the liquid on

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their upward movement and descending no closer than 2.5 cm from the bottom of the beaker. The basket assembly housing the tablets is moved up and down by a typical motor-driven system at a frequency of 28-32 cycles per minute. Note the time it takes for the tablet to completely vanish from the glass tube in this manner.

### ***Dissolution study***

The dissolution rate of ezetimibe from tablets was measured using a USP Type II (Paddle technique) dissolution test apparatus (LABINDIA, DS 8000) with phosphate buffer pH7.4 as the dissolution fluid at 37 °C and a stirrer speed of 50 rpm throughout the investigation. Each test sample (5ml) was taken at different intervals, such as 2.5 min, 5 min, 7.5 min, 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min. A UV-Vis Spectrophotometer was used to evaluate the samples at 232 nm (ELICO Double beam SL 210). Each time a sample of dissolving fluid was extracted, it was replaced with new fluid. The dissolution of each produced tablet was replicated four times (n=4).

### ***Comparative Studies***

To compare dissolution profiles, a simple model-independent technique employs a difference factor ( $f_1$ ) and a similarity factor

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( $f_2$ ). In the comparative studies of a new formulation, it is recommended to use the original brand of its medicine (in this case: Ezentia) with a new manufacturing date: 12/2020.

### ***Drug Excipient Compatibility Studies***

The Fourier Infrared Spectroscopy<sup>[1]</sup> (FTIR) spectra of samples was obtained on a Bruker ALPHA II FTIR system (Bruker OPTIK GmbH, Rudolf-Plank-Str, Germany) by using KBr disc method 2mg sample in 300 mg of KBr scanning range was 4000-600  $\text{cm}^{-1}$  and the resolution was 1 $\text{cm}^{-1}$ .

### ***Mean Dissolution Time (MDT)***

The MDT is the first statistical point in the cumulative dissolution process that accurately estimates the drug release rate. It measures the time it takes for the medication to dissolve. It accurately describes the rate of medication release. Greater drug retarding capacity is indicated by a higher MDT value. MDT equation, where M is the amount of drug dissolved between times  $t_i$  and  $t_{i-1}$ ,  $t_{\text{mid}}$  is the time at the midpoint between times  $t_i$  and  $t_{i-1}$ , and I is the number of dissolution samples.

$$\text{MDT}_{\text{in vitro}} = \frac{\sum_{i=1}^I t_{\text{mid}} \Delta M}{\sum_{i=1}^I \Delta M}$$

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### **Dissolution Efficiency (DE)**

The area under dissolution curve upto certain time 't', expressed as certain time 't' percentage area of rectangle described by 100 % dissolution in the same time. Most common way of assessment is to compare the time it takes for different quantities of active medication to be released into solution.

$$DE = \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \times 100$$

### **Statistical Analysis**

Data was analyzed using a first-order and zero-order kinetics model. Using design expert software (design expert version 13 stat-Ease Inc.com, USA), finding dissolution parameters such as PD<sub>5</sub> (percent drug dissolved in 5 min), t<sub>50</sub> (time required to dissolve 50 % of the drug), and DE<sub>10</sub> (dissolution efficiency) are subjected to ANOVA (Analysis of Variance), 3D Surface plots, Counter plots, Desirability, and other statistical parameters.

## **RESULTS**

The three independent factors such as X<sub>1</sub> concentration of Soluplus, X<sub>2</sub> concentration of Acacia: Tragacanth and X<sub>3</sub> concentration of Primellose were tested to 2 level factorial designs was shown in Table 1.

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#### **Dissolution behavior of different solid dispersions**

The solid dispersion in eight proportions: K1 release 100 % within 60 min, F1, F2 (40-60 min) and SD1, SD2, SD3, SD4, SD5 (40-60 min) were made and quantified according to the dissolution profile. Under phosphate buffer pH 6.8, pure drug release of more than 2 h and *in vitro* performance, Figure.2 depicts the situation.

#### **Drug excipients compatibilities**

The FTIR spectrums of pure drug and mixtures with various excipients shown in the Figure 1. The characteristic peaks at 1271 cm<sup>-1</sup>, 1220 cm<sup>-1</sup>, 1157 cm<sup>-1</sup>, 1118 cm<sup>-1</sup>, 1066 cm<sup>-1</sup>, 1013 cm<sup>-1</sup> (Due to C-F Stretch) 3239 cm<sup>-1</sup> (Due to O-H Stretch) 3239 cm<sup>-1</sup> (Due to N-H Stretch) 900 cm<sup>-1</sup>, 851 cm<sup>-1</sup>, 830 cm<sup>-1</sup> (Due to N-H Rocking) 1445 cm<sup>-1</sup>, 1271 cm<sup>-1</sup>, 1220 cm<sup>-1</sup> (Due to O-H) 1715 cm<sup>-1</sup>, 1613 cm<sup>-1</sup> (Due to C=O Stretch) 1613 cm<sup>-1</sup>, 1591 cm<sup>-1</sup>, 1509 cm<sup>-1</sup>, (Due to N-H Bending) confirming the drug structure.

#### **Tablet properties**

The data of tablet properties have been shown in a summarized comparative in Table 2. The hardness of all tablet formulations was found to be between 4 and 4.5 kg/cm<sup>2</sup>, with the highest hardness

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in (F7), indicating an enhancement in hardness-related binding properties of ezetimibe tablets.

The friability test is important for determining physical strength of tablets and ensuring that all the manufactured formulations could meet pharmacopeial criteria with a percentage weight loss of less than 1 %.

The disintegration time of all the formulation tablets is 10 min, F2 is 4 min and 20 sec, F3 is 5 min and 38 sec, F4 is 5 min and 58 sec, F5 is 5 min and 58 sec, F6 is 4 min and 28 sec, F7 is 4 min and 58 sec, and F8 is 8 min and 28 sec, respectively. All produced pills disintegrated in 4 min, 28 sec to 14 min, 20 sec. F2, F8 formulations with a higher level of Soluplus, Acacia: Tragacanth, and Primellose were found to have a high level of disintegration. Content active ingredient.

The medication concentration of all manufactured pills was between 95 and 97 percent. According to IP, the above quality control criteria of the prepared tablets meet the standard specification of uncoated tablets.

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**Dissolution in vitro**

Figure.3 demonstrates the in vitro dissolving profile of preparation tablets. In comparison to other formulations, the F1, F4 formulation releases 100 % of the medication in 2.5 min. The F1 formulation, which contains 2.5 mg Soluplus, 4 % Acacia: Tragacanth, and 2.5 percent Primellose, has a much superior dissolution performance. The F4, 4 mg Soluplus, 6 % Acacia Tragacanth, 4 % Primellose has a much superior dissolving performance. The F3 formulation, which contains 100 percent drug release, takes 60 min to complete. The F4 formulation provides 100 % drug release in 2.5 min. The F5 formulation provides 100 % medication release in 7.5 min. The F6 formulation provides 100 % medication release in 10 min. The F7 formulation provides 100 % medication release in 7.5 min. The F8 formulation provides 100 % medication release in 10 min. To increase variability, all formulations result in increased solubility.

**Model Dependent**

The correlation coefficient values in all situations were greater first order release kinetics rather than zero order release kinetics. “The drug release parameters,  $t_{1/2}$ ,  $DE_{10}$ ,  $PD_5$ ,  $DR_{90}$ ,  $MDT$ , and the dissolution



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rate constant ( $K_1$ ) were computed are shown in Table.3.

**Comparative studies**

The tests compared the optimized Ezetimibe tablet formulation F6 (100 % drug release 10 min) to the commercially available tablet (Ezentia). The value of  $f_1$  is

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11.713 and  $f_2$  was determined to be 99.89, indicating that two curves are equivalent. As a result, the dissolving profiles of the optimized formulation F6 and the market tablet are close or identical shown in Figure 5.

**Table 1.** Experimental design  $2^3$  Factorial Design

S.n	Factor	High (+)	Low (-)	Central point
1	X1: Soluplus(mg)	4	2.5	3.25
2	X2: Acacia: Tragacanth (%)	6	4	12.5
3	X3: Primellose (%)	4	4	6.5

**Table 2.** Physical properties of prepared Ezetimibe tablet formulations

S.no	Formulation	Hardness (Kg/cm <sup>2</sup> )	Friability (%)	Disintegration time (min .sec)	Drug content (%)
1	F1	4.2	0.767	10	95.30
2	F2	4.4	0.789	14	96.18
3	F3	4.1	0.994	5.38	95.97
4	F4	4.3	0.691	5.58	97.58
5	F5	4.1	0.690	5.58	97.13
6	F6	4.2	0.674	4.28	96.190
7	F7	4.4	0.794	4.58	97.178
8	F8	4.3	0.930	8.28	97.973

**Table 3.** Dissolution parameters of prepared Ezetimibe tablet formulation

Formulation	PD <sub>5</sub>	t <sub>1/2</sub> (min)	DE <sub>10</sub>	Drug release 90%	MDT	K <sub>1</sub> (min <sup>-1</sup> )	'r' value 1 <sup>st</sup> order	'r' value zero order
F1	100	2	50	5	26.18	1.8424	.893	0.745
F2	15.85	5	23.23	54	35.58	0.1013	0.933	0.921
F3	9.6	25	8.287	49	41.39	0.0617	0.967	0.873
F4	100	9.1	50	2	26.18	1.8424	0.993	0.890
F5	93.55	6	80.85	5	30.95	0.198	0.996	0.874
F6	80.1	3	69.1	8	31.50	0.2644	0.709	0.928
F7	76	2	73.37	7	31.30	0.0524	0.948	0.929
F8	79	4	76.9	6	33.42	0.344	0.934	0.830

**Table 4.** Analysis of variance (ANOVA) of various responses

Percentage Drug Dissolve in 10min (DE <sub>10</sub> )						
Source	Sum of square	Df	Mean Square	F- Value	P-Value	Remarks
Model	3557.76	1	3557.76	6.17	0.0348	Significant
c-Primellose	3557.76	1	3557.76	6.17	0.0348	
Residual	5193.62	9	577.07			
Lack of Fit	5193.62	7	741.95			
Pure Error	0.0000	2	0.0000			
Cor Total	8751.37	10				
Percent Drug Dissolve in PD <sub>5</sub>						
Model	5.82	7	0.8311	16.69	0.0207	Significant
A-Soluplus	0.0249	1	0.0249	0.4994	0.5307	
B- Acacia:Tragacanth	0.0769	1	0.0769	1.54	0.3024	
C- Primellose	1.38	1	1.38	27.75	0.0133	
AB	2.33	1	2.33	46.80	0.0064	
AC	0.0576	1	0.0576	1.16	0.3608	
BC	0.0145	1	0.0145	0.2918	0.6266	
ABC	1.93	1	1.93	38.77	0.0084	
Residual	0.1494	3	0.0498			
Lack of Fit	0.1494	1	0.1494			
Pure Error	0.0000	2	0.0000			

Cor Total	5.97	10				
<b>Time require to 50% drug release (50%)</b>						
Model	408.41	7	58.34	324.13	0.0003	Significant
A-Soluplus	24.15	1	24.15	134.17	0.0014	
B-Acacia:Tragacanth	72.60	1	72.60	403.33	0.0003	
C-Primellose	85.15	1	85.15	473.05	0.0002	
AB	24.15	1	24.15	134.17	0.0014	
AC	17.70	1	17.70	98.34	0.0022	
BC	113.25	1	113.25	629.16	0.0001	
ABC	71.40	1	71.40	396.66	0.0003	
Residual	0.5400	3	0.1800			
Lack of Fit	0.5400	1	0.5400			
Pure Error	0.0000	2	0.0000			
Cor Total	408.95	10				

**Table 5.** Comparison of predicted and experimental responses for optimization

Parameter			
Independent Variables	X <sub>1</sub>	X <sub>2</sub>	X <sub>3</sub>
Composition(mg)	24.15	72.60	85.15
Response	DE <sub>10</sub>	PD <sub>5</sub>	T <sub>50</sub>
Predicted value	63.623%	87.1442 %	5.670 min
Experimental value	61.23%	85.132%	5.321 min
Predicted error (%)	-43.10	-52.26	-20.36

**Data Analysis**

For statistical optimization, the three responses Y1 (DE10), Y2 (PD5), and Y3 (T50) were chosen and fitted to a specified model. Tables.4 summarize Design Expert software was used to compute DEV, Mean, C.V percent, Adj R-squared, Pred R-square, Adeq accuracy, BIC, AICc, -2 log likelihood, F values, and P values, DE10, PD5, and T50 were the dependent responses measured, and two parameters DE10, PD5, and T50 were used as mathematical modeling to confirm the

experimental design using a polynomial equation.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3$$

Where Y= Is the dependent variable,  $\beta_0 =$  Is the mean response of 8 runs and  $\beta_1 \beta_2 \beta_3$  is the estimated coefficient for corresponding factor X<sub>1</sub> each represent the average result of changing 1 factor at a time from it low to high value. The interaction time (X<sub>1</sub>X<sub>2</sub>, X<sub>1</sub>X<sub>3</sub>, X<sub>1</sub> X<sub>2</sub> X<sub>3</sub>) defeat the changes in the response when three factors simultaneously change.

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**a. Responses DE<sub>10</sub> (Y1)**

The DE<sub>10</sub> analysis of variance yielded a statistically significant result of  $p < 0.0348$ , as shown in Table.4. The model equation DE<sub>10</sub> can be used to describe the parameter DE<sub>10</sub> = -48.84805 + 14.05892 X<sub>3</sub>. The presence of a positive sign for X<sub>3</sub> suggests that the concentration of Primellose (superdisintegrant) is increasing, as is the concentration of DE<sub>10</sub>. DE<sub>10</sub> has an R-square of 0.4065, showing that the independent and dependent variables are well correlated. The 'F' valued for DE<sub>10</sub> was found to be of model 6.17 and independent variable X<sub>3</sub> = 3557.76 and other statistical parameters such as Adj.R<sup>2</sup> = 0.3406, PRESS = 7286.11, Adeq precision = 4.1176, BIC = 103.74, AICc = 104.45, - 2 log likelihood = 98.95, Mean = 42.53, Std. DEV = 24.02, C.V% = 56.48, Pred R square. = 0.1674.

**b. Responses PD 5 (Y2)**

The PD<sub>5</sub> model's analysis of variance yielded a statistically significant result of  $p < 0.0207$ . Table.4 shows the results of the PD<sub>5</sub> analysis of variance. The model equation can be used to describe the parameter PD<sub>5</sub>. PD<sub>5</sub> = + 59.51651 - 17.22639 X<sub>1</sub> - 5.92350 X<sub>2</sub> - 6.71609 X<sub>3</sub> + 1.77912 X<sub>1</sub> X<sub>2</sub> + 2.10804 X<sub>1</sub> X<sub>3</sub> + 0.723844 X<sub>2</sub> X<sub>3</sub> - 0.218350 X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> - 0.218350 X<sub>1</sub> X<sub>2</sub> X<sub>3</sub>.

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The presence of a positive sign for X<sub>3</sub> indicates that the concentration of primellose (superdisintegrant) is increasing, as is the percent drug dissolve in 5 min (PD<sub>5</sub>). The R-square score of 0.9750 for PD<sub>5</sub> indicates that the independent and dependent variables are well correlated. The 'F' valued for PD<sub>5</sub> was found to be of model 16.69 and independent variable X<sub>1</sub> = 0.0249, X<sub>2</sub> = 0.0769, X<sub>3</sub> = 1.38 and other statistical parameters such as Adj.R<sup>2</sup> = 0.9165, Adeq precision = 12.3125, BIC = 3.11, AICc = 71.93, - 2 log likelihood = -16.07, Mean = 3.92, Std. DEV = 0.2232, C.V% =, Pred R square. = -4.8982.

**c. Response T<sub>50</sub> (Y3)**

The T<sub>50</sub> analysis of variance model yielded a statistically significant  $p < 0.0003$  result. Table.4 shows the T<sub>50</sub> analysis of variance. The model equation can determine the attractiveness of the parameter T<sub>50</sub>. Y<sub>3</sub> = -357.97543 + 86.97778 X<sub>1</sub> + 41.47222 X<sub>2</sub> + 49.22222 X<sub>3</sub> - 9.78889 X<sub>1</sub> X<sub>2</sub> - 11.95556 X<sub>1</sub> X<sub>3</sub> - 5.56944 X<sub>2</sub> X<sub>3</sub> + 1.32778 X<sub>1</sub> X<sub>2</sub> X<sub>3</sub>. The positive indication for X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> suggests that the concentration of Soluplus, Acacia: Tragacanth, Primellose (superdisintegrant) increases by 50 % in t<sub>50</sub>. The R<sup>2</sup> value of 0.9987 for T<sub>50</sub> indicates that the independent and

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dependent variables are well correlated. The 'F' value for  $T_{50}$  was found to be of model 324.13 and independent variable  $X_1=24.15$ ,  $X_2=72.60$ ,  $X_3=85.15$  other statistical parameters such as Std. DEV =0.4243, Mean =7.15, C. V % =5.94, PRESS=127.20, -2 log likelihood =-1.94, Adj R-squared=0.9956, Pred R-squared=0.6890, Adeq precision=63.5678, BIC=17.25, AICc=86.06.

The contour and response surface as a function of three factors at the same time, with all other parameters held constant, are more useful in understanding both the individual and interaction effects of three components. Figure.4 is shown contour and response surface plots, as well as the desirability, overlay plot, and optimized plots of all formulation components.

### **Optimization**

The optimal formula had a greater desirability concern (0.72465), indicating that the formulation was suitable. Each answer is fine-tuned to the desired target point (Y1) to obtain product,  $DE_{10}$  was set to be the objective,  $PD_5$  (Y2) was set to be the target, and  $T_{50}$  (Y3) was set to be maximized. Table.5 shows three independent variables for optimizing in

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accordance with response goals by using a desire function, with  $X_1$ ,  $X_2$ , and  $X_3$  being 3.25 mg, 5 %, and 6.5 percent for accordingly with a corresponding desirability function of 0.72645. The statistical optimization was performed on the optimized formulation to ensure that all of the dissolution parameters were met, allowing the theoretical prediction to be confirmed. In vitro percentage drug release  $DE_{10}$  was found to be 61.23 percent,  $PD_5$  was found to be 85.124, and  $t_{50}$  was found to be 85.132. Table.8 shows the results for observed and close agreement with model prediction.

For relative errors percent between anticipated and experimental values were determined, and the results were -3.908 percent, -2.363 percent, and -6.155 percent, respectively. The experimental values matched the anticipated values, demonstrating the model's predictability and validity.  $DE_{10}$  was 61.23 percent,  $PD_5$  was 85.123 percent, and  $T_{50}$  was 5.321 minutes in the optimized formulation. The optimal formulation's drug release follows a first-order kinetic model. The percentage prediction error was used to compare the predicted value to the experimental value in order to measure the prediction's dependability and accuracy.

## DISCUSSION

The dissolution behavior of different solid dispersions good drug release property than pure drug release of more than 2 hours and in vitro performance shown in Figure 2. The FTIR spectrum of pure drug and mixtures with various excipients were similar it indicates no chemical interaction between the drug and excipients are shown in Figure.1. The physical properties of tablets such as hardness, friability and drug content and disintegration time fulfill official specifications as per IP shown in Table.2. The order of drug dissolution of various formulations is displayed in

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ascending order shown in Figure.3,  $F2 < F3 < F6 < F8 < F7 < F5 < F1 < F4$ . The comparison of dissolution profiles of the optimized formulation (F6) and the market tablet are identical are shown in Figure.5. The dependent variables such as DE<sub>10</sub>, PD 5 and T<sub>50</sub> are shown analysis of variance yielded a statistically significant shown in Table.4. The higher the desirability value, the better the formulation and the optimal equations can be obtained directly from the desire function response surface plots shown in Figure.4.

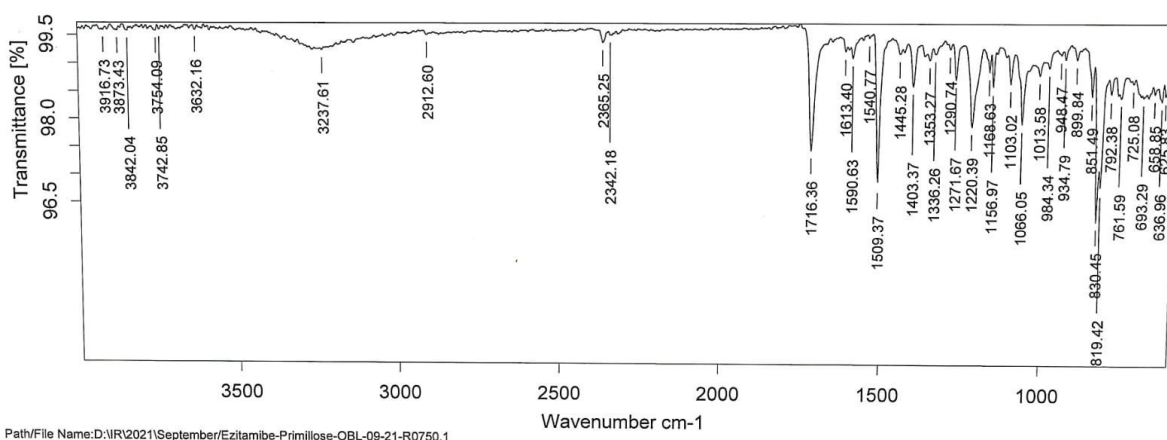
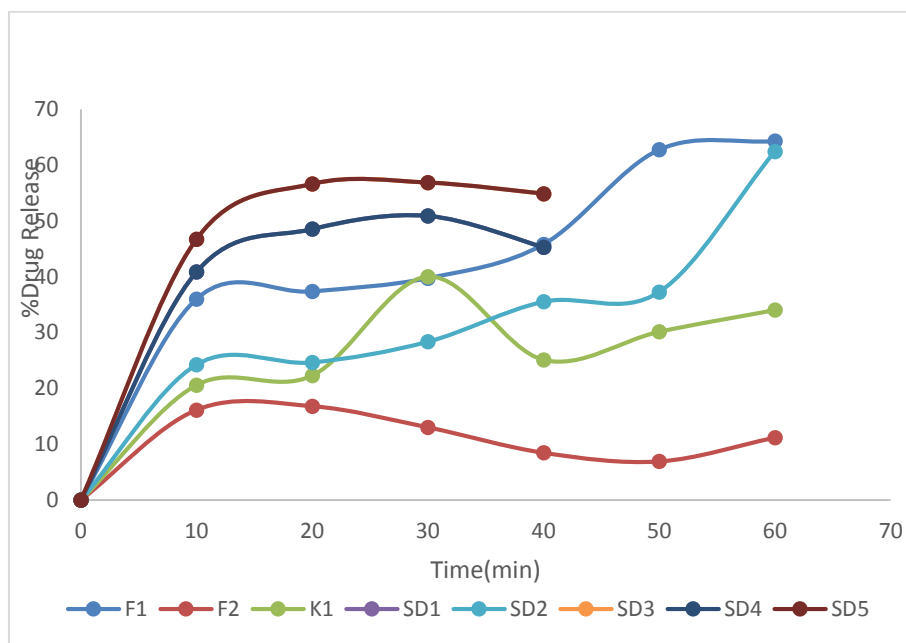


Figure 1. FTIR of Ezetimibe



**Figure 2.** Mean dissolution profile of Ezetimibe drug and its solid dispersions(n=4)(SD±0.125).



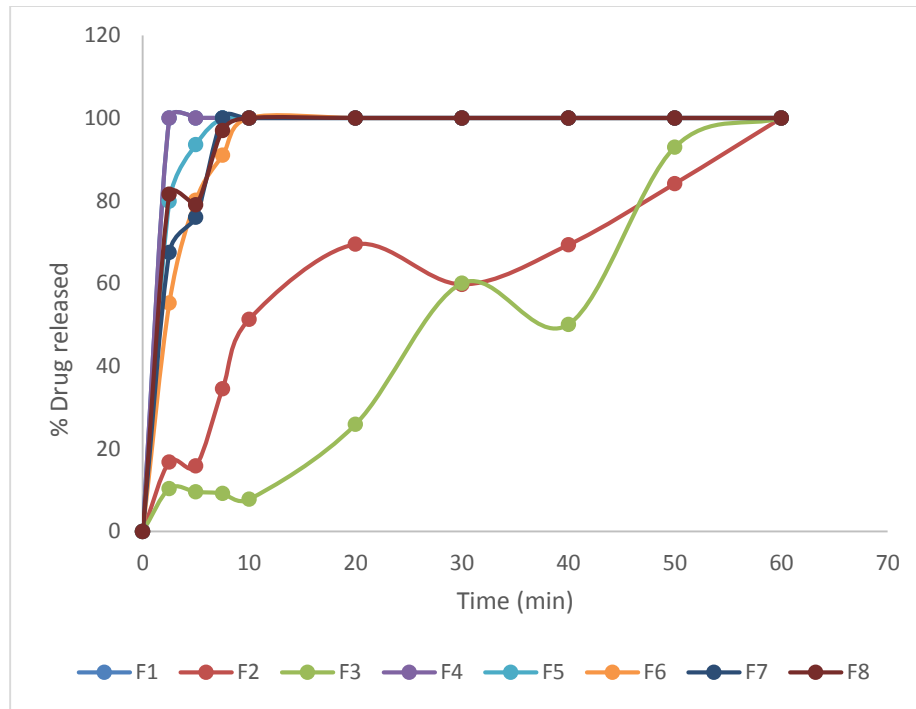
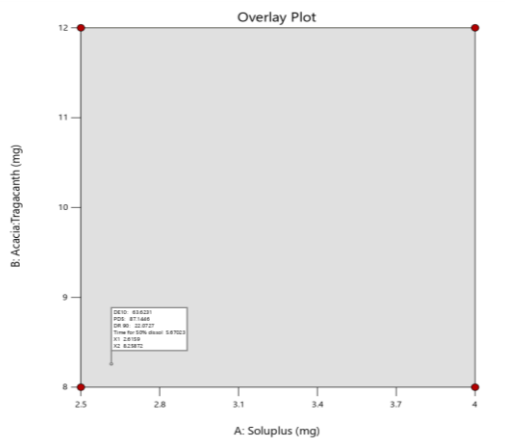
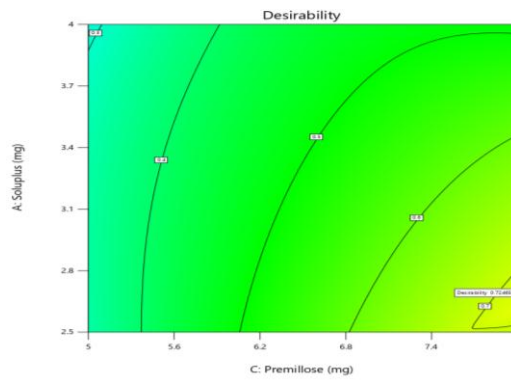


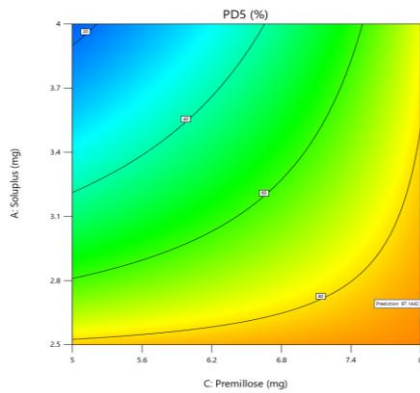
Figure 3. Mean dissolution profile of ezetimibe tablet formulation F1-F8(n=4)(SD±0.325).



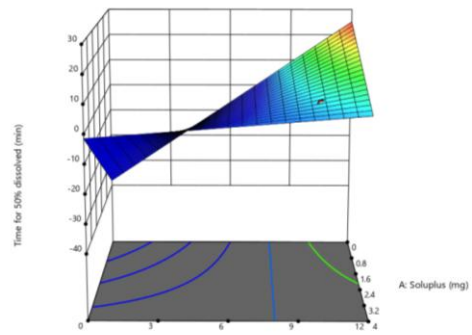
A. Overlay plot for DE<sub>10</sub>, PD<sub>5</sub>, t<sub>50</sub>



B. Desirability plot

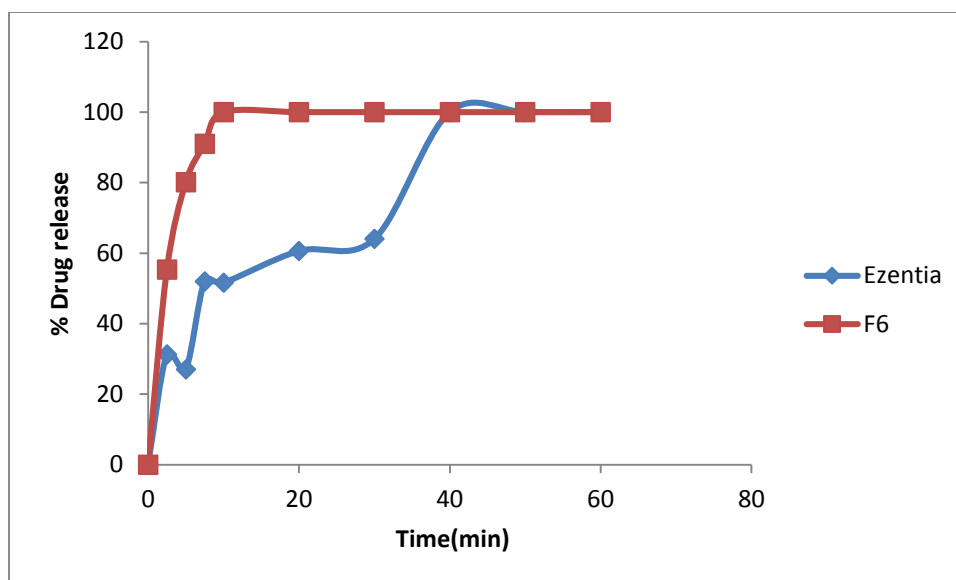


C. Contour plot for PD<sub>5</sub>



D. 3D Surface plot for t<sub>50</sub>

Figure.4 Overlay, Desirability, Counter plot 3D, Surface plot T50.



**Figure 5.** Comparative dissolution profile of optimised formulation (F6) and marketed tablets (Ezentia)(n=4)(SD±0.229).

## CONCLUSION

The current study successfully conceived and developed 2<sup>3</sup> factorial designs to optimize ezetimibe formulation. When solid dispersions were compared to pure medication with various carriers, the dissolution of the solid dispersions was dramatically improved. The FTIR spectra of pure drug and combinations with diverse excipients were comparable, indicating that the drug and excipients have no chemical

interaction. The manufactured tablets' (F1 to F8) quality control characteristics meet the standard IP specification for uncoated tablets. The F1 formulation, which contains 2.5mg of Soluplus, 4 % Acacia: Tragacanth and 2.5 percent Primellose as a considerably quick dissolving performance, and the F4 formulation, which contains 4mg of Soluplus, 6 % Acacia: Tragacanth, and 4 % Primellose as a significantly rapid dissolution performance. The order of medication

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dissolution of diverse formulations is rising

**F2 > F3 > F6 > F8 > F7 > F5 > F1 > F4.**

The dissolution characteristics of optimized formulation (F6), (100 % drug release in 10 min) and market tablets are comparable or identical. DE10, PD5, and T50 had statistically significant  $p < 0.0001$  in ANOVA (Analysis of Variance). To verify the theoretical prediction, statistical optimization was performed on the optimized formulation to satisfy all of the dissolution parameters. The optimal formulation's drug release follows a first-order kinetic model.

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#### REFERENCES

[1]. Azin Jahangiri *et al.* Evaluation of physicochemical properties and *in vivo* efficiency of atorvastatin calcium/ezetimibe solid dispersions. *Eur.J. of Pharma. Sci.* 2016; 82: 21–30.

**Formulation of Ezetimibe by using Soluplus**

[2]. Amanda Solaiman *et al.* Application of general multilevel factorial design with formulation of fast disintegrating tablets containing croscaremellose sodium and Disintequick MCC-25. *Int. J. Pharmaceutics.* 2016; 501(1-2): 89-95.

[3]. Thomas Taupitz, Jennifer B. Dressman, Sandra Klein. New formulation approaches to improve solubility and drug release from fixed dose combinations: Case examples pioglitazone/glimepiride and ezetimibe/simvastatin. *Eur. J Pharma. Biopharma.* 2013; 84(1): 208-18.

[4]. Ashis Kumar mehatha, vidyadhara suryadevara *et al.* Formulation and optimization of Ezetimibe containing solid dispersions using Kollidon VA64. *Turk J Pharm Sci.* 2014; 11(2): 113-26.

[5]. Neelima Rani T, Indira Muzib Y. Design and Evaluation of Ezetimibe Rapidmelts by Direct Compression and Sublimation Methods. *Asian J. Pharmaceutics.* 2016; 10(4): 518.

[6]. Mayuri Desai, Divya Shah, Jayant Sarolia, Pranav Shah *et al.* Formulation and evaluation of ezetimibe loaded solid lipid nanoparticles. *Indo Am. J. Pharma. Res.* 2017; 7.

[7]. Tripura Sundari P and Mounika P *et al.* Formulation and evaluation of smedd

**Ramarao et al.**

containing ezetimibe by employing arachis oil as oil and Tween 80, PEG 400 as surfactant system. *Eur. J. Bio. Med. Pharma. Sci.* 2018; 5(7): 431-40.

[8]. Sancheti P. P, Karekar P *et al.* Preparation and physicochemical characterization of surfactant based solid dispersions of ezetimibe. *Pharmazie.* 2019; 64: 227–31.

[9]. Viswanadh kunam, Vidyadhara suryadevara *et al.* Solubility and dissolution rate enhancement of ezetimibe by solid dispersion and pelletization techniques using soluplus as carrier. *Int J App Pharm.* 2019; 11(4): 57-64.

[10]. Asfia Kauser, Fatima Nasreen *et al.* Formulation and in vitro evaluation of anti-diabetic bi-layered tablet-Metformin and Ezetimibe. *IOSR J. Pharmacy Bio. Sci.* 2018; 13(2).

[11]. Ajit M. Chanale, Manish A. Raskar *et al.* Formulation and evaluation of solid self-emulsifying drug delivery system of Ezetimibe. *Der Pharmacia Let.* 2016; 8 (11): 164-76.

[12]. Azin Jahangiri, Mohammad Barzegar-Jalali *et al.* Physicochemical characterization of atorvastatin calcium/ezetimibe amorphous nano-solid dispersions prepared by electro spraying

**Formulation of Ezetimibe by using Soluplus** method. *Artificial Cells, Nanomed Bio.* 2017; 45(6): 1138–45.

[13]. Rehmana Rashid, Dong Wuk Kim *et al.* Effect of hydroxypropyl cellulose and Tween 80 on physicochemical properties and bioavailability of ezetimibe-loaded solid dispersion. *Carbohydrate Polym.* 2015; 130: 26-31.

[14]. Arulkumaran K.S.G, Padmapreetha J *et al.* Enhancement of solubility of ezetimibe by liquisolid technique. *Int. J. Pharma. Chem. Anal.* 2014; 1(1): 14-38.

[15]. Ranjit Prasad Swain, Avasarala Nagamani *et al.* Formulation and evaluation of gastro-bilayer floating tablets of Ezetimibe as immediate release layer and Atenolol as sustained release layer. *Ind.J. Pharma. Edu. Res.* 2019; 53(2).

[16]. Jyothi Bhandari', Neha Kanswami, Lakshmi P.K *et al.* Nano co-crystal engineering technique to enhance the solubility of Ezetimibe. *J Young Pharmacists.* 2020; 12.

[17]. Patil Dhananjay, Bachhav Rakesh, Gosavi Dipika *et al.* Formulation and evaluation of Ezetimibe lyophilized dry emulsion tablets. *J. Drug Deliv Thera.* 2019; 9(3): 630-35.

[18]. Nisha Thakre, Kapil Khatri *et al.* Development and characterization of solid

**Ramarao et al.**

dispersion of Ezetimibe by using solvent evaporation method. *Asian J Phar. Pharma.* 2016; 2(2): 44-49.

[19]. Sateesh Kumar Vemula Saritha Aila *et al.* Formulation and evaluation of Ezetimibe liquisolid tablets: An approach to enhance the dissolution rate. *Bri. J. Pharma. Res.* 2015; 7(6): 440-50.

[20]. Rehmana Rashid Dong Wuk Kim, Abid Mehmood Yousaf *et al.* Comparative study on solid self-nanoemulsifying drug delivery and solid dispersion system for enhanced solubility and bioavailability of ezetimibe. *Int. J. Nanomed.* 2015; 10; 6147.

[21]. Carlos Torrado-Salmerón, Víctor Guarnizo-Herrero, Teresa Gallego-Arranz *et al.* Improvement in the Oral bioavailability and efficiency of new Ezetimibe formulations: Comparative study of a solid dispersion and different micellar systems. *Pharmaceutics.* 2020; (12): 617.

[22]. Chowdary K.P.R, Tarakaramarao CH, Factorial study on the evaluation of formulation variables on the dissolution rate of Etoricoxib tablets. *Asian J. Chem.* 2011; 23(3): 958-60.

[23]. Inayat Bashir Pathan, Prakash Ram Shingare, Pritish Kurumkar. Formulation design and optimization of novel mouth dissolving tablets for venlafaxine

**Formulation of Ezetimibe by using Soluplus**

hydrochloride using sublimation technique. *J Pharmacy Res.* 2013; 6: 593-98.

[24]. Mohamed Abbas Ibrahim, Amal El Sayeh F. Abou El Ela. Optimized furosemide taste masked orally disintegrating tablets. *Saudi Pharm. J.* 2017; 25: 1055–62.

[25]. Ramarao CHT, Chowdary KPR. Optimization of irbesartan tablet formulation by 2<sup>3</sup> factorial design. *World J. Pharma. Sci.* 2015; 4(02): 277-85.

[26]. Ramarao CHT, Gunta. Preethi. Statistically optimization and formulation development of bromofenac sodium ophthalmic drug delivery. *Suranaree J. Sci. Technol.* 2022; 29(6):070060; 1-10.

[27]. Sameer G. Late and Ajay K. Banga. Response surface methodology to optimize novel fast disintegrating tablets using  $\beta$  Cyclodextrin as diluent. *AAPS Pharm Sci Tech.* 2010; 11(4): 1627.

[28]. Srinivasa Rao.B, Ramarao CHT. Design and characterization of Alfuzosin Hcl gastroretentive floating matrix tablets employing HPMC K100 M. *Indian Drugs.* 2018; 55 (11): 71-73.

[29]. Srinivasarao B and Vijayaratna J. Sustained release matrix tablets of Diclofenac sodium employing Kollidon

**Ramarao et al.**

SR, PEG 6000, Lactose mono hydrate and Eudragit S100 in colon target. *Indian Drugs*. 2017; 54(10): 38-43.

[30]. Challa TR, Reshma K. Experimental design statistically by Design Expert software: A model poorly soluble drug with dissolution enhancement and optimization. *Inter J Drug Deliv Technol*. 2022; 12(3):1367-75.

[31]. Ch T, Madhuri S. Statistically 2 level factorial by design expert: *In-vitro* design and formulation of Levitiracetam extended release tablets. *Indian J Pharma. Edu. Res*. 2022; 56(4):1-8.

[32]. RamaraoCHT, Somireddy. Madhuri. *In vitro* design and formulation of Levitiracetam extended release tablets, *Res J. Pharm. Tech*. 2022; 15(8):1-4.

[33]. Semjonov K, Lust A, Kogermann K, Laidmäe I, Maunu SL, Hirvonen S-P, *et al*. Melt-electro spinning as a method to improve the dissolution and physical stability of a poorly water-soluble drug. *Eur. J. Pharma. Sci*. 2018; 121:260–8.

[34]. Mehra N, Aqil M, Sultana Y. A grafted copolymer-based nanomicelles for topical ocular delivery of everolimus: Formulation, characterization, *ex-vivo* permeation, *in-vitro* ocular toxicity, and

**Formulation of Ezetimibe by using Soluplus**

stability study. *Eur. J Pharma. Sci*. 2021; 159: 105735.

[35]. Altamimi MA, Neau SH. Investigation of the *in vitro* performance difference of drug-soluplus® and drug-PEG 6000 dispersions when prepared using spray drying or lyophilization. *Saudi Pharma. J*. 2017; 25: 419–39.

[36]. Zhang J, YangW, VoAQ, Feng X, YeX, KimDW *et al*. Hydroxypropyl methyl cellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. *Carbohydrate Polym*. 2017; 177: 49–57.

[37]. Boleslavská T, Světlík S, Žvátora P, Bosák J, Dammer O, Beránek J, *et al*. Preclinical evaluation of new formulation concepts for abiraterone acetate bioavailability enhancement based on the inhibition of pH-induced precipitation. *Eur. J. Pharm. Biopharm*. 2020; 151:81–90.

[38]. LiM. Drug dissolution enhancement via nano composites vs. amorphous solid dispersion prepared by nano extrusion for dissolution enhancement. *Eur J Pharm Biopharm*. 2017; 119: 68-80.

**Ramarao et al.**

[39]. Bakshi, J., Mehra, M., Grewal, S. *et al.* Berberine loaded Tragacanth-Acacia gum nanocomplexes: Synthesis, characterization and evaluation of *in vitro*

**Formulation of Ezetimibe by using Soluplus**

anti-inflammatory and antioxidant activity. *J Clust Sci* .2022.