

Formulation and Evaluation of Nano Co-Crystal Based Oral Disintegrating Tablet of Ezetimibe

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ABSTRACT

Background: Low solubility, poor permeability, and hepatic drug degradation are the primary factors responsible for the poor bioavailability issues of orally administered drugs. Ezetimibe, a biopharmaceutics classification system (BCS) Class II anti-cholesteremic drug, has a bioavailability between 35% and 65% due to its substantial intestinal and first-pass metabolism. **Objectives:** An alternative method for drug administration is to be attempted on an orally disintegrating Ezetimibe tablet to avoid low bioavailability, as mentioned earlier. **Materials and Methods:** The solubility issues of the drug were tackled by converting the drug into nano co-crystals using nicotinamide as a cofomer utilizing the solvent anti-solvent method, followed by spray drying. The formulations were optimized using a custom experimental design. The optimum nano co-crystal formulation was converted into an orally disintegrating tablet using crospovidone as a super disintegrating agent and evaluated. **Results:** Nano co-crystals solubility was 0.030 to 0.049mg/mL. The release of the drug in a pH of 6.8 phosphate buffer was found to be 0.27.10±0.011 to 30.02±0.003%. Compatibility studies by FTIR confirm the absence of the drug's reaction with the excipients. X-ray, as well as DSC, indicated reduced Ezetimibe's crystalline nature. The disintegration time of ODT was marked down as 28 sec. ODT's *in vitro* release profile in PBS p 6.8 reveal a 20-fold increase in drug release compared to the pure drug. **Conclusion:** Therefore, ODTs containing nano co-crystals of Ezetimibe could provide a better alternative to improve solubility and the dissolution rate, which may enhance the bioavailability.

Keywords: Ezetimibe, Micro crystalline cellulose, Oral Disintegrating Tablets, Nano co-crystals, Fast release, Dissolution.

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INTRODUCTION

The pharmacy journey has advanced from mortar and pestle to highly advanced complicated equipment for the better dosage form. Even with many options for the route of administration, patients prefer the oral route of administration as the accepted one. Patient compliance, preference, convenience of administration, precise dose, affordability, and extended shelf-life of the medication all contribute to the wide acceptability of oral drug administration.¹

Orally Disintegrating Tablets (ODTs) are a viable option for addressing pediatric, geriatric uncooperative conditions. They seem like conventional tablets; however, they have one clear distinction: they dissolve quickly in the mouth and hence do not require to be swallowed. When ingesting the drug, no

liquid is necessary, which is a major advantage. The first-pass metabolism of the liver is eluded if the medicine is dissolved within the buccal cavity instead of being digested. Adverse effects from metabolites synthesized by liver enzymes can be minimized by pre-gastric absorption.²

The adequate water solubility of API is one of the prime requirements in preparing ODTs. One of the most critical factors for achieving the optimum medication concentration in systemic circulation is solubility, which is proportional to the therapeutic effectiveness of a drug.² Many pharmaceutical firms have reported that 40 percent of active new chemical entities abbreviated as NCEs are water soluble only to a limited extent and poorly absorbed following oral administration. Poorly water-soluble medicines may require substantial doses to obtain optimum plasma concentrations following oral administration. Especially Biopharmaceutics Classification System, abbreviated as BCS, class II and class IV medications, has the threat of poor bioavailability due to solubility concerns.³

Improving solubility is a significant part of oral administering drugs, leading to an improved dissolution rate. Numerous



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technologies have emerged to overcome the issues of insoluble compounds, which have made a significant change. These approaches include chemical modifications such as pH adjustment, co-crystallization, co-solvency, physical modification such as a decrease in particle size, transformation in crystal habit and complexation, and dispersal of the drug in carriers.

Among these techniques, co-crystallization is opted as the technique and nano co-crystals as the formulation approach to alter the solubility of the BCS class II drug Ezetimibe. Solids are crystalline and composed of single-phase materials with two or more distinct molecular and ionic components (drug and cofomer, the latter being chemically inactive). They are typically in a stoichiometric ratio of not solvates or simple salts, known as co-crystals. Pharmaceutical co-crystals alter/improve physical properties, such as solubility, hygroscopicity, compaction behaviour, and dissolution.⁴

Co-crystallization combined with a nanosization procedure may lead to nano co-crystals with enhanced saturation solubility because of the considerable increase in surface area, which may result in an improvement of the rate of dissolution as well as bioavailability.⁵ Nano co-crystals are pure solid particles that are crystalline in form and range in sizes between 10 and 400 nm.^{6,7}

Hyperlipidemia is a medical disorder caused by an abnormal elevation in blood lipids, including lipoproteins, cholesterol, and triglycerides. It is the primary cause of cardiovascular diseases worldwide due to the development of atherosclerotic plaque, which blocks normal blood flow to the extremities, brain and heart. In the present era, countless studies have demonstrated an association between hyperlipidemia and cardiovascular illnesses such as stroke, coronary artery disease, ischemia, and peripheral vascular disease.^{8,9}

Ezetimibe, an anti-cholesteremic drug used to treat high cholesterol levels, is generally given together with statins. It falls within the class II BCS category, which has minimal water solubility. The reported bioavailability of the drug is 35-50% owing to its intestinal metabolism and substantial first-pass effect. A mean Ezetimibe peak plasma concentration of 3.4-5.5 mg/mL in 4 hr following oral delivery of a 10 mg dosage. Food administration, at the same time, does not have an action on the extent of drug absorption, but the absorption rate is affected by the food.¹⁰⁻¹²

So, there was a need to select an alternate system of drug delivery to avoid above mentioned side effects. Thus, ODT was selected as formulation and nano co-crystals as a solubility-enhancing method in this study.

MATERIALS AND METHODS

Watson India Limited, Mumbai, sent Ezetimibe as a free sample, SD Fine Chemicals in Mumbai supplied Nicotinamide. All the chemicals, reagents as well as solvents utilized were of laboratory quality.

Pre-formulation studies

Pre-formulation analysis is the initial step in forming a drug's dosage form. These studies investigate the physicochemical characteristics of the drug on its own and in combination with excipients.¹³

Compatibility studies by FTIR

A Fourier Transform Infrared Spectrum (FTIR) of ezetimibe, and the excipients were studied using IR spectrophotometer (Thermo-Nicolet 6700) using the potassium bromide pellet technique in the 4000-400 cm^{-1} range.¹⁴

Saturation solubility studies

A surplus quantity of Ezetimibe in 10 mL of water was added and kept under shaking for 72 hr in a bath shaker. The samples were filtered, the drug concentration is determined spectrophotometrically at 231 nm.¹⁵⁻¹⁷

Methodology selection

Though many methods are available for the preparation of co-crystals, slurry crystallization and anti-solvent were selected due to their ease of preparation and the possibility of scaling up.¹⁸

In the slurry crystallization method, the drug ezetimibe dissolved in solvent methanol leads to a solution. After stirring at room temperature for 1 hr, the solvent was removed, and the solid material was parched at room temperature.¹⁹

Anti-solvent addition method is adding a weighed quantity of drug into solvent methanol and dissolving it by stirring. The drug solution is added to the anti-solvent water with continuous stirring at room temperature, resulting in white suspension and suspension subjected to evaporation for a suitable time and temperature to a white crystalline powder.²⁰

The saturation solubility studies of the co-crystals are conducted and compared against the drug's solubility. The method yielded a good percentage yield and exhibited the highest solubility for the drug converted to co-crystals.

Preliminary studies for co-former selection

The co-formers, such as acetamide, nicotinamide, L-ascorbic acid, L-tyrosine, glycine, saccharine, and maltose, were screened for suitability to prepare the co-crystals. The saturation solubility studies of the co-crystals are conducted and compared against the drug's solubility. The cofomer which exhibited the highest

solubility for the drug was chosen for further preparation of co-crystals.

Preparation of Ezetimibe co-crystals

Based on the preliminary studies of co-former selection and method of preparations, the formulations were prepared by anti-solvent method using the co-former nicotinamide.

This method involved two steps

Step 1

Ezetimibe and co-former were dissolved in a beaker containing a suitable quantity of solvent, methanol.

Step 2

The solution was added to water (anti-solvent for the drug) under mechanical stirring. The suspension was evaporated under a specified temperature, resulting in the co-crystals complete formation.²⁰

Preparation of Ezetimibe Nano co-crystals

Adopting the same procedure as above, after mixing the drug solution with an anti-solvent, a high-pressure homogenizer and subsequent spray drying were carried out to reduce the particle size to the nano range. The spray drying is carried out in the required conditions, such as 100-120°C and 80-90°C inlet and outlet temperature, respectively, 3mL/m in feed pump rate, and obtained formulations were evaluated for various properties.^{21,22}

Optimization of the formulations

The processing conditions for the preparing co-crystals were optimized using custom design, using JMP software.

The drug: co-former ratio, Solvent: Anti-solvent ratio, Evaporation time, and Evaporation temperature were selected factors on the response's solubility, compressibility index, and dissolution rate. The factors chosen and the responses selected in the experimental design are given in Table 1.¹⁹ The design generated 12 experimental trials, as shown in Table 2. Evaluation of co-crystals

Saturation solubility of Ezetimibe co-crystals

The saturation solubility is carryout by dissolving 10 mg of formulation (co-crystals) in 10 mL of a phosphate buffer of pH 6.8. The sample, after vortex mixing for 72 hr, was filtered. The drug concentration was measured via a Shimadzu UV-spectrometer at 231 nm after suitable dilution.²⁰

Drug content determination

A co-crystal formulation containing equivalent Ezetimibe (10 mg) was weighed into a 10 mL volumetric flask and diluted using methanol. The same solution was diluted suitably to Beer's

concentration range. The absorbance of the prepared solution was measured at 231 nm using methanol as a blank using a UV-spectrophotometer.²⁰

In vitro drug release study

USP dissolution apparatus – II was utilized for performing *in vitro* drug release study for F1-F12 formulations. The co-crystal formulation was introduced into the dissolution media, phosphate buffer pH 6.8 and stirred at 50 rpm. After collecting samples at 10, 15, 30, 45, 60, 90 and 120 min intervals, the samples were subjected to UV-spectroscopic analysis at 231 nm.²⁰

Evaluation of Nano co-crystals

Saturation solubility of Ezetimibe Nano co-crystals

The saturation solubility is carryout by dissolving 10 mg of formulation (nano co-crystals) in 10 mL of a phosphate buffer of pH 6.8. The sample, after vortex mixing for 72 hr, was filtered. The drug concentration was measured via a Shimadzu UV-spectrometer at 231nm after suitable dilution.²¹

Drug content determination

Co-crystals formulation containing an equivalent amount of Ezetimibe (10 mg) was weighed into a 10 mL volumetric flask and diluted using methanol. A 1 mL volume was diluted from the prepared solution to 10 mL. A volume of 0.5 mL of the above solution was further diluted to 10 mL using methanol. The absorbance of the prepared solution was measured at 231 nm using methanol as blank using UV-spectrophotometer.²⁰

In vitro drug release study

USP dissolution apparatus – II was utilized for performing *in vitro* drug release study for F1-F12 formulations. The nano co-crystal formulation was introduced into the dissolution media, phosphate buffer pH 6.8 and stirred at 50 rpm. After collecting samples at 10, 15, 30, 45, 60, 90 and 120 min intervals, the samples were subjected to UV-spectroscopic analysis at 231 nm.²¹

Evaluation of the experimental design

Based on the model fit, the optimum formula was identified and studied further.

Evaluation of the optimized formulations

Dissolution and Saturation solubility studies

Dissolution studies of optimized formulation and saturation solubility studies were performed using the above-mentioned procedure.

Surface Electron Microscopy (SEM)

Microscope model JEOL JSMT-330 (JAPAN) was used to examine the morphological characteristics of the formulation.

After placing on a sample stub, brass stubbed, and placed onto the gold sputtering system, the sample sputtered gold for 30 sec at ~ 70 mTorr pressure. After removing the brass stub from the gold sputtering system, samples were placed into the sample chamber under a vacuum at a voltage of 1-30V. Surface photographs were taken under suitable magnifications.²¹

Particle Size

The average particle size and size of the particle distribution of nano co-crystal were studied using Horiba SZ-100 nano particle Dynamic Light Scattering (DLS) system. Sample dispersions were studied for their particle size at a scattering angle of 90° at a temperature of 25.2°C.²¹

X-ray Diffraction (XRD)

The scattering pattern of the ezetimibe and the crystals collected using an X-ray diffractometer (D8 Discover, Bruker Axs,

Germany). The pattern is gathered between an angle of 10 to 900 and at a distance of 0.01.¹⁸

Preparation of Oral Disintegrating Tablet of Ezetimibe Nano co-crystals

The optimum formula contains 10 mg of ezetimibe, 3% crospovidone, 90% microcrystalline cellulose, and 0.75% magnesium stearate (as shown in Table 3) was blended to form a directly compressible mix. The powder was compressed into tablets of unit weight 400mg.²²

Evaluation of blends before compression

Angle of repose

The funnel method is used for determining the angle of repose. The precisely measured blend is placed in a funnel. The funnel's height is modified such that the funnel's tip brushes against the peak of the blend's heap. The drug-excipient combination allows the drug, which is the nano co-crystals, to flow easily through the funnel and onto the surface. The powder cone's diameter or radius is calculated, and the angle of repose is determined using the equation below.²³

$$\tan\theta = \frac{h}{r}$$

where h and r are the cone's height and the radius of the cone base respectively.

Table 1: Factors and responses chosen in the experimental design.

Factors	Upper limit	Lower limit
Drug: co-former ratio (%)	67	40
Solvent: anti-solvent ratio (%)	50	20
Evaporation temperature (°C)	30	50
Evaporation time (h)	3	6
Responses	Upper limit	Lower limit
Solubility (mg/mL)	0.05	0.03
Rate of dissolution %	30	25
Compressibility index %	15	10

Table 2: Experimental design with coded values.

Sl. No.	Drug: co former ratio (%) 1=1:1.5mg/mg 0=1:0.5mg/mg	Solvent: anti-solvent ratio (%)	Evaporation Temperature (°C)	Evaporation time (h)
1	1	0	30	6
2	1	0	30	1
3	1	0	30	3
4	0	0	30	1
5	1	1	50	6
6	0	1	50	6
7	0	1	50	6
8	1	0	30	3
9	0.5	0.5	40	6
10	0.5	0.5	40	1
11	1	0	30	3
12	0	1	50	3

Table 3: Formulation of ODT.

Sl. No.	Excipients	Concentration %/(qty taken)
1	Nano co-crystal	25mg (10 mg drug equivalent)
2	Magnesium stearate	0.75 (3 mg)
3	Crospovidone	3 (12 mg)
4	Microcrystalline cellulose	9 (360 mg)

Bulk density

Pour a proportionate mix into a graduated cylinder and quantify the weight and volume to estimate apparent bulk density. The following formula used for computing the bulk density:²³

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{volume of powder}}$$

Tapped density

A graduated cylinder carrying a known mass of drug-excipients blend is used to determine it. At two-second intervals, the cylinder could fall from a height of 10 cm onto a firm surface under its weight. The tapping kept going until there was no more change in volume. The following formula was used in computing the tapped density:²³

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Compressibility index

Compressibility index is used to measure the blend's flowability and compressibility. The following formula can be used to compute the compressibility index:²³

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{untapped density}}{\text{Tapped density}} * 100$$

Hausner ratio

The Hausner ratio is a comparable metric for indicating flow characteristics. The following formula may be used to compute the Hausner ratio:²⁴

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Untapped density}} * 100$$

Porosity

Porosity of the powder blend is calculated by the formula:

$$1 - \frac{v_t}{v_b} * 100$$

V_t = true volume, V_b is bulk volume.²⁵

Evaluation of Ezetimibe ODTs

Assay of the tablets

The tablet was assessed by crushing five tablets in a mortar and weighing the powder. (10mg drug equivalent) was taken and dissolved in 10mL of methanol. Via a UV-spectrometer for, absorbance of the solution at 231nm was measured.²⁶

Weight variation

Weight variation is carried out by weighing 20 tablets. The mean was measured, and the individual weight was also measured. The percentage deviation was calculated.²⁶

Hardness

A Monsanto hardness tester was utilized to measure the crushing strength of the tablets. Five tablets from the same batch were randomly tested, and the mean reading was recorded in Kg/cm².²⁶

Disintegration test

Six glass tubes, "3 long, open at the tip, and pressed up against a 10" screen at the bottom of the basket rack assembly, are the components in the USP disintegration equipment. One tablet was positioned in each tube, and the basket rack was immersed in a 1 L beaker containing distilled water at 37±2°C. The tablets remain beneath the liquid's surface on their upward motion and sink no closer than 2.5cm from the beaker's bottom.²⁷

Friability Test

After weighing, ten samples were placed in Roche friability tester and allowed for 25 rotations per minute (rpm) for 4 min. The tablets were weighed after dedusting. The following formula can be used to compute the percentage of friability.²⁸

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} * 100$$

where, W_1 = Weight of the tablet before test, W_2 = Weight of the tablet after test.

In vitro dissolution test

USP type II dissolution apparatus was utilized for performing in vitro drug release study of F1-F15 formulations. The ODT

formulation was then introduced into the dissolution media, Phosphate Buffer Solution (PBS) pH of 6.8 accommodating 0.1% w/v SLS (PBS 6.8pH preparation mentioned above) and stirred at 50 rotations per minute (rpm) and kept at a temperature of 37°C. Samples were collected at 10, 15, 30, 45, 60, 90 and 120 min, diluted suitably using the same media. The drug content of the sample was determined after analysing sample after spectroscopic method at 231nm.²⁸

Stability Studies

According to ICH recommendations, the selected formulation of ODTs is submitted to a stability study to assess their stability in terms of physical features and disintegration time.²⁸

Fourier Transform Infrared Spectroscopy (FTIR)

The IR spectra of optimum nano co-crystal formulation and ODT were compared against pure drug samples using the potassium bromide pellet method in the 4000-400 cm⁻¹.²⁸

Differential Scanning Calorimetry (DSC)

The thermal behaviour of Ezetimibe, an optimum formula of nanocrystal and ODT, was analyzed by differential scanning calorimetry. The samples were heated at 0-200°C at 5°C/min below a nitrogen flow, 40°C/min.

RESULTS AND DISCUSSION

Saturation solubility studies

Saturation solubility studies of the pure drug in water and PBS 6.8 with 0.1% SLS was determined to be 0.0072±0.00021 mg/mL and 0.0067±0.00028 mg/mL, respectively.

Preliminary studies for the selection of methods of preparation and co-formers

The co-crystals are produced using an anti-solvent addition procedure with seven co-formers. Based on saturation solubility studies, nicotinamide, co-former superior in solubility profile to other coformers was used to prepare co-crystals.

The co-crystals prepared by the anti-solvent method were analyzed for production yield, drug content, saturation solubility and *in vitro* release of a drug. The % CDR was found to be 8.3±0.15 to 19.64±0.06 at 10 min. 22.18±0.26 to 28.30±0.36% at 120 min. As per USP, the drug solubility ranges from very soluble (less than 1 part of solute/1 part of solvent) to practically insoluble (greater than 10,000 parts of solvent per 1 part of solute). Ezetimibe demonstrated a 0.0072±0.00021 mg/mL. All co-crystal formulations increased the solubility from 0.015 to 0.030 mg/mL. Co-crystal can improve drug solubility and dissolution rate, mainly due to changing crystal packing, which decreases the lattice energy and hydrophilic nature of co-formers. In addition, co-former solubility played a role in increasing co-crystal solubility due to solvation barrier reduction and correlated with

the dissolution rate of co-crystal. Co-crystals with nicotinamide have demonstrated higher solubility when compared to ezetimibe alone. Because of ezetimibe's decreased crystallinity, ezetimibe is anticipated to disperse better in co-crystal form.

The nano co-crystals were obtained by high-pressure homogenization solvent anti-solvent mixture and subsequent spray drying. The *n* formulations were analyzed for drug content, production yield, saturation solubility, compressibility index (as shown in Table 4) and *in vitro* drug release. The solubility of the formulation ranged from 0.03 mg/mL to (0.04980). ~05 mg/mL in comparison to 0.0076mg/mL of pure drug, it was almost 2-3-fold compared to co-crystals. The drug content of the formulations ranged between 44%-89%. The compressibility index ranged between 9.9%-13.8%.

The highest release of drug observed for 120 min was 14.97±0.007 to 26.95±0.06% at 10 min and 25.47±0.063 to 30.02±0.003% at 120 min. The dissolution rate showed a 5-9-fold increase compared with pure drug dissolution. Spray drying is a rapid and continuous solid engineering method that uses a hot air stream to generate dry powder from a solution or suspension. The co-crystal formation in spray drying happens due to solvent evaporation and simultaneous diffusion of solutes in the droplets by heat and mass transfer. There is a chance of sudden internal pressure build-up within the co-crystals, and on drying, the pressure reduction converts it to a more porous form. In addition, the reduced particle size and increased surface area to volume contributed to improved dissolution rate and solubility. However, there was no appreciable change in the dissolution rate from nano co-crystals (shown in Figure 1).

Evaluation of experimental design

Statistical evaluation of experimental design designated the influence of each factor selected on the responses. The level of significance is indicated by *p* values < 0.05. Highly influencing factors for the responses were found to be the time of evaporation and solvent: antisolvent ratio. Drug to conformer ratio was also a significant factor in the model fit. Time of evaporation is found to be the least influencing factor.

Higher *R*² and *P* values less than 0.05 indicates the correlation between the predicted and actual responses. For solubility, highly influencing factors were solvent: anti-solvent ratio and drug: conformer ratio. The solvent: the anti-solvent ratio was the most influencing factor for the compressibility index. Furthermore, the rate of dissolution was found to be influenced by the rate of evaporation.

Desirability

The desirability function is widely used in optimization to tackle the problem of optimizing multiple responses simultaneously. The desirability was found to be 0.47 (Figure 2) at drug: co former

Table 4: Evaluation of nano co-crystals.

Sl. No.	Formulation	Drug content (%) \pm SD (n=3)	Production yield (%) \pm SD (n=3)	Saturation solubility (mg)	Compressibility index (%)
1	F1	88.12 \pm 0.33	88.49	0.031 \pm 0.01	13.85 \pm 0.25
2	F2	81.23 \pm 0.84	81.84	0.034 \pm 0.01	12.96 \pm 0.34
3	F3	57.78 \pm 0.56	57.52	0.035 \pm 0.01	13.05 \pm 0.56
4	F4	44.56 \pm 0.22	44.28	0.037 \pm 0.01	13.19 \pm 0.22
5	F5	88.78 \pm 0.071	88.71	0.042 \pm 0.01	13.27 \pm 0.26
6	F6	75.17 \pm 0.97	75.11	0.039 \pm 0.01	12.12 \pm 0.67
7	F7	86.45 \pm 0.67	86.20	0.041 \pm 0.01	10.12 \pm 0.97
8	F8	89.90 \pm 0.33	89.24	0.050 \pm 0.01	9.9 \pm 0.45
9	F9	70.14 \pm 0.85	70.52	0.037 \pm 0.01	12.0 \pm 0.47
10	F10	53.67 \pm 0.42	53.096	0.046 \pm 0.01	13.21 \pm 0.78
11	F11	54.34 \pm 0.69	54.37	0.044 \pm 0.01	12.21 \pm 0.45
12	F12	75.67 \pm 0.81	75.22	0.042 \pm 0.01	12.2 \pm 0.12

Table 5: Pre-compression parameters.

Sl. No.	Pre compression parameters		Post compression parameters	
1	Angle of Repose ($^{\circ}$)	35.37	Drug content (%)	95.51
2	Bulk density (g/mL)	0.392	Hardness (Kg/Cm 2)	4.55
3	Tapped density (gm/mL)	0.49	Friability (%)	1.01
4	Compressibility index (%)	13.87	Disintegrating time (S)	28 \pm 0.012
5	Hausner ratio	0.12	% Weight variation	\leq 5%
6	Void volume (mL)	4		
7	Porosity (%)	20		

53%, solvent: antisolvent ratio 35% evaporation time of 4.5 hr, evaporation temperature 40 $^{\circ}$ C.

Prediction Formula

The polynomial prediction equation indicates factors positive and negative effects on solubility. The factor Drug: conformer has a negative impact on solubility, whereas all the other factors had positive impact on solubility. The optimum formula at the above mentioned factor levels predicted the following responses are given in equations 1, 2 and 3.

Solubility

$0.0405 = 0.04056 + -0.001732 * \text{"Drug:coformer (%)"} - 53.5) / 13.5) + 0.0025616 * \text{"Solvent: antisolvent ratio"} - 35) / 15) + 0.000794 * \text{"Time of evaporation (h)} - 4.5) / 1.5) + 0.00156 * \text{"Evaporation temperature (}^{\circ}\text{C)} - 40) / 10) - \text{Equation 1.}$

Compressibility index

$11.89 = 12.0269 + -0.4541 * \text{"Drug: co former (%)"} - 53.5) / 13.5) + -0.589 * \text{"Solvent: antisolvent ratio"} - 35) / 15) + -0.3974 * \text{"Time$

of evaporation (h") - 4.5) / 1.5)+0.395 * "Evaporation temperature ($^{\circ}$ C") - 40) / 10) -Equation 2.

Dissolution rate

$25.74 = 26.591 + -0.8433 * \text{"Drug: co former (%)"} - 53.5) / 13.5) - 0.853 * \text{"Solvent: antisolvent ratio"} - 35) / 15) + 1.8599 * \text{"Time of evaporation (h)} - 4.5) / 1.5) + 0.6883 * \text{"Evaporation temperature (}^{\circ}\text{C)} - 40) / 10) - \text{Equation 3.}$

Evaluation of optimum formulation

The optimum formula selected based on prediction table and design space, was evaluated for solubility (mg/mL), drug content uniformity (%), compressibility index (%), and rate of dissolution (%). The solubility of the optimum formulation was found to be 0.041 mg/mL. The compressibility index of optimum formulation was found to be 13%. The rate of dissolution was found to be 24.12%.

Surface morphology of optimized formula

The SEM morphological evaluation showed columnar crystal habits some are uneven surfaces, as shown in Figure 3.

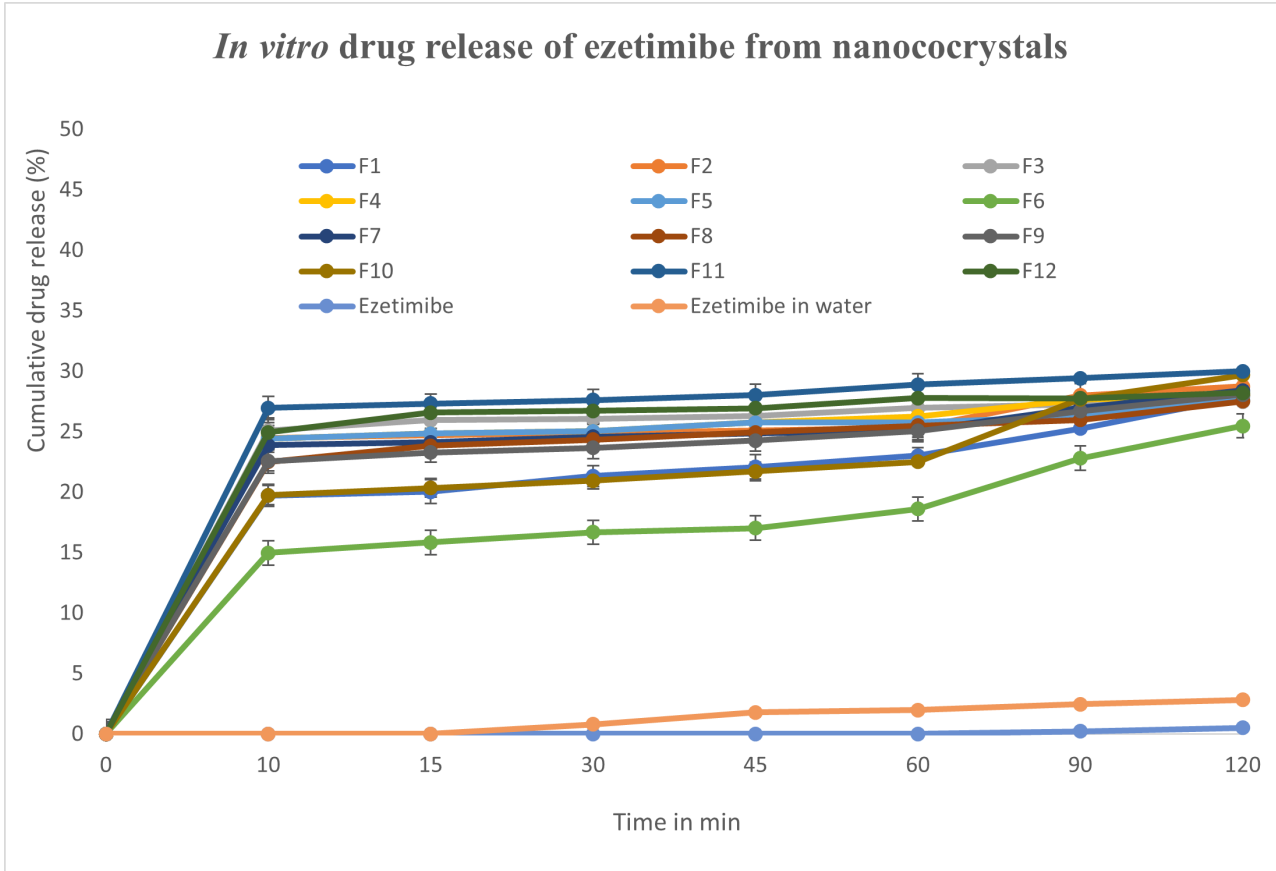


Figure 1: In vitro drug release studies of ezetimibe from nano co-crystals.

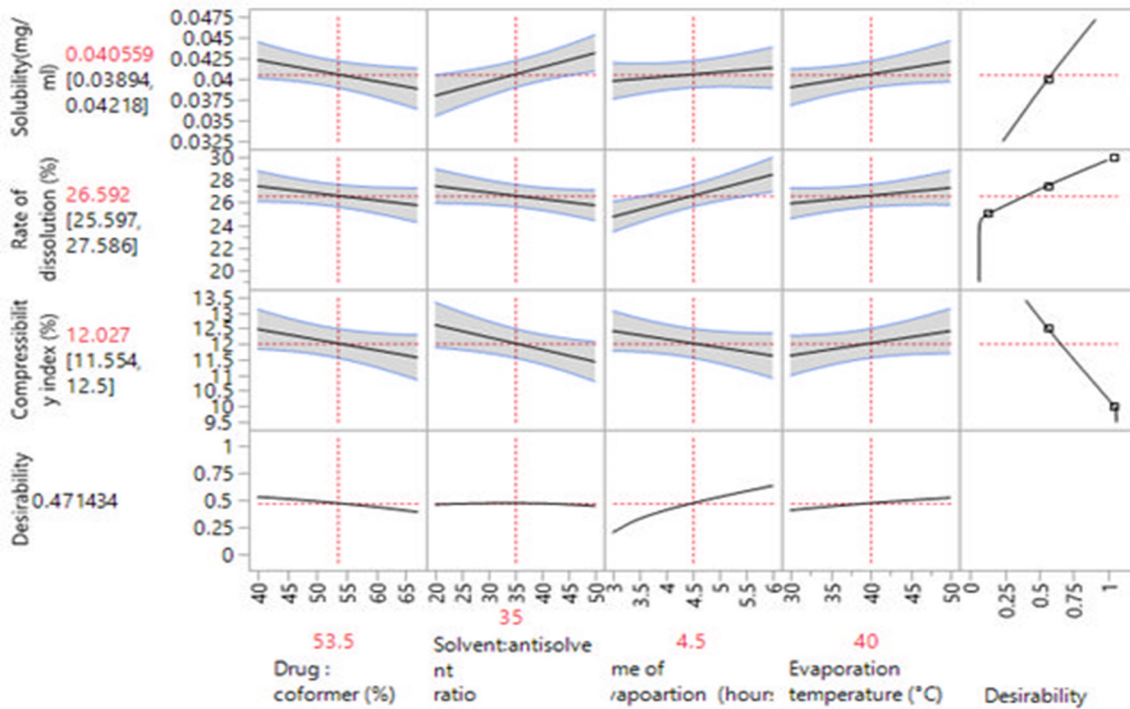


Figure 2: Desirability plot.

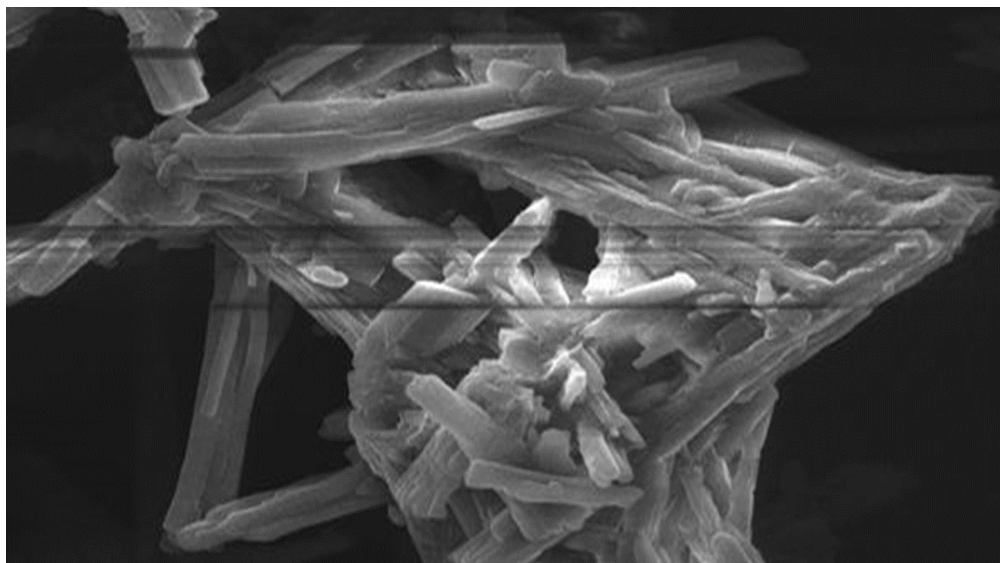


Figure 3: Surface Morphology of optimum formulation.

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	57.2 nm	12.9 nm	52.7 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	57.2 nm	12.9 nm	52.7 nm

Cumulant Operations

Z-Average : 93.2 nm

PI : 0.405

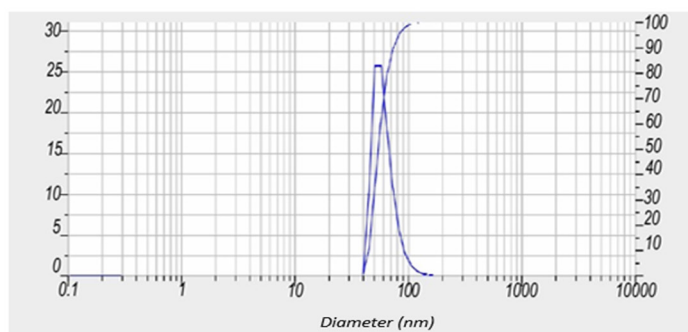


Figure 4: Particle size of optimum formulations.

Particle size

The particle size of the optimum formulation was found to be 92 nm and poly dispersability index is found to be 0.405 (Figure 4). So it indicates that homogenization process could considerably reduce the size of the particles to nano sizes followed by spray drying.

Powder X-ray Diffraction

PXRD patterns depicted in Figure 5 showed sharp and more significant number peaks, which confirms the crystalline nature

of Ezetimibe. Whereas in an optimum formula the intensity and the number of peaks were found to be much lesser than pure drug, indicating the reduced crystallinity of the formulation when converted into co-crystals.

Compatibility studies of optimum formula by FTIR

Compatibility studies by FTIR (Figure 6) indicated that there is no interaction between the drug and excipients utilized. The existence of a characteristic peak shows no way the processing conditions affected the characteristic property of the drug.

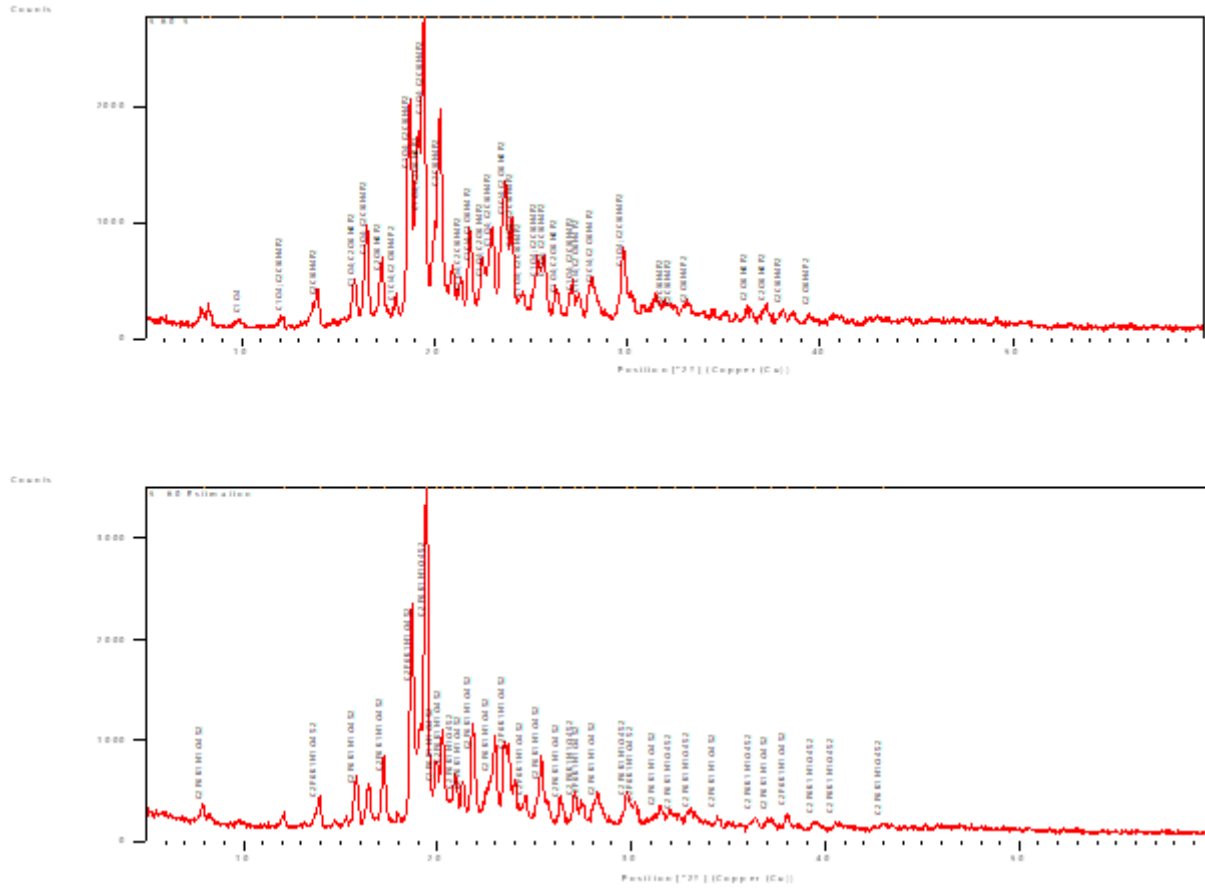


Figure 5: PXRD of Pure drug, Optimum formulations.

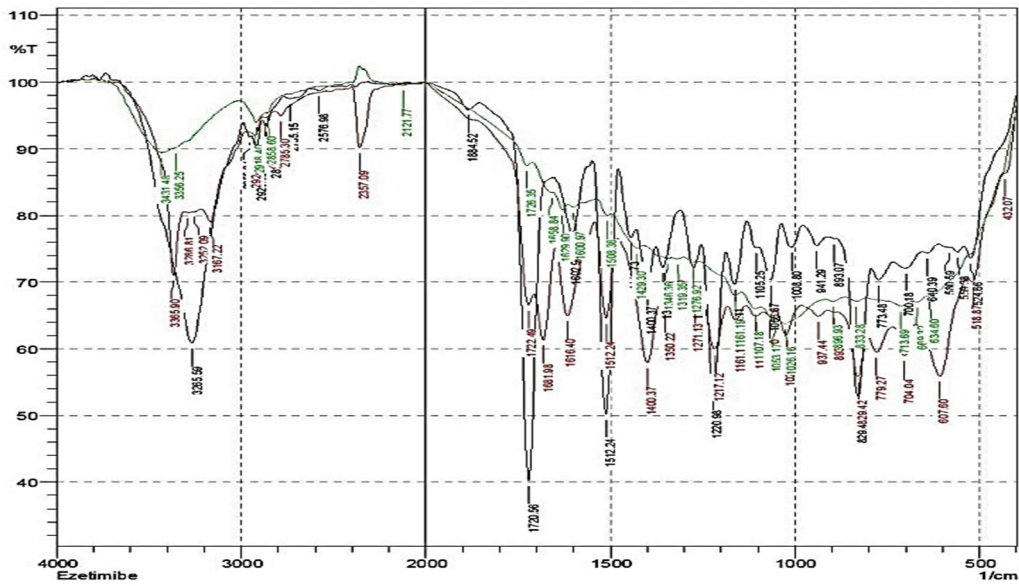


Figure 6: Merged spectra of ezetimibe, physical mixture, and optimum formulations.

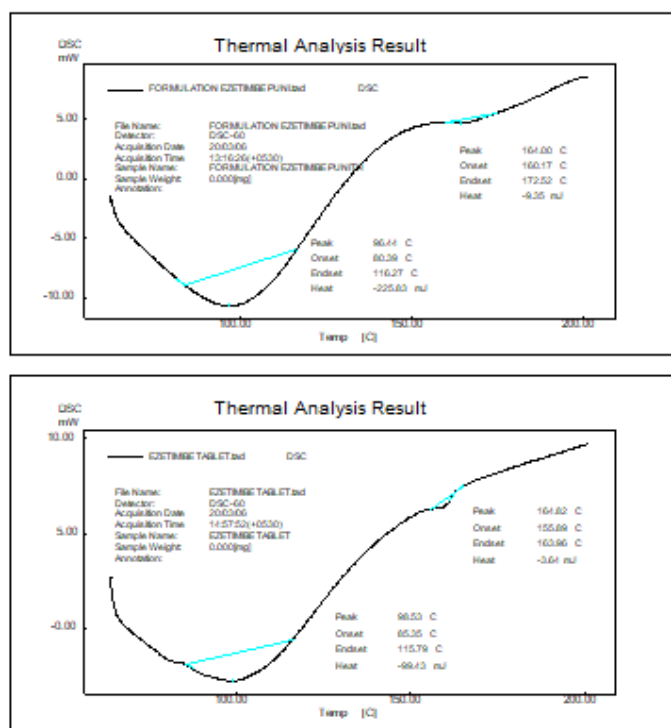


Figure 7: DSC Thermogram of Ezetimibe, Ezetimibe Optimum co-crystal formula, ODT.

Pre-compression parameters nano co-crystal blends and post-compression

Pre-compression parameters of nano co-crystals blend and post compression parameters

The pre-compression parameters such as angle of repose were determined to be 35.37° which demonstrates fairly good flow property. Bulk density is found to be 0.392 g/mL, tapped density is found to be 0.49 gm/mL, compressibility index was 13.87%, Hausner ratio 0.12%, void volume 4mL, porosity 20%, as shown in Table 5. These powder characteristics indicate that the nano co-crystals have fairly enough flow property and compression properties to be converted into a tablet dosage form.

In vitro drug release profile of ODTs

The *in vitro* drug release of oral disintegrating tablet is carried out in PBS pH 6.8 buffer with 0.1% sodium lauryl sulphate. And the % cumulative drug release is found to be $55.27 \pm 0.26\%$ to $64.43 \pm 0.32\%$. The rapid water uptake and super disintegrating properties of crospovidone were found to increase the drug release through ODT. An about 20-fold increase in the drug release was observed in comparison to pure drugs and also a 2.5-fold increase in comparison to co-crystals and nano co-crystals.

Differential Scanning Calorimetry (DSC)

A Thermogram of the pure drug revealed an endothermic peak at 166.79°C . In contrast, in nano co-crystal formulations, peaks shifted to a lower range of 96.44°C , and in the ODT formulation

with Ezetimibe Nano co-crystals, the peak shifted to 98.53°C as shown in Figure 7. The reduction in the peak height indicates the reduced crystallinity of ezetimibe when transformed into nano co-crystals. An amorphous product with an increment in solubility compared to pure ezetimibe may increase quicker drug release from the ODTs.

Stability studies of ODT

The disintegration time of selected ODTs at $25 \pm 0.5^\circ\text{C}$ 60% RH $\pm 5\%$ and $40 \pm 0.5^\circ\text{C}$ 75% RH $\pm 5\%$ was found to be 28 and 29 S. There were no changes observed in the physical characteristics also.

CONCLUSION

Oral disintegrating tablets of ezetimibe nano co-crystals could be a practical approach to facilitate drug release quickly with improved solubility and drug dissolution rate. The solvent-anti-solvent method was found to be an inexpensive method for preparing co-crystals. The optimum formula predicted by the model could result in nanocrystal formulations' quality attributes within expected specifications. To conclude, an ODT containing nano co-crystal of ezetimibe may be a practical technique for enhancing solubility and bioavailability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ODT: Oral disintegrating tablets; **NCE:** New Chemical entities; **BCS:** Biopharmaceutics Classification system; **FTIR:** Fourier transform infrared spectroscopy; **UV:** Ultraviolet; **DLS:** Dynamic light scattering system; **PBS:** Phosphate buffer solution; **DSC:** Differential scanning calorimetry.

SUMMARY

The nano co-crystals of ezetimibe were prepared via the antisolvent addition method followed by spray drying. The formulation trials were optimized using a custom design approach. The nano-co-crystal-based ODTs were found to be a promising approach to tackle the poor solubility and bioavailability of ezetimibe.

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