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Formulation, Optimization, and Evaluation of Ezetimibe for Chronotherapeutic Drug Delivery Using Compression-Coating Technology

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ABSTRACT

Objectives:

The purpose of the present study was to Formulation, optimization and evaluation of drug for chronotherapeutic drug delivery using compression coating technology for hypercholesterolemia.

Material and Methods:

The drug delivery system was designed to deliver the drug at a time when it could be needed for the most in the early morning (4 to 6 a.m.) for patients in case of hypercholesterolemia. The pulsatile concept was applied to the dosage form by having a lag phase followed by an immediate release. The prepared system consisted of two parts: a core tablet containing the active ingredient and fracture outer shell with delay-release polymer having diffusion characteristics. Solid dispersion was carried out by screening of betacyclodextrin, Polyvinyl pyrrolidone (PVP K30), and HPMC using three different drug complex ratios 1:1, 1:2, and 1:3 by a solvent evaporation method through spray dryer. The immediate-release core tablet (IRCT) was prepared by using a superdisintegrant with active ingredients. Screening of IRCT was carried out by pre and post compression parameters, disintegration time and an in-vitro dissolution study. The pulsatile release tablet (PRT) of optimized IRCT was made by Glyceryl Behenate and Dibasic Calcium Phosphate. Optimization of polymer concentration of PRT was carried out by pre and post-compression parameters, pulsatile lag time, and an in-vitro dissolution study. A 3^2 factorial design was employed to optimize the PRT. The design consisted of two dependent variables R1, and R2 independent variables X1 and X2. The two independent formulation variables selected for the study including Concentration of coating polymer and Concentration of lubricant. The dependent variables are Lag Time and Thickness.

Results:

XRD, DSC and FTIR spectra showed that solid dispersion was formed by the drug and PVP K30 complex. IRCT batch RR1 containing 22mg croscarmellose sodium to achieve good 30sec disintegration time and 98.34% drug release at the end of 20 minutes of Ezetimibe respectively. PRT formulation DR6 showed good pre and post-compression parameters with a satisfactory drug release of 98.34% for Ezetimibe respectively with a lag time of 6 hours. The 3^2 factorial design was used for the optimization of PRT parameters. A total of 9 experiments were performed for two factors at three levels each. The optimized batch showed 98.27% DR for Ezetimibe in 6.2 hrs (within 20 min after lag time) with pulsatile lag time up to 6.0 hrs and thickness of 5.10 kp.

Conclusion:
It was concluded that tablet within the tablet, pulsatile drug delivery of Ezetimibe (BCS class-II drugs) was successfully formulated with the advantage of enhanced solubility, and pulsatile release behavior and had an added benefit of suitable for chronopharmacotherapy of diseases that show circadian rhythms in their pathophysiology.
Keywords: Chronotherapeutic drug delivery, Circadian rhythm, Solid dispersion, Spray dryer, Ezetimibe, PVP K-30, Croscarmellose sodium, Glyceryl behenate, Full factorial design.

(1) INTRODUCTION

Chronotherapeutic drug delivery system is dependent on the circadian rhythm of the human body. The disturbance in circadian rhythm leads to physiological disorders. This drug delivery system is time-dependent as per the diseases. In this, the drug will be released after a predetermined lag time. In this article, the drug ezetimibe is of BCS class II, used for Hypercholesterolemia. Hypercholesterolemia is a lipid disease in which low-density lipoprotein increases. Ezetimibe inhibits the absorption of cholesterol from the small intestine. The main target of the drug is sterol transporter which is responsible for the uptake of cholesterol from the intestine. The sterol transporter, Niemann Pick C1-Like 1 is targeted. This drug is BCS class II which has low solubility. Thus the solubility was enhanced by the Solid dispersion technique using the spray drying method.[1-5]

To avoid disturbance in the circadian rhythm, the compression coating technique is used. In which 2 most important parts, firstly the core tablet which contains the drug with immediate release. For immediate release, the super disintegrating agent was added and this was by wet granulation method. Secondly, the coating shell which is made of polymer and other excipients used to obtain the predetermined 6hrs lag time. So at the required time, the drug gets released and provides the therapeutic effects at the site of action.[6-8]

The screening of polymers for solid dispersion was carried out based on solubility. While, the ratio of drug-polymer and solid contents for the spray drying method was done and the optimization of process parameters was based on the practical interferences of spray rate, inlet temperature, atomization, etc.[9-12]

The different super disintegrants were used for screening from which the croscarmellose sodium was finalized based on the disintegration time. Therefore, for the 6hrs delayed release glyceryl behenate and dibasic calcium phosphate were used. The multimedia dissolution was performed with 0.1N HCl and pH 6.8 phosphate buffer.[12-13]

(2) MATERIALS AND METHODS

(2.1) Materials

Ezetimibe was obtained as a gift same from Sun Pharmaceuticals Industries Ltd. Vadodara, India; PVP K30 from Ashland Industrial Ltd. Mumbai, India; Croscarmellose sodium from Dupont, Signet Excipients Pvt. Ltd., Mumbai, India; Sodium starch glycolate from Roquette India Private Limited, Viramgam, Gujarat, India; Crospovidone from ISP Technologies. Inc, Karnataka, India; Magnesium stearate from Peter Greven GmbH & Co. KG, Germany; Colloidal silicon dioxide from Cabot Sanmar Ltd. Maharashtra, India; Lactose monohydrate 200M from DFE Pharma India Llp, Cuddalore, Tamil Nadu, India; Glyceryl behenate from Eronic Industrial Ltd Vadodara, India; Dibasic calcium phosphate from S.D. fine chemical limited Vadodara, India.

(2.2) Methodology

(2.2.1) Solid dispersion by spray drying method:

Solid dispersion is a technique used for enhancing the solubility of ezetimibe which is a BCS class II drug.[14-16] Many methods are available for solid dispersion but the solvent evaporation by spray drying method was selected based on the solubility. The main principle is drying by evaporation, the removal of solvent from the solid content by evaporation.[17-19] By this the storage life of solid dispersion or the powder increases. The main parts of the spray dryer are: 1) Feeding system 2) Atomizer 3) Drying Chamber 4) Cyclone Chamber 5) Bag Filter.[20-24] The spray dryer works as both an open and close loop, for this article, the close loop was used. The advantages of using this method are it is a fast, continuous, and reproducible method; cost-effective; easy scalability. The 1:2 drug: polymer ratio was used for spray drying with 10% of solid content for this formulation. The ezetimibe and PVP K30 were dissolved in methanol. The prepared solution was sprayed in the spray dryer through a gun. The optimization of solid content, atomization, inlet temperature, and feed rate was carried out with respective criteria and their inference.[25-29]

(2.2.2) Preparation of core tablet:

The super disintegrant was selected based on the screening method. The Croscarmellose sodium, Sodium starch glycolate, and Crospovidone were used in the screening method with different levels such as (11, 16.5, and 22 mg). From which the Croscarmellose sodium with 22mg was selected for the final formulation shown in Table 2. The solid dispersion powder and the other excipients except for magnesium stearate and colloidal silicon were passed from the #40 mesh. The granulation was done with the required quantity of water and the wet mass was sifted with #10, dried, and resifted with #30mesh. The blending was done for 10mins with magnesium stearate and colloidal silicon. The blend was ready for compression and compressed with a 6 mm FFBE with one side break line punch.[30-35] The formula is given in Table **1.**

Table 1 Composition of core tablet

Sr. No.	Ingredients	Example	Quantity (mg per tablet)
1.	Solid dispersion powder	Ezetimibe + PVP K30	30
2.	Super disintegrating agent	Croscarmellose sodium	22
3.	Diluents	Lactose monohydrate 200M	47
4.	Lubricant	Magnesium stearate	0.6
5.	Glidant	Colloidal silicon dioxide	0.3
6.	Color	Ferric oxide red, Indigo blue, Ferric oxide yellow	0.1
		Total	100

(2.2.3) Preparation of press-coated tablet:

The Glyceryl behenate, PVP K-30, and Dibasic Calcium Phosphate were sifted from a #40 mesh sieve. Granulation was prepared with the required amount of water and passed the wet granules from the #10 mesh sieve to break the lumps. Dried the granules at 60°C in a Hot air oven for 1 hour and checked LOD.[36-37] Sifted the dried granules from a #40 mesh sieve and sifted the magnesium stearate and colloidal silicon

dioxide. Added the sifted lubricant and glidant, and blended for 10 minutes. The prepared blend was used for the preparation of the tablet. The 40% of the blend was added and precompressed. Then kept the core tablet in the center and added the remaining amount of blend and compressed. The was compressed in 10 mm FFBE with one side breakfast line punch.[38-42] The formula is given in Table **2**.

Table 2. Composition of press-coated tablet

Sr. No.	Ingredients	Example	Quantity (mg per tablet)
1.	Core Tablet	-	100
2.	Delayed release polymer	Glyceryl Behenate	160(40%)
3.	Binder	PVP K-30	32(8%)
4.	Diluent	Dibasic Calcium Phosphate	202(50.5%)
5.	Lubricant	Magnesium Stearate	4(1%)
6.	Glidant	Colloidal Silicon Dioxide	2(0.5%)
		Total	500

(2.2.4) In-vitro Dissolution Study:

The test was performed with the paddle (USP Apparatus II) at 50 rpm, 37 °C ± 0.5 °C. The different dissolutions with 6 units of tablet were done for individual batches. The dissolution was carried out in the 0.1N HCl for 3hrs. Further, the media was changed with Phosphate Buffer pH 6.8 for 3hrs 20mins. After that, the drug release was calculated. 6 hrs lag time was achieved.[43-47]

(2.2.5) Optimization for delayed release coat tablet:

The 2 factors were taken for optimization of a press-coated tablet. X1 = % Coating Polymer and X2 = % Binder with Y1 = Lag time (hrs) as a response. The 3 levels were taken for 2 factors. Levels for % Coating Polymer were 30, 40, and 50. While for Binder % levels were 6, 8, and 10 given in Table **3**. All the batches were prepared and evaluated. Batch 5th was the optimized batch with % coating polymer 40 and the binder % 8. This batch had the 6hrs of lag time which was the required formulation parameter. All batches were designed by using the Design Expert version 13.[48-51] The software itself suggests the linear model and gives the equation. 3.

Table 3 Factors and Levels for the Design

Sr.No.	Factors	Levels		
		-1	0	+1
1.	Coating Polymer (%)	30	40	50
2.	Binder (%)	6	8	10

(3) EXPERIMENTAL

(3.1) Identification of drug

(3.1.1) Melting point determination of drug

The melting point analysis utilized the Mettler Toledo MP 70 melting point system. A single-sided sealed capillary was filled with the drug and placed in the microchamber. The instrument was set to a specified

temperature range, and the analysis was initiated. The drug sample melted within the capillary, and the recorded temperature was noted for analysis.[52-55]

(3.1.2) Differential Scanning Calorimetry (DSC)

To identify the temperature characteristics of ezetimibe, (DSC) investigation DSC-2 instrument, which is a part of the STAR system made by Mettler Toledo. Samples ranging in weight from 2 to 4 mg were heated using a nitrogen flow rate of 20 ml/min in aluminium pans with a tight lid. The temperature was increased from 25°C to 400°C at a scanning rate of 10°C/min. For comparison, empty aluminum pans were utilised as the ref. standard during the DSC measurements.[56-59]

(3.1.3) Fourier transform infrared spectroscopy

Using a FTIR Spectrophotometer (Spectrum Two, PerkinElmer), the drug's identity and purity were assessed. The procedure involved mixing samples with potassium bromide (KBr) to create a 10% mixture. The samples included the medicine by itself, the polymers by itself, and the drug in conjunction with the polymers. The materials were then crushed into pellets after being ground with KBr in a mortar and pestle. The spectrum recorded at a resolution of 2 cm-1 over a frequency range of 4000 to 400 cm-1 after these pellets were placed in the light path. KBr's background spectrum was used as a reference point when evaluating the drug's purity and identity.[60-63]

(3.1.4) Powder X-ray diffraction (XRD)

XRD analysis was performed on the pure drug to ascertain the quantity of crystals present in the sample. The drug sample will be affixed to a glass slide by applying vacuum grease, ensuring a uniform thickness of 0.5 mm. The slide will be vertically aligned in the X-ray diffractometer at 0 degrees, utilizing a Cu K-α 1 tube as the X-ray source set at 40 KV and 50 mA. A scan ranging from 2 to 600 2θ will be performed at a speed of 0.0122 2θ/s, allowing for a comprehensive examination of the crystal structure and arrangement of the drug sample.[64-65]

(3.1.5) Solubility study

Solubility denotes the maximum amount of a substance that can dissolve in a given solvent at constant temperature and pressure, leading to the creation of a saturated solution.[66]

Method

Solubility of drugs will be investigated using the orbital shaker flask method. The evaluation will encompass various mediums, including buffer pH 6.8, 0.1N HCL, and water. The process will entail placing an more quantity of each drug into individual 10mL glass flasks containing the corresponding medium, sealing the flasks to prevent any loss of solvent. Saturation will be verified by observing any remaining undissolved material in the suspension. The flasks will be left untouched in an Orbital Shaking Incubator at 37°C and 120rpm for 24 hours to achieve equilibrium. Following this, 1ml of the supernatant will be extracted, filtered through 0.45micron syringe filter, and examined using a UV–visible spectrophotometer (SHIMADZU UV-1800 PC (E) 230V, Tokyo, Japan). The solubility of the drug will be assessed and quantified in milligrams per milliliter, taking into account of the drug that has dissolved in solution following a period of equilibrium.[67-69]

(3.2) Development of UV spectrophotometric method

(3.2.1) Calibration curve in Phosphate buffer 6.8pH

Creating a spectrophotometric technique to measure Ezetimibe levels in compression-coated tablets. Calibration curve will be performed using methanol-drug mixture with 6.8pH phosphate buffer in third

dilution after the first and second stock solution in methanol+6.8 pH phosphate buffer using same as per above dilution scheme.

(3.2.2) Calibration curve in 0.1N HCL

It will be performed using methanol-drug mixture with 0.1N HCL in third dilution after the first and second stock solution in methanol using same as per above dilution scheme.

(3.2.3) Calibration curve in Water

Calibration curve will be performed using methanol-drug mixture with Water in third dilution after the first and second stock solution in methanol using same as per above dilution scheme.

(3.3) Solubility enhancement by solid dispersion

1. Solvent evaporation method

A suitable organic solvent will be used to dissolve the medication and polymer simultaneously. After that, the mixture will be allowed to rest overnight for the solvent to evaporate, forming a solid dispersion. This process will facilitate extensive molecular mixing, which will help increase the stability and solubility of the final product. This technique is often used to create solid dispersions to enhance the drug's bioavailability and dissolution.[70-72]

2. Kneading method

Solid dispersions using the kneading technique, a predetermined quantity of drug and carriers will be meticulously mixed in a glass vessel. A solvent, which may consist of water or a mixture of water and some alcohol, will be slowly added while simultaneously grinding the drug and polymers with a mortar and pestle. This process creates a slurry that facilitates the reduction of particle size, thus improving bioavailability. Following this, the resulting mixture will undergo drying and be passed through a mesh to achieve homogeneity. The drying step will aim to remove the solvent, resulting in a solid dispersion characterized by a uniformly distributed blend of drug and carrier components, thus promoting optimal therapeutic efficacy through improved mixing and bioavailability.

HPMC AS, HPMC E3LV, TPGS, Poloxamer, Soluplus, and Beta cyclodextrin polymer will be used to enhance solubility with using above technique.[73-75]

3. Spray Dry

Drug + Polymer in organic solvent (methanol) 10% solid concentration. Solution was atomized by N2 gas. Flow rate: 700L/h, Aspirator: 35 m3/h, Feed rate: 4ml/min, Inlet temp.: 70-75 °C. Collect powder & keep under vaccum for 48hrs to remove residual solvents.[76]

4. Microwave-induced fusion method

Drug + Carrier(different ratios), 5mins mix in mortar and pestle. Put in oven for 3mins at 590W constant power. Solidify at room temperature. Collect & keep in desiccator for 24hrs. Pass powder from sieve 30#.[76]

5. Mixed-grinding method

Drug + Carrier, mix till homogenous mixture obtained. Triturating of mixture 10-15min. Pass powder from30# sieve.[76]

6. Physical mixture method

Drug + Carrier, mixing by spatula for 5min & sieve from 30#.[76]

7. Co-grinding method

Drug + Carrier. Triturate in mortar pestle for 20mins. Sieve powder by 30# sieve.[76]

(3.4) Preliminary trails

(3.4.1) Screening of super disintegrant for rapid-release core tablet:

Utilizing insights from literature reviews and considering the characteristics of super disintegrants, a selection process was initiated to identify a super disintegrant suitable for achieving a rapid release core tablet. Various trial batches were then prepared to assess the disintegration time of different super disintegrants, aiming to ensure compatibility with the drug and the desired action at the targeted site.[76]

(3.4.2) Screening of polymer for delayed release coat tablet:

Building on the literature findings and understanding the characteristics of different grades of (HPMC), Eudragit and POLYOX, glyceryl behenate a selection procedure was implemented to identify a polymer suitable for achieving a pulsatile release tablet. Trial batches will be subsequently manufactured to evaluate the pulsatile release of different polymers, ensuring compatibility with the drug and the desired action at the targeted site.[76-77]

(3.4.3) Screening of excipients for solubility enhancement:

Leveraging insights from literature reviews and the characteristics of various excipients, a systematic study was conducted to select an excipient for solubility enhancement, aiming to increase bioavailability and provide the desired action at the targeted site. Trial batches will then be prepared to assess the solubility enhancement properties of different excipients, ensuring their effectiveness in the formulation.[77]

(3.5) Preparation and Optimization formulation of drug:

(3.5.1) Preparation of rapid-release core tablet:

The inner core immediate release tablet of telmisartan and cilnidipine will be produced using the direct compression technique or top spray granulation method in Fluidized bed processor FBP. Various concentrations of super disintegrants like sodium starch glycolate, croscarmellose sodium, and crospovidone will be employed. Core tablet will include super disintegrant, solubilizer, microcrystalline cellulose, colloidal silicon dioxide and ferric oxide red or brilliant blue FCF. Blend will be compressed in Kambert tablet compression machine using to obtain the core tablet.[78]

(3.5.2) Preparation of pulsatile release coat tablet:

Using a range of polymers, like glyceryl behenate, HPMC K100M, HPMC E5, HPMC K15M, ethyl cellulose, Eudragit L100, Eudragit S100, Eudragit RLPO, and PEO WSR (Poly ethylene oxide) Polymer Coagulant (POLYOX) to control the release rate, pulsatile release tablets will be formulated using the press-coated technique. Initially, 50% of the barrier layer material will be weighed and added to the die. And finally, the central tablet will be placed there. Lastly, the die will be filled with the remaining half of coating layer material and compacted.

All polymer for pulsatile release, solubility enhancement, punch and die size for core& coat tablet also both formulas will be finalized after preliminary batches trails.[78]

(3.6) Evaluation parameter

(3.6.1) Pre-compression study[78-79]

Bulk density (ρb)

Bulk density is the relationship between the mass of a powder and its volume, specifically its bulk volume. It will be determined by adding an accurately weighted amount of powder in a measuring cylinder. The vol. occupied by the powder will then be measured to ascertain the bulk volume. The formula below will

then be used to determine the powder's bulk density; this value is typically given in grammes per millilitre, or g/ml.

$$\rho_b = \frac{M}{V_b}$$

Where,
ρb= Bulk density
M = Mass of powder
Vb= Bulk volume of powder

Tapped density (ρt)

Tapped density represents the relationship between the weigh of a powder sample and its tapped vol.. It will be assessed using an density tester, comprising a graduated cylinder kept to a tapping apparatus. To measure it, a precisely weighed powder sample will be added to the measuring cylinder with care. Initially, the volume will be recorded, and then the sample will be tapped til no reduction in vol. is observed. The last final volume, termed as tapped volume, will be noted. Tapped density will be computed using the formula provided below, usually denoted in (g/ml).

$$\rho_t = \frac{M}{V_t}$$

Where,
ρt = Tapped density
M = Mass of powder
Vt= Tapped volume of powder

Angle of repose

The angle of repose represents the maximum angle formed between the surface of a powder pile and a horizontal plane. This will be evaluated using the funnel method, where a funnel will be placed about 2-4 cm above a platform. The drug or blends will be poured until the upper tip of the pile touches the lower tip of the funnel. The diameter of the resulting powder cone will be measured, and the radius will be calculated. The angle of repose will then be determined using the provided formula.

$$\textit{Angle of repose } (\theta) = \tan^{-1}\frac{h}{r}$$

Where, h = Height of the pile (in cm)
r = Radius of pile (in cm)
θ = Angle of repose

Compressibility index

Compressibility-index serves as an indicator of the compression of the sample and offers insights into its flow characteristics. Expressed as a percentage, it is determined through a particular formula.

$$Compressibility\ Index = \frac{TD - BD}{TD} * 100$$

Where, TD = Tapped Density
BD = Bulk Density

Hausner's Ratio

Hausner's ratio was a measure of powder flowability. It was calculated as the ratio of tapped density to bulk density using the following equation.

$$HR = \frac{\rho_t}{\rho_b}$$

Where, ρt = Tapped density respectively

ρb = Bulk Density

(3.6.2) Post-compression parameter[78-80]

Uniformity of Weight

20 tablets will be chosen at random, and each tablet will be individually weighted on electronic balance. The average weight will then be determined from these measurements. The maximum % deviation allowed as per USP and IP is depicted in Table 3.5 % of

$$\%weight\ variation = \frac{(Initial\ weight - Average\ weight)}{Average\ weight} \times 100$$

Thickness and Diameter

To evaluate size and shape of tablets, their thickness and diameter will be measured. Thickness and diameter measurements will be conducted using a vernier caliper and reported in millimeters. Three tablets from each formulation will be assessed for thickness and diameter, and an average thickness will be checked.

Hardness

It refers to the resistance encountered when a tablet is broken under diametric compression. The hardness of the tablet will be checked using a Dr. Schleuniger Pharmatron Tester and reported in units of kg/cm2.

Friability

Tablets, each weighing 6.25 grams, will be placed into a rotating drum, and their initial weight will be recorded. Subsequently, they will be transferred to a Roche friabilator and rotated at 25 rpm for 100 revolutions. After this process, the tablets was removed from the friability, any fine particles will be eliminated, and their weight will be measured once more and documented. The percentage of friability will be determined using a specific formula:

$$\%Friability = \frac{(Initial\ weight - Final\ weight)}{Initial\ weight} \times 100$$

Disintegration Test

It was carried out employing a Disintegration apparatus. A medium of 900 ml of water or the appropriate buffer, kept at 37±0.5 °C, will be utilized. Six tablets, chosen randomly, will be placed into the glass tubes and the apparatus will be started. The time needed for the tablets fully dissolve will be noted and documented as the disintegration time (n = 6). It will be ensured that no residue remains on the sieve during the assessment. This disintegration test will be specifically conducted for (IR) tablets.

In-vitro dissolution studies:

For core tablets (RRCT)

A USP Type II (paddle type) apparatus will be used for in-vitro dissolution research. At a temperature of 37°C, the dissolving test will be conducted using 900ml of 0.1N HCl (pH 1.2), phosphate buffers of pH 6.8 and water, For 45 minutes, the paddle will spin at 50 revolutions per minute. To maintain sink conditions, a 5 ml sample will be taken out at predetermined intervals and replaced with an equivalent

volume of fresh buffer. A UV-visible spectrophotometer set at λmax will be used to filter, dilute, and analyse the extracted samples for drug content. For every formulation, the percentage of drug release will be ascertained.

For Pulsatile Release coat Tablets (PRT)

A USP Type II (paddle type) apparatus will be used for dissolution tests the pulsatile delivery systems. The experiment will involve 900 millilitres of 0.1N HCl (pH 1.2), pH 6.8. The paddle will spin at 50 revolutions per minute. A 5 ml sample will be taken out at predetermined intervals, and to keep sink conditions stable, an equivalent volume of new buffer will be introduced. Using a UV-visible spectrophotometer set to λmax, the extracted samples will be filtered, diluted, and examined for drug content. For every formulation, the percentage release and lag time will be ascertained.

Stability study

The most advantageous formulation will undergo stability studies by the guidelines provided by (ICH). For a month, the chosen formulation will be tested in a humidity chamber with stability evaluations conducted at 30 ± 2˚C, 65 ± 5% RH, and at 40 ± 2˚C, 75 ± 5% RH. At specified intervals, samples will be extracted for analysis. The assessment will encompass a thorough examination for any potential physical and chemical alterations in the formulation. Analytical methods will be employed to determine the cumulative % drug release and drug content, ensuring a comprehensive evaluation of the formulation's stability over the specified testing period.

(4) RESULTS AND DISCUSSION

(4.1) Pre-formulation study

(4.1.1) Drug Identification Study

(4.1.1.1) Melting point determination

It was measured using the Mettler Toledo instrument. The melting point was observed and recorded. The recorded melting point was then compared to a standard range of melting point of Ezetimibe which concluded that the drug is free from impurities, and is pure in nature.

(4.1.1.2) FTIR study of pure API

The FTIR study conducted on the drug sample was compared with the standard Ezetimibe, and the comparison confirms purity of Ezetimibe. The analysis indicates that the spectra of the drug align closely with standard, validating the integrity and purity of the Ezetimibe sample under investigation.

(4.1.2) Analytical Method Development

The standard curve of Ezetimibe in Phosphate Buffer (pH 6.8), 0.1N HCl, and Water was analyzed in the range of 2-10µg/ml at the wavelength of 234nm. The selected range was linear in the regression coeffect at 234nm.

(4.1.2.1) Calibration curve of Ezetimibe in Phosphate Buffer pH 6.8

Ezetimibe showed its highest absorbance at 234 nm and followed Beer's law within the concentration range of 2-10 µg/ml. The linear regression analysis of absorbance versus concentration resulted in the equation y = 0.0272x - 0.0015, with a correlation coefficient of R^2=0.993. The calibration curve for Ezetimibe was linear across concentrations ranging from 2 to 10 µg/ml.

(4.1.2.2) Calibration curve of Ezetimibe in 0.1N HCL

Ezetimibe exhibited its maximum absorbance at 234 nm and obeyed Beer's law in the range of concentration 2-10 µg/ml. linear regression of absorbance on concentration gave equation y = 0.0848x -

0.1306 with a correlation co-efficient of R2=0.9884. Calibration curve of Ezetimibe was liner in concentration range 2-10 µg/ml.

(4.1.2.3) Calibration curve of Ezetimibe in Water

Ezetimibe exhibited its maximum absorbance at 234 nm and obeyed Beer's law in the range of concentration 2-10 µg/ml. linear regression of absorbance on concentration gave equation y = 0.0421x + 0.0595 with a correlation co-efficient of R2=0.9901. Calibration curve of Ezetimibe was liner in concentration range 2-10 µg/ml.

(4.1.3) Solubility Studies

(4.1.3.1) Solubility of Ezetimibe in Water

CALCULATION:

1. PURE DRUG (Abs.: 0.071)

y = 0.0421x + 0.0595
0.071= 0.0421x + 0.0595
0.071- 0.0595 = 0.0421x
0.0115 = 0.0421x
x = 0.273 µg / ml

2. SPRAY DRIED (Abs.: 0.310 with 10 times dilution)

y = 0.0421x + 0.0595
0.310 = 0.0421x + 0.0595
0.310 - 0.0595 = 0.0421x
0.2505 = 0.0421x
x = 5.950µg/ml

3. PHYSICAL MIXTURE (Abs.: 0.451)

y = 0.0421x + 0.0595
0.451 = 0.0421x + 0.0595
0.451 - 0.0595 = 0.0421x
0.3915 = 0.0421x
x = 9.299µg/ml

4. CO-GRINDING (Abs.: 0.309)

y = 0.0421x + 0.0595
0.309 = 0.0421x + 0.0595
0.309 - 0.0595 = 0.0421x
0.2495 = 0.0421x
x = 5.926µg/ml

(4.1.3.2) Solubility of Ezetimibe in Phosphate Buffer pH 6.8

CALCULATION:

1. PURE DRUG (Abs.: 0.044)

y = 0.0272x - 0.0015
0.044 = 0.0272x - 0.0015
0.044 + 0.0015 = 0.0272x
0.0455 = 0.0272x

x = 1.672 µg / ml

2. SPRAY DRIED (Abs.: 0.718)

y = 0.0272x - 0.0015
0.718 = 0.0272x - 0.0015
0.718 + 0.0015 = 0.0272x
0.7195 = 0.0272x
x = 26.452µg/ml

3. PHYSICAL MIXTURE (Abs.: 0.434)

y = 0.0272x - 0.0015
0.434 = 0.0272x - 0.0015
0.434 + 0.0015 = 0.0272x
0.4355 = 0.0272x
x = 16.011µg/ml

4. CO-GRINDING (Abs.: 0.186)

y = 0.0272x - 0.0015
0.186 = 0.0272x - 0.0015
0.186 + 0.0015 = 0.0272x
0.1875 = 0.0272x
x = 6.893µg/ml

(4.1.3.3) Solubility of Ezetimibe in 0.1N HCl

CALCULATION:

1. PURE DRUG (Abs.: 0.083)

y = 0.0848x - 0.1306
0.083 = 0.0848x - 0.1306
0.083 + 0.1306 = 0.0848x
0.2136= 0.0848x
x = 2.518µg/ml

2. SPRAY DRIED (Abs.: 0.424)

y = 0.0848x - 0.1306
0.424 = 0.0848x - 0.1306
0.424 + 0.1306 = 0.0848x
0.5546 = 0.0848x
x = 6.540µg/ml

3. PHYSICAL MIXTURE (Abs.: 0.312)

y = 0.0848x - 0.1306
0.312 = 0.0848x - 0.1306
0.312 + 0.1306 = 0.0848x
0.4426 = 0.0848x
x = 5.219µg/ml

4. CO-GRINDING (Abs.: 0.194)

y = 0.0848x - 0.1306
0.194 = 0.0848x - 0.1306

0.194 + 0.1306 = 0.0848x
0.3246 = 0.0848x
x = 3.827µg/ml

(4.1.4) Development of Formulation

(4.1.4.1) Optimization of Process parameters of Spray Dryer (with PVP-K30)

Table 4 Optimization of Process Parameters of Spray Dryer

Optimization of Process parameters of Spray Dryer (with PVP-K30)			
Sr.No.	Parameters	Criteria	Inference
1.	Optimization of Solid Content	7%	On higher solid content there is a chance of Gun Blocking, at 10 % solid content we get perfect solid dispersion.
		9%	
		10%	
		12%	
2.	Optimization of the atomization	1.4	At an increasing atomization rate, we get smaller size particles and at a slower atomization rate we get bigger particles but at a 1.6 atomization rate, we get the perfect size of particles.
		1.5	
		1.6	
		1.7	
		1.8	
3.	Optimization of inlet temperature	Lower 70°C	If we keep a lower temperature there is a chance of sticking on the wall, at a higher temperature chance of powder get degrade but at 90°C we get perfect powder.
		Medium 90°C	
		High 120°C	
4.	Optimization of the feed rate	Lower 4ml/min	Spray rate determines the Physicochemical properties of the particles. At 7ml/min we get perfect particles with perfect properties.
		Medium 7ml/min	
		Higher 10ml/min	

(4.1.4.2) Screening and Optimization of Super-disintegrants for Immediate Release Core Tablet

Table 5 Formulation of Rapid Release Core Tablets

Formulation of Rapid Release Core Tablets									
Ingredients (mg/tab)	**RR1**	**RR2**	**RR3**	**RR4**	**RR5**	**RR6**	**RR7**	**RR8**	**RR9**
Solid dispersion	30	30	30	30	30	30	30	30	30

Croscarmellose sodium	22	16.5	11	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	22	16.5	11	-	-	-
Crospovidone	-	-	-	-	-	-	22	16.5	11
Lactose	47	52.5	58	47	52.5	58	47	52.5	58
Magnesium Stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Colloidal Silicon Dioxide	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Ferric oxide Red	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total	100	100	100	100	100	100	100	100	100

(4.1.4.3) Disintegration time for core tablet screening

All the batches were prepared. The disintegration was checked by the disintegration apparatus. The warm water at 37℃ temperature was kept in a vessel and the 6 units of tablet were taken per batch and the results were noted. The RR1 batch had a disintegration time of 30secs which was the most relevant data for the formulation given in Figure 1.

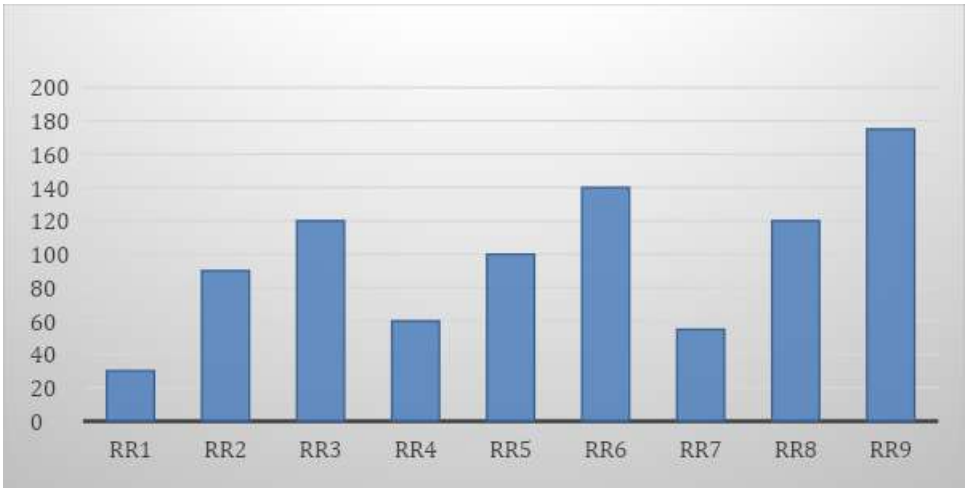


Figure 1 Formulation vs Disintegration time(secs)

(4.1.4.4) Dissolution test

The different dissolutions with 6 units of tablet were done for individual batches. The dissolution was carried out in the 0.1N HCl for 3hrs. Further, the media was changed with Phosphate buffer pH 6.8 for 3hrs 20mins. After that, the drug release was calculated and shown in Figure 2.

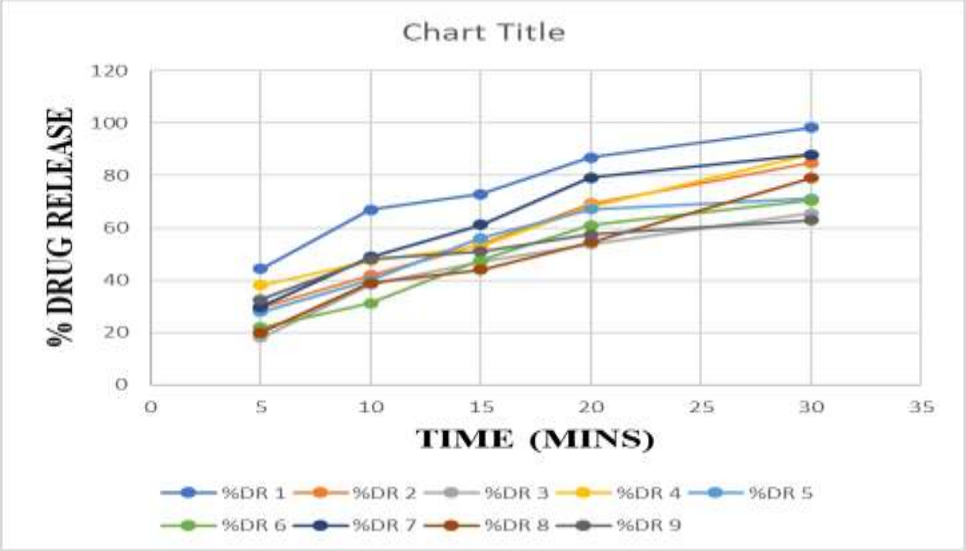


Figure 2 Time(mins) vs %Drug Release

Figure 3 Process for Core Tablet Formation

Tablet 6 Pre-Compression Evaluation of Preliminary Batches for Rapid Release Core Tablet

Batch No.	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)	Flow Property
IR1	0.50 ± 0.00	0.55 ±0.00	8.33±0.14	1.09±0.00	27.97 ± 0.09	Excellent
IR2	0.37 ± 0.01	0.43 ±0.00	13.85±0.67	1.16±0.02	33.73 ± 0.10	Good

IR3	0.51 ± 0.00	0.56 ±0.01	8.51±0.43	1.09±0.01	36.28 ± 0.12	Fair
IR4	0.44 ± 0.00	0.49 ±0.01	9.26±0.89	1.1±0.01	30.25 ± 0.22	Excellent
IR5	0.66 ± 0.01	0.73 ±0.00	10.81±1.65	1.12±0.02	34.69 ± 0.25	Good
IR6	0.62± 0.01	0.69 ±0.01	12.5±1.43	1.14±0.01	37.62 ± 0.29	Fair
IR7	0.38 ± 0.00	0.44 ±0.00	14.29±1.72	1.17±0.1	29.61 ± 0.26	Excellent
IR8	0.47 ± 0.00	0.52 ±0.01	9.8±0.85	1.11±0.02	34.29 ± 0.23	Good
IR9	0.51 ± 0.00	0.59 ±0.01	12.77±0.55	1.15±01	34.73 ± 0.27	Good

Table 7 Post- Compression Evaluation of Preliminary Batches for Rapid Release Core Tablet

Post Compression Parameter						
Batch No.	**Uniformity of Weight (mg)**	**Thickness (mm)**	**Hardness (kp)**	**Friability (%)**	**Drug Content (%)**	**Disintegration Time (sec)**
IR1	100 ± 2.43	2.85 ± 0.02	3.5 ± 0.33	0.28 ± 0.12	98.15 ± 2.28	30 ± 2.87
IR2	99.25 ± 3.70	2.79 ± 0.04	3.56 ± 0.33	0.33 ± 0.07	96.13 ± 3.32	120 ± 2.87
IR3	98.90 ± 2.56	2.90 ± 0.02	3.50 ± 0.37	0.29 ± 0.10	97.87 ± 1.48	240 ± 2.05
IR4	100 ± 2.48	2.80 ± 0.03	3.57 ± 0.26	0.47 ± 0.02	96.04 ± 1.88	60 ± 4.92
IR5	99.45 ± 1.83	2.79 ± 0.02	3.52 ± 0.21	0.24 ± 0.03	97.81 ± 0.45	145 ± 2.94
IR6	99.05 ± 3.28	2.75 ± 0.02	3.55 ± 0.36	0.32 ± 0.17	96.70 ± 2.00	195 ± 2.16

IR7	98.85 ± 3.73	2.81 ± 0.02	3.50 ± 0.25	0.34 ± 0.01	97.51 ± 1.62	65 ± 2.49
IR8	99.64 ± 2.87	2.78 ± 0.02	3.54 ± 0.08	0.35 ± 0.06	96.80 ± 2.61	130 ± 2.87
IR9	100 ± 3.81	2.79 ± 0.02	3.56 ± 0.25	0.36 ± 0.02	95.12 ± 1.95	220 ± 3.09

(4.1.4.4) Optimization for delayed release coat tablet

3^2 Full Factorial Design

The 2 factors were taken for optimization of a press-coated tablet. X1 = % Coating Polymer and X2 = % Binder with Y1 = Lag time (hrs) as a response. The 3 levels were taken for 2 factors. Levels for % Coating Polymer were 30, 40, and 50. While for Binder % levels were 6, 8, and 10. All the batches were prepared and evaluated. Batch 5^{th} was the optimized batch with % coating polymer 40 and the binder % 8. This batch had the 6hrs of lag time which was the required formulation parameter shown in Table 4.12. All batches were designed by using the Design Expert version 13. The software itself suggests the linear model and gives the equation.

Table 8 Factors and Levels for the Design

Sr.No.	**Factors**	**Levels**		
		-1	0	+1
1.	Coating Polymer (%)	30	40	50
2.	Binder (%)	6	8	10

Table 9 Design Matrix of Press-coated Tablet

		Coded values		**Actual values**			
StdOrder	RunOrder	(X1) Coating polymer (%)	(X2) Binder (%)	(X1) Coating polymer (%)	(X2) Binder (%)	(Y1) Lag Time (hrs)	(Y2) Thickness (kp)
2	1	-1	0	30	8	4.4	5.34
4	2	0	-1	40	6	4.9	5.20
8	3	1	0	50	8	8.4	4.36
9	4	1	1	50	10	10.1	4.12
5	**5**	**0**	**0**	**40**	**8**	**6.0**	**5.10**
1	6	-1	-1	30	3	3.8	5.45
3	7	-1	1	30	10	5.0	5.22
7	8	1	-1	50	6	7.4	4.48
6	9	0	1	40	10	7.1	5.02

Table 10 Pre-compression study of blends of coating materials for Pulsatile release tablet

Batch No.	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)	Flow Property
PR1	0.7±0.01	0.83 ±0.01	15.66 ±1.55	1.22±0.01	38.42±0.62	Fair
PR2	0.69 ±0.00	0.82 ±0.01	15.85 ±0.83	1.24±0.01	39.78±0.55	Fair
PR3	0.69 ±0.01	0.81 ±0.02	14.81 ±1.48	1.15±0.00	32.62±0.21	Good
PR4	0.69 ±0.00	0.8 ±0.01	13.75 ±0.92	1.17±0.02	33.18±0.35	Good
PR5	0.68 ±0.00	0.79 ±0.02	13.92 ±1.62	1.16±0.01	31.21±0.81	Good
PR6	0.68 ±0.01	0.77 ±0.02	11.69 ±0.41	1.15±0.01	34.61±1.04	Good
PR7	0.67 ±0.01	0.76 ±0.01	11.840.96	1.15±0.02	33.55±0.68	Good
PR8	0.67 ±0.00	0.75 ±0.02	10.67 ±1.33	1.13±0.01	31.89±0.77	Good
PR9	0.65±0.00	0.76 ±0.02	10.56 ±1.33	1.16±0.01	31.50±0.67	Good

Table 11 Post compression parameter for Pulsatile release coat tablet

Batch No.	Uniformity of Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Drug Content (%)
PR1	502.43 ± 3.21	6.62 ± 0.04	7.62 ± 0.04	0.33 ± 0.18	98.19 ± 1.68
PR2	501.65 ± 1.98	6.61 ± 0.02	8.69 ± 0.02	0.27 ± 0.12	98.05 ± 0.92
PR3	500.35 ± 1.83	4.48 ± 0.01	6.44 ± 0.01	0.43 ± 0.10	97.62 ± 2.08
PR4	503.11 ± 4.51	8.56 ± 0.04	4.36 ± 0.04	0.51 ± 0.09	98.13 ± 1.94
PR5	502.49 ± 3.25	5.10 ± 0.01	7.10 ± 0.01	0.38 ± 0.14	98.78 ± 1.39
PR6	499.32 ± 1.73	7.45 ± 0.02	8.83 ± 0.02	0.32 ± 0.07	98.55 ± 0.54
PR7	403.84 ±	5.56 ±	6.71 ±	0.23 ±	97.98 ±

	5.22	0.03	0.03	0.03	2.76
PR8	401.57 ± 3.81	4.07 ± 0.03	9.47 ± 0.03	0.15 ± 0.08	98.23 ± 1.42

Table 12 ANOVA for report Lag Time(hrs)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	34.21	5	6.84	272.65	0.0003	Significant
A-polymer	26.88	1	26.88	1071.30	< 0.0001	
B-binder	6.20	1	6.20	247.15	0.0006	
AB	0.5625	1	0.5625	22.42	0.0179	
A^2	0.5339	1	0.5339	21.28	0.0192	
B^2	0.0272	1	0.0272	1.08	0.3742	
Residual	0.0753	3	0.0251			
Cor Total	34.28	8				

Table 13 Fit Statistics for Lag Time(hrs)

Std. Dev.	0.1584	**R^2**	0.9978
Mean	6.34	**Adjusted R^2**	0.9941
C.V. %	2.50	**Predicted R^2**	0.9751
		Adeq Precision	48.4517

Final equation in terms of coded factors:

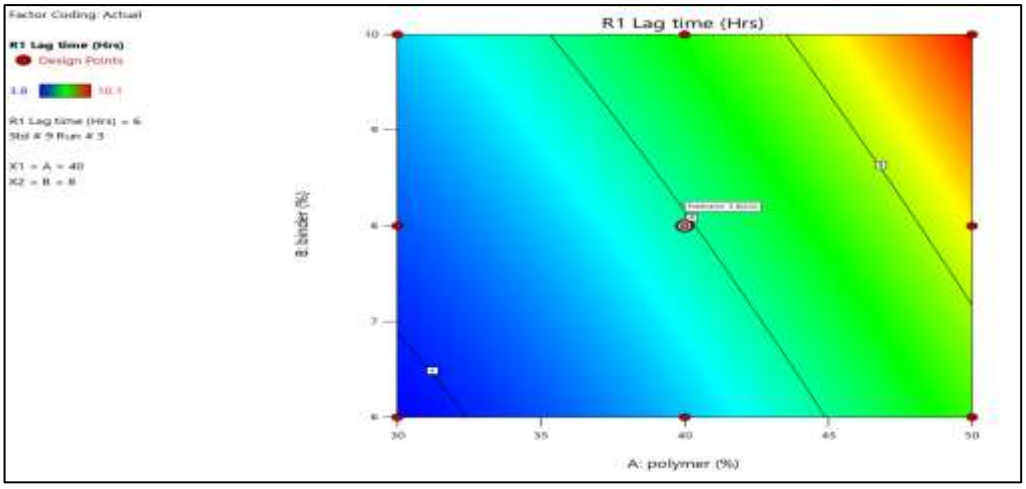
Lag Time = $5.92 + 2.12\ A + 1.02\ B + 0.3750\ (A)(B) + 0.5167\ A^2 + 0.1167\ B^2$

Final equation in terms of actual factors:

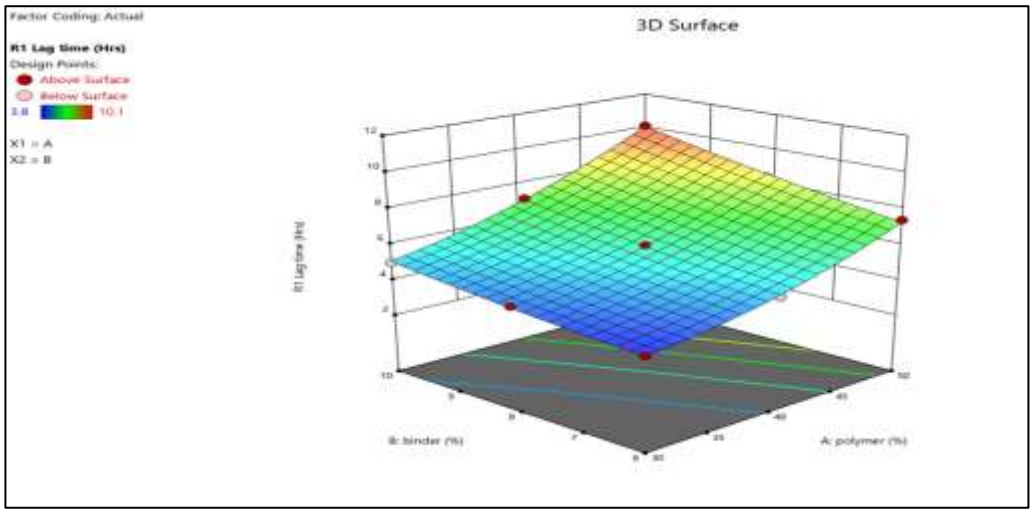
Lag Time = 5.92 + 2.12 Coating Polymer + 1.02 Binder + 0.3750 (Coating Polymer) (Binder) + 0.5167 $(\text{Coating Polymer})^2$ + 0.1167 $(\text{Binder})^2$

From the ANOVA Table 4.15 shown the model F-value of 272.65 implies the model is significant. The shows P-value of 0.0003 which was less than 0.05 implies the model is significant.

The R^2 should be near to 1 or 1, that shows the model has linearity. The R^2 found was 0.9978 shown in table 4.16. The difference between Adjusted R^2 and Predicted R^2 should be less than 0.02.



(a)



(b)

Figure 4 (a) Contour Plot of Lag Time (b) 3D Surface Plot of Lag Time

From the Contour Plot and 3D surface view, we can observe the graphical analysis of the effects of two factors on the Lag Time. The red region shows the maximum Lag Time and the blue shows shows the minimum Lag Time. For ratio at the -1 level, the blue region is there and for the +1 level, the color changed from green to red that shows the increase in Lag Time as we increase the ratio. The graph shows that with the increase in Coating polymer and Binder the lag time increases.

Table 14 ANOVA for report Thickness (kp)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.81	5	0.3618	174.52	0.0007	significant
A-polymer	1.55	1	1.55	747.86	0.0001	
B-binder	0.0988	1	0.0988	47.67	0.0062	
AB	0.0042	1	0.0042	2.04	0.2487	
A^2	0.1549	1	0.1549	74.74	0.0033	
B^2	0.0007	1	0.0007	0.3243	0.6089	

Residual	0.0062	3	0.0021			
Cor Total	1.82	8				

Table 15 Fit Statistics for Thickness (kp)

Std. Dev.	0.0455	**R^2**	0.9966
Mean	4.92	**Adjusted R^2**	0.9909
C.V. %	0.9252	**Predicted R^2**	0.9603
		Adeq Precision	34.2509

Final equation in terms of coded factors:

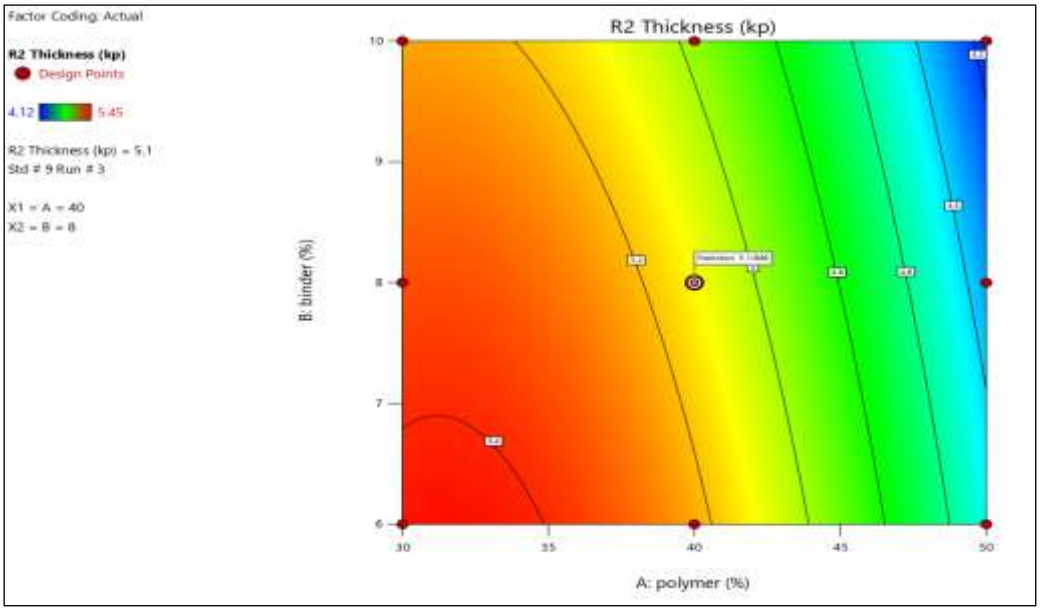
Thickness = 5.12 - 0.5083 A - 0.1283 B - 0.0325 (A)(B) - 0.27832 A^2 + 0.01832 B^2

Final equation in terms of actual factors:

Thickness = 5.12 - 0.5083 Coating Polymer - 0.1283 Binder - 0.0325 (Coating Polymer) (Binder) - 0.2783 Coating $Polymer^2$ + 0.0183 $Binder^2$

From ANOVA Table 4.17 shows the model F-value of 174.52 implies the model is significant. The shows P-value of 0.0007 which was less than 0.05 implies the model is significant.

The R^2 should be near to 1 or 1, that shows the model has linearity. The R^2 found was 0.9966 shown in table 4.18. The difference between Adjusted R^2 and Predicted R^2 should be less than 0.02.



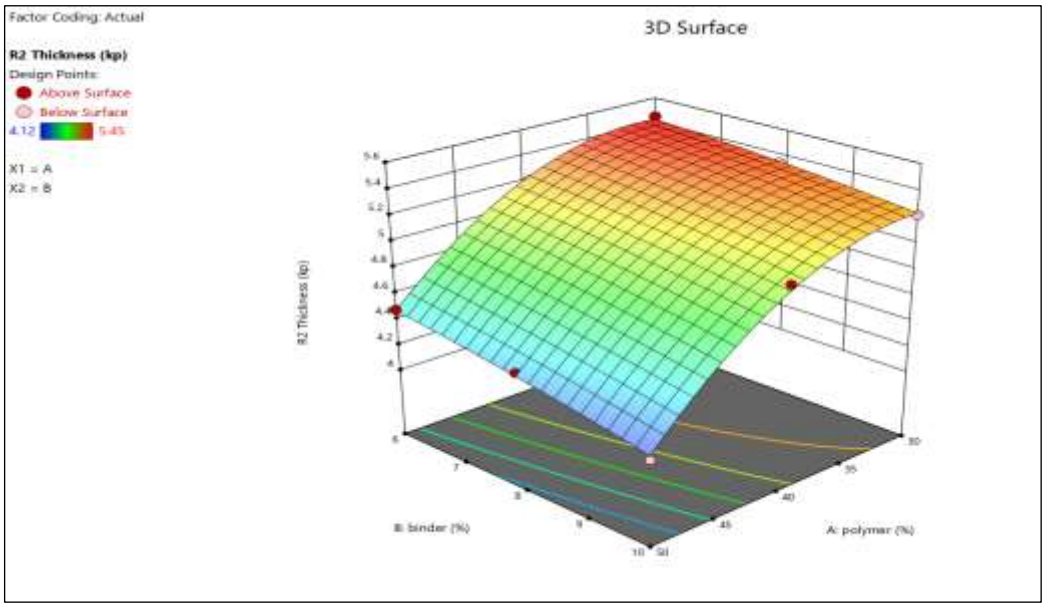


Figure 5 (a) Contour Plot of Thickness (b) 3D Surface Plot of Thickness

From the contour plot and 3D surface view, we can observe the graphical analysis of the effects of two factors on the Thickness. The red region shows the maximum Thickness and the blue shows shows the minimum Thickness. For the ratio at the -1 level, the red region is there and for the +1 level, the color changed from yellow to blue that shows the decrease in Thickness as we increase the ratio. The graph shows that with the increase in Coating polymer and Binder, the thickness decreases. When we had narrowed down the lag time selection region from 5.5-7.0 hrs and the thickness selected was 4.8-5.0. The design expert has shown the following design space that will give the desired range of result. This plot was named as overlay plot as shown in Fig. 4.25.

The overlay plot shows the prediction values of factors that we had taken in the design. As per using these predicted values the validation of the checkpoint batch was required. The formulation was prepared by using predicted values and the evaluation parameter (response) was studied.

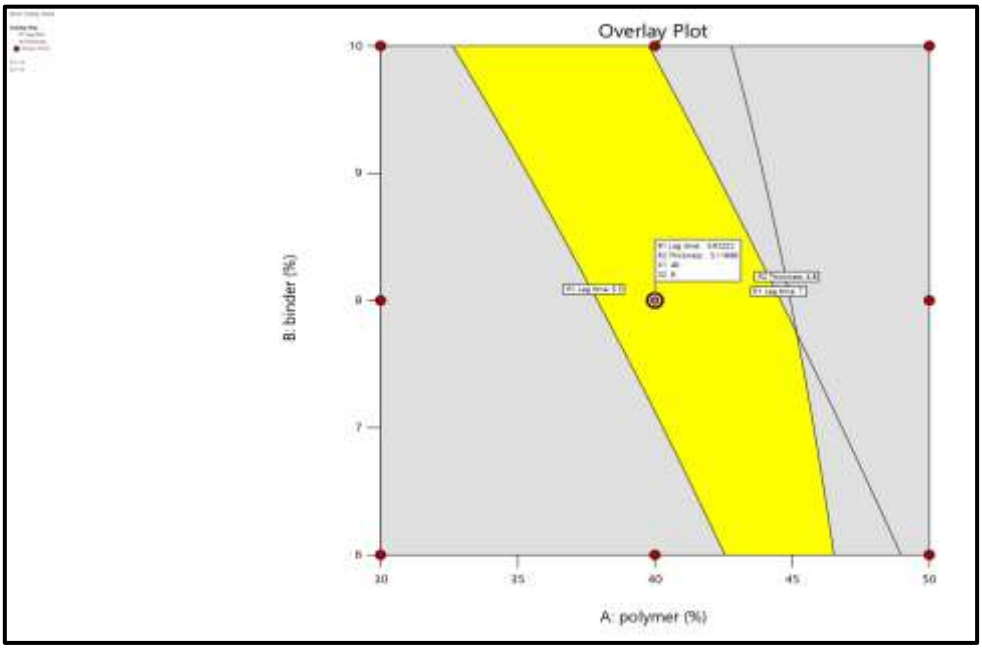


Figure 6 Flag Marked Overlay plot for Predicted Batch

(4.1.4.5) Validation of Check Point Batch

After prediction was done by DOE, a checkpoint batch was formed and all the evaluation parameters were done on that batch. First matching the data was done with the predicted v/s actual batch. Here, for the X1 factor i.e. coating polymer concentration was 40%, and X2 factor i.e. Binder concentration 8% was selected.

Table 16 Check Point Batch

Parameter	Predicted value	Experimental value	%Error
Lag Time (hrs)	5.922	6.00	0.078
Thickness (kp)	5.118	5.10	0.018

By checking predicted v/s actual value as per Table 4.19 and Fig.4.25, the DOE was very much useful and providing a very appropriate prediction, by which we can obtain a particular batch of which lag time and thickness were obtained as per our requirement by using same ingredients. On the basis of evaluation, we conclude that the check point batch was validated.

(4.1.5) Evaluation of Check Point Batch

(4.1.5.1) Pre-Compression Parameters

Table 17 Pre-Compression Parameters for Check Point Batch

Post Compression Parameter						
Batch No.	**Bulk density (g/cm^3)**	**Tapped density (g/cm^3)**	**Compressibility index (%)**	**Hausner's ratio**	**Angle of repose (θ)**	**Flow Property**
IR1	0.64 ±0.00	0.76 ±0.02	13.97 ±1.62	1.14±0.01	31.23±0.81	Good

(4.1.5.2) Post-Compression Parameters

Table 18 Post-Compression Parameters for Check Point Batch

Post Compression Parameter						
Batch No.	**Uniformity of Weight (mg)**	**Thickness (mm)**	**Hardness (kp)**	**Friability (%)**	**Drug Content (%)**	**Disintegration Time (sec)**
IR1	501.89 ± 3.25	5.10 ± 0.01	7.10 ± 0.25	0.36 ± 0.14	98.27 ± 1.39	30 ± 1.74

5.2.4.3 In-vitro Dissolution Study

Table 19 In-vitro Study Drug Release

Time (mins)	% DR 1
0	**0**

60	**0**
120	**0**
180	**0**
240	**0**
300	**0**
360	**48.52**
365	**66.96**
370	**72.87**
375	**86.88**
380	**98.27**

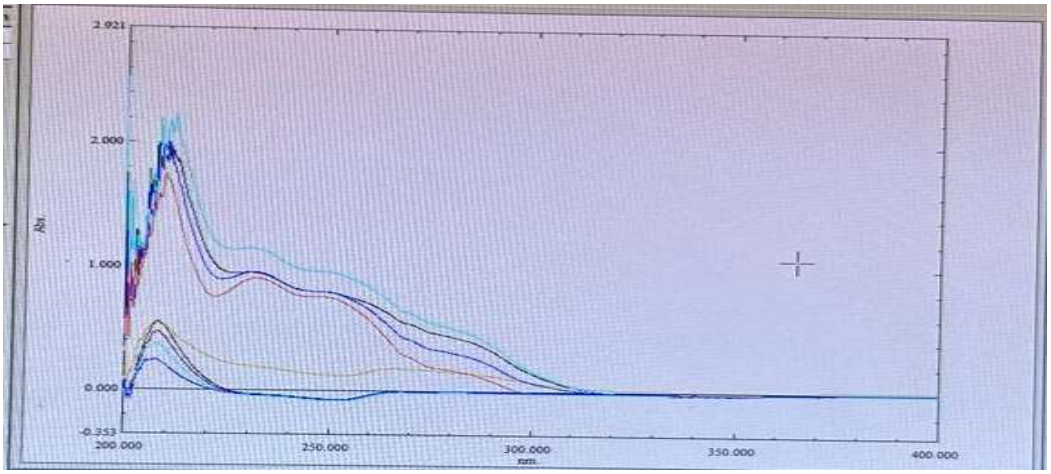


Figure 7 UV-Spectrum for Check Point Batch

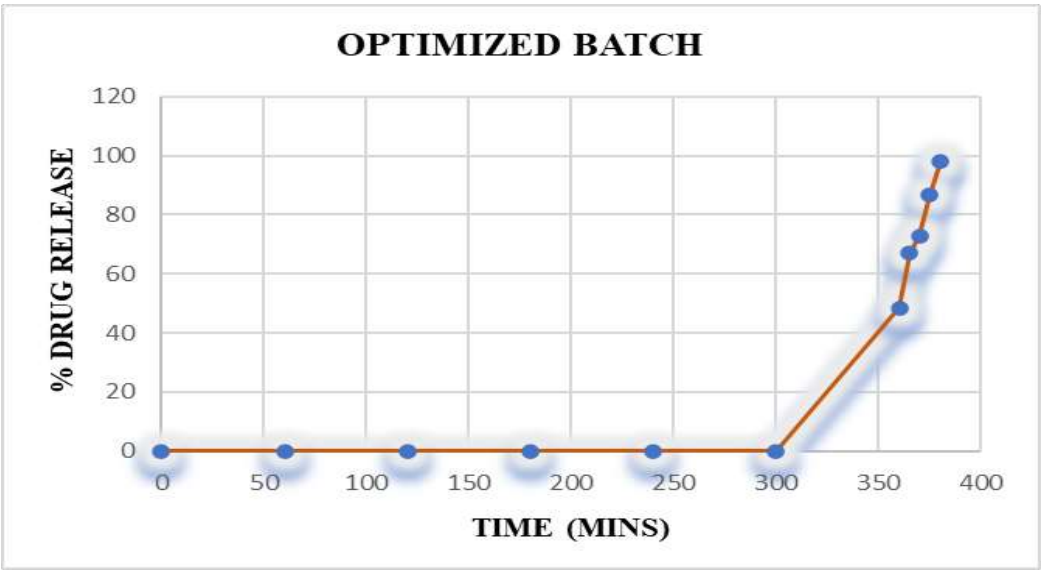


Figure 8 In-vitro Study Drug Release

(4.1.6) Stability Studies

The Press-coated tablet was kept at 40°C/75% RH for 15 days and 30 days. The difference in the result of both formulations after the stability period was checked.

Table 20 Stability studies

Parameter	The result of fresh formulation	Result at 40°C/75% RH (After 15 days)	Result at 40°C/75% RH (After 30 days)
Lag Time (hrs)	6.00	6.05	5.994
Thickness (kp)	5.10	5.12	5.12

(5) SUMMARY AND CONCLUSION

This study aimed to Formulation, optimization, and evaluation of Ezetimibe for chronotherapeutic drug delivery using compression-coating technology. The rapid-release formulation was coated with hydrophilic and pH-independent polymers, Glyceryl behenate and Dibasic calcium phosphate in combination.

The Solid dispersion between the Drug and PVP K30 was assessed using, XRD, DSC, and FTIR spectroscopy indicating the prepared drug-polymer complex. Method development and validation were carried out for the estimation of a drug in Phosphate buffer pH 6.8 media. The rapid release core tablets were prepared through a wet granulation process, using various concentrations of super disintegrant screened. (SSG, CCS and Crospovidone). The tablet blends demonstrated excellent to good flow characteristics and the drug content remained within the specified limits. Formulation IR1, with 22mg croscarmellose sodium, exhibited quick disintegration (30 seconds). Based on disintegration, formulation IR1 was selected for press coating. The optimized tablets were coated with fracture hydrophilic and pH-independent polymers (Glyceryl Behenate and Dibasic Calcium Phosphate). The weight uniformity, hardness, thickness, and friability of the pulsatile release tablets were found to be within acceptable ranges. The drug content met the Pharmacopeial limits. Dissolution studies demonstrated that formulation PR6 achieved 98.34 % drug release for Ezetimibe, after 6 hours 20mins with a 6-hour lag time. The optimization of the formulation was done by using 32 factorial design. The design consisted of 2 dependent variables Y1 and Y2 and independent or controlled variables Factor X1 and X2. The two independent formulation variables selected for the study were Factor 1 Coating Polymer and Factor 2 Binder. The dependent variables were R1 Lag time and R2 Thickness (kp). The design layout was generated by the Design Expert software. The batches underwent evaluation using various parameters and the formulation of the Optimized batch containing Glyceryl Behenate and Magnesium Stearate (40% and 8%) demonstrated the desired drug release in 6.20 hours (within 20 min after lag time) with a 6.0 hours pulsatile lag time and 5.10 kp thickness.

The optimized batch was carried out for accelerated stability testing, which shows no significant changes in the physical appearance as well as drug release, indicating the stability of formulation during storage.

Conclusion

An attempt has been made to develop a pulsatile release tablet containing BCS class-II drug Ezetimibe

using press coating technology. Solubility enhancement was carried out by PVP K30 polymer using a complex formation with a drug. Glyceryl Behenate and Dibasic Calcium Phosphate were able to delay the drug release up to 6 hours for the pulsatile release of drug. 32 factorial design was explored to develop the PRT of Ezetimbe. Concentration of Coating polymer was found critical for the successful development of pulsatile release tablet. The developed formulation will be definitely helpful at the industry scale.

LIST OF ABBREVIATIONS

HC	Hypercholesterolemia
LDL-C	Low-density lipoprotein cholesterol
AH	Acquired hypercholesterolemia
HDL	High-density lipoprotein
BMI	Body mass index
LDLR	Low-density lipoprotein receptors
FH	Familial hypercholesterolemia
DDSs	Drug delivery systems
PDDS	Pulsatile Drug Delivery System
HPMC	Hydroxypropyl methylcellulose
ASDs	Amorphous Solid dispersions
PWSDs	Poorly water-soluble drugs
SD	Solid Dispersion
SPL	Spironolactone
NPC1L1P	Niemann-Pick C1-like 1 protein
TGG	Thiolated gum ghatti
SD	Solid Dispersion
CCD	Central Composite Design
RSD	Response Surface Methodology
DSC	Differential Scanning Calorimetry
KBr	Potassium bromide
XRD	X-ray Diffraction

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