East Point College of Pharmacy

East Point Campus, Jnana Prabha, Virgo
Nagar PostBengaluru – 560049, Karnataka

Approved
by
Pharmacy Council of India, New Delhi

Affiliated
to
Rajiv Gandhi University of Health Sciences
Karnataka
Bengaluru – 560041
India

LAB MANUAL

MOLECULAR PHARMACEUTICS (NANOTECH & TARGETED DDS) PRACTICAL

M. PHARM 1st SEMESTER

EAST POINT COLLEGE OF PHARMACY
East Point Campus, Jnana Prabha, Virgo Nagar Post,
Bengaluru – 560049, Karnataka

M. Pharmacy (Pharmaceutics)	
Programme Outcome (PO)	
PO1	An ability to independently carry out research /investigation and development work.
PO2	An ability to write and present a substantial technical report/document
PO3	Students should be able to demonstrate a degree of mastery over the area as per the specialization of the program. The mastery should be at a level higher than the requirements in the appropriate bachelor's program
PO4	Graduates will demonstrate comprehensive knowledge and practical skills in advanced pharmaceutical development, encompassing drug analysis, drug formulation, and evaluation of novel drug delivery systems.
PO5	Students will acquire a deep understanding of regulatory processes and compliance, preparing dossiers for submission to regulatory agencies worldwide. They will navigate the intricacies of innovator and generic drug concepts, ensure adherence to global guidelines, and exhibit expertise in Biopharmaceutics& Pharmacokinetics.
PO6	Graduates will integrate technological advancements into pharmaceutical research and development, utilizing computational modelling, design of experiments, and prototype modelling.

Programme Specific Outcomes (PSO)	
PSO1	Apply appropriate tools and techniques for design and development of Pharmaceutical Dosage forms, cosmeceuticals and drug delivery systems
PSO2	Comprehend the pharmacokinetic parameters of drugs, dose calculations and biopharmaceutical approaches in problem solving
PSO3	Acquaint knowledge on investigational new drugs and regulatory submissions

Course Outcomes (CO's)	
Code: MPH205P Molecular Pharmaceutics (NANOTECH AND TARGETED DDS) Practical	
CO 1	Formulate different vesicular carriers for novel drug delivery and analysis of drug release profile
CO 2	Evaluate the different vesicular carriers for novel drug delivery
CO 3	Apply the knowledge of computer simulations in Pharmacokinetics and Pharmacodynamics studies, Use DoE and QbD techniques in product development

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EAST POINT COLLEGE OF PHARMACY
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Experiment No. 01

Effect of Temperature in Solvent Evaporation Process on Microsphere Properties

AIM: To study the effect of temperature in micro capsule preparation.

PRINCIPLE:

Microencapsulation by the solvent evaporation method is a complex process, which can be influenced by many process parameters, e.g. solvent evaporation rate,) temperature) solubility of polymer, drug and excipients in both emulsion phases,) dispersion stirring rate,) viscosity, solubility, volume and volume ratio between the inner and outer phases,) the quantity of polymer and drug,) and the physio-chemical properties and concentration of the stabilization.) Some authors have previously studied the effects of preparation temperature on microsphere formation and characteristics: mean microsphere diameter and size distribution width,) particles morphology,) porosity,) and drug loading.)

One can find only one report on the effect of temperature on microspheres containing ethyl cellulose. We have previously reported that temperature (40, 50, 60 °C) had an insignificant effect on mean diameter or drug encapsulation yield using ethyl cellulose as a matrix polymer) However, these results differ from the findings of the above mentioned authors.) Thus, the objective of this study was to investigate the effect of preparation temperature on ethyl cellulose microsphere properties in a different temperature range. Lower temperatures were examined, where more pronounced influences were expected. Average particle size and microsphere morphology, drug content and release kinetics, and drug crystal state in microspheres were evaluated.

FORMULA:

INGREDIENTS	QUANTITY
Paracetamol	500 mg
Ethyl cellulose	2 g
Dichloromethane	10 ml
Span 80	0.24 ml
Water	200 ml

Procedure

Microspheres were prepared using a solvent evaporation technique in an acetone/liquid paraffin solvent system. 0.24 ml span were dissolved in 200 ml of water. 2g of ethyl cellulose and Dichloromethane of 10 ml of mixed together. (10, 25, 35, 40 °C). The system was stirred at 250 rpm at the above-mentioned constant temperatures for 1 h. The microspheres were filtered, washed with n-hexane, and dried overnight at room temperature under reduced pressure. Microspheres were prepared in triplicates at each of the defined temperatures. All the experiments for microsphere characterization were performed with one-day-old samples, except in the cases specified otherwise.

Evaluation:

Particle Size Analysis

Microsphere size was determined with sieve analysis. Sieves with mesh sizes 630, 500, 400, 315, 250, 200, 160, 125, 100, 80, 63, and 50m m were used. Sifting time was 20 min.

Drug Content Determination

A known quantity of microspheres (ca. 10 mg) was dispersed in 96% ethanol and stirred for an hour. A small volume of the sample was filtered, diluted with ethanol, and the Paracetamol concentration was determined spectrophotometrically at 249 nm.

Release Studies.

The USP XXVI paddle method was used to determine of Paracetamol release kinetics. Approximately 80 mg of microspheres were dispersed in 1 l of phosphate buffer saline pH 7.4 and stirred at 100 rpm at 37 °C for 6 h. Samples were taken at 5, 10, 15,30, 60, 120, 180, 240, 300 and 360 min and Paracetamol concentration was determined spectrophotometrically at 249 nm. We have studied Paracetamol release from whole samples (only a fraction of particles agglomerates bigger than 630mm, which had also been excluded from the mean particle size calculation, was cast aside) and from the size fraction 160—200m m.

Report:

Studied effect of temperature in micro capsule preparation.

Experiment No. 02

Preparation And Evaluation Of Alginate Beads Of Diclofenac Sodium

AIM: - To Preparation and evaluation of alginate beads

INTRODUCTION:

The drug delivery systems that can precisely control the release rates or target drugs to specific body site have an enormous impact on the health-care system. The last two decades, in the pharmaceutical industry, have witnessed an avant-grade interaction among the field of polymer and material science, resulting in the development of novel drug delivery systems.

The physicochemical characteristics of drugs vary considerably, so different microsphere formulations are often developed according to specific clinical needs. Emulsion gelation methods are most commonly used to prepare microspheres.

Diabetes mellitus (DM) is a chronic metabolic disorder affecting people worldwide, with significant morbidity and mortality caused by its micro- and macro-vascular complications, affecting various vital organs and structures in humans.

It has been estimated that by year 2030, the diabetic population will rapidly increase from 21.7 million to 79.4 million in India. However, prevalence is much more than this estimation, as many patients are asymptomatic and unaware about this and go undiagnosed. Voglibose belongs to class of competitive α-glucosidase inhibitors (α-GIs). It was discovered in Japan in 1981, after its isolation from validamyan on culture media-the producing organism being Streptomyces hygroscopicus var. limonons. However, it became commercially available treatment for DM in Japan from 1994.Voglibose is an amine substituted cyclohexane polyol.

FORMULA

INGREDIENTS	QUANTITY
Sodium alginate	100 mg
Castor oil	2.5 ml
liquid paraffin	2.5 ml
vegetable oil	2.5 ml
Diclofenac sodium	50 mg

PROCEDURE:

The oil entrapped calcium alginate beads were prepared by emulsion gelation method. The polymer was dissolved in water with stirring at 100 rpm. Selected oils (2.5 ml) were added to polymer solution. The drug 50 mg was added to it.

The homogenized or nonhomogenized mixture was extruded into 5% calcium chloride solution with gentle agitation

37°C ± 0.5°C at room temperature. The formed beads were allowed to stand for 5 min in the solution, decanted, filtered, and finally dried overnight at room temperature

EVALUATION

Size distribution and size analysis

Gel beads were separated into different size fractions by sieving for 10 min using a mechanical shaker containing standard sieves as per Indian Pharmacopoeia specifications. The particle size distribution was determined and the means particle size of gel beads was calculated by the formula.

Study of the morphology of gel beads

The mean diameter of 50 dried beads and morphological examination of dried beads were performed using optical microscopy.

Measurement of buoyancy property

For the evaluation of the floating property, approximately 100 beads were counted and pasted on one side of the glass slide secured to the United States Pharmacopoeia disintegration apparatus. The apparatus was run for 5 h, and at predetermined time intervals (30 min), the slide was taken out and the number of beads still adhering to the slide was counted

In vitro release of microspheres

The in vitro release studies were carried out at 37± 0.5°C and at 100 rpm by buffer change method using 0.1 N HCl (1 h), 4 pH (1 h), 6 pH (3 h), 6.8 pH (3 h), and 7.4 Ph. (2 h) phosphate buffers (200 ml) in sink conditions using a diffusion cell. Accurately weighed samples of gel beads were added to the donor cell. At pre-set time intervals; 5 ml of aliquots are withdrawn and replaced by an equal volume of fresh dissolution medium. The aliquots were analyzed UV spectrophotometrically at 276 nm-λ max after proper dilution.

Time (Mins/ Hrs)	Abs (nm)	Conc in µg/ml [$X=\frac{Y\pm c}{m}$]	Conc in mg/ml [X′=X/1000]	Amt in 1 ml [X′ *100]	Amt in 10 ml (mg)	Amt in 900 ml (mg)	Cleared amt (mg)	CDR (mg)	% CDR

Report:

Experiment No. 03

Preparation and evaluation of albumin microsphere

AIM: - To prepare and evaluate the albumin microsphere containing Paracetamol.

PRINCIPLE:

Microspheres are defined as spherical empty particles with size varying from 1-1000 µm containing a core substance. They are made of polymeric waxy or other protective material i.e. biodegradable synthetic polymers and modified natural polymers such as starches, gums, protein, fats, and waxes. The natural polymers include albumin and gelatin other synthetic materials include poly lactic acid and poly glycolic acid etc.

Albumin microspheres are mainly prepared by emulsion polymerization using either heat denaturation of the particles at elevated temperature (100-180 ˚C) or chemical cross linking (glutaraldehyde). The microspheres prepared by above methods are hydrophobic in nature and therefore small amount of surface active agent is needed to disperse them in parenteral preparation.

Formula:

Ingredients	**Quantity (mg)**
Paracetamol	20
Span 80	1
Bovine serum albumin	125
Liquid paraffin	130

Procedure:

20 mg of drug and 125 mg of Bovine serum albumin were dissolved in 0.5 ml of water and this was added to 30 ml of liquid paraffin at 4˚C which was ultra-sonicated for 2 minutes. Thus formed emulsion was added to 100 ml oil which contained 1ml span (temperature 105-126˚C), the addition was made drop by drop (40 drops/mins). The obtained microspheres were filtered and washed with n-hexane to remove excess of oil and dried.

Evaluation:

Micromeritic properties:

The average particle size of the microspheres was determined by wing optical microscope The flow properties and packing properties were investigated by measuring the angle of repose, tapped density and bulk density

Drug entrapment:

Accurately weighed microspheres equivalent to 200mg of drug was suspended in 25m ut methanol and sonicated for 3 mins. The solution was then filtered, diluted suitably and analyzed for drug content spectrophotometrically at 258nm. The percentage drug entrapment was calculated as

$$\%\text{Drug Entrapment} = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \text{X100}$$

Dissolution studies:

The dissolution test was performed in the USP XXIII dissolution test apparatus by paddle method. The dissolution media used was 900ml of phosphate buffer pH 7.4 maintained at 37± 0.50C and rotated at 100r/min. Aliquots samples were withdrawn at specified time intervals and replaced with the same volume of fresh media, filtered, and analyzed spectrophotometrically (Shimadzu 1600) at 258n, for cumulative drug release.

Report:

The microspheres were prepared and evaluated and the percentage entrapped is …….

Experiment No. 04

Preparation and evaluation of albumin microsphere

AIM: - To prepare and evaluate the albumin microsphere containing Paracetamol.

PRINCIPLE:

Microspheres are defined as spherical empty particles with size varying from 1-1000 µm containing a core substance. They are made of polymeric waxy or other protective material i.e. biodegradable synthetic polymers and modified natural polymers such as starches, gums, protein, fats, and waxes. The natural polymers include albumin and gelatin other synthetic materials include poly lactic acid and poly glycolic acid etc.

Albumin microspheres are mainly prepared by emulsion polymerization using either heat denaturation of the particles at elevated temperature (100-180 ˚C) or chemical cross linking (glutaraldehyde). The microspheres prepared by above methods are hydrophobic in nature and therefore small amount of surface active agent is needed to disperse them in parenteral preparation.

Formula:

Ingredients	Quantity (mg)
Paracetamol	20
Span 80	1
Bovine serum albumin	125
Liquid paraffin	130

Procedure:

20 mg of drug and 125 mg of Bovine serum albumin were dissolved in 0.5 ml of water and this was added to 30 ml of liquid paraffin at 4˚C which was ultra-sonicated for 2 minutes. Thus formed emulsion was added to 100 ml oil which contained 1ml span (temperature 105-126˚C), the addition was made drop by drop (40 drops/mins). The obtained microspheres were filtered and washed with n-hexane to remove excess of oil and dried.

Evaluation:

Micromeritic properties:

The average particle size of the microspheres was determined by wing optical microscope The flow properties and packing properties were investigated by measuring the angle of repose, tapped density and bulk density

Drug entrapment:

Accurately weighed microspheres equivalent to 200mg of drug was suspended in 25m ut methanol and sonicated for 3 mins. The solution was then filtered, diluted suitably and analyzed for drug content spectrophotometrically at 258nm. The percentage drug entrapment was calculated as

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Report:

The microspheres were prepared and evaluated and the percentage entrapped is …….

Experiment No. 05

Preparation and Evaluation of Liposomes

AIM: To prepare and evaluate liposomes containing sodium salicylate

PRINCIPLE:

Liposomes are sealed sacs in a micron or submicron range dispersed in an aqueous enviroment the wall of the sacs consist of bilayers ensure the formulation of the internal aqueous compartment which can differ from the outside medium. The presence of two different enviroment in the carrier, the aqueous internal miller and the membrane makes the liposomes a unique model for studying biological membrane and versatile carrier for a broad spectrum of hydrophobic , amphipathic and hydrophobic natured agent .

Formula:

Ingredients	Quantity(mg)
Phosphotidyl choline	75
Cholestrol	38
Stearyl amine	27
Sodium salicylate	20

Procedure:

The vesicles are prepared by film hydration method. accurately weighed amount of **phosphotidyl choline, cholestrol , stearyl amine were dissolved** in 10ml of 9:1 mixture of choloform and methanol .the solution was subjected to rotary vaccum evaporater in RBF which was maintained at 55 in waterbath at 150rpm for about 15 minute , then the film was hydrated with drug solution (10ml) and the resulting solution was kept in rotation for 15mints without applying pressure , then the preparation was evaluated for size , zeta potential and entrapment

Evaluation:

1 ml of preparation was taken in a gelatin pouch and kept in 50ml of water. The water was replaced for every 10 minutes untill the concentration of the dissolved drug became zero

REPORT:

Experiment No. 06

PREPARATION AND EVALUATION OF NIOSOMES

AIM: To prepare and evaluate Niosomes.

PRINCIPLE:

Niosomes are vesicles mainly consisting of non – ionic surfactants. One of the reasons for preparing niosomes is assumed, higher chemical stability of surfactant than that of the phospholipids which are used in the preparation of liposomes.

Niosomes can be prepared from several classes of non- ionic surfactant. Eg- Polyglycerol, alkyl ethers, cross ethers, polyoxy ethylene ethylene and ethers. Often a charged surfactant is intercalated in the bilayers in order to introduced electrostatic repulsion between vesicles thus increasing their stability. This is especially recommended at higher surfactant concentration.

One of the aim of developing delivery system is controlling the release of drugs from the carrier system in order to achieve controlled uptake by the body. The release can be controlled by various parameters such as composition, size and number of bilayers of vesicles.

FORMULA :

Ingredients	Quantity Taken
Cholesterol	38 mg
Span 60	43.1 mg
Sodium salicylate	20 mg

PROCEDURE:

The vesicles are prepared by film hydration technique, accurately weighed. Cholesterol and Span 60 were dissolved in 10 ml of 9:1 mixture of chloroform and methanol. The solution was subjected to rotary vaccum evaporator in RBF which was maintained at 75° c in water bath at 150 rpm for about 15 mints and the resulting solution was kept in rotation for 15 mints without

applying pressure. Then the preparation was evaluated for size and entrapment efficiency before and after autoclaving.

EVALUATION:

Vesicle size, size distribution analysis

The vesicle size of the sample of niosomes was analysed by using particle size analyser (Malvern instrument).

REPORT:

Experiment No. 07

FORMULATION AND EVALUATION OF SPHERULS

AIM: To formulate and evaluate of Paracetamol spheruls

MATERIALS REQUIRED

Paracetamol, HPMC, chloroform, agar-agar, liquid paraffin I.P, petroleum ether, cyclohexane, ethyl cellulose, three blade motor stirrer.

PRINCIPLE:

Paracetamol, also known as acetaminophen or APAP, is a medicine used to treat pain and fever. It is typically used for mild to moderate pain relief. Acetaminophen is an odorless, slightly bitter-tasting white crystalline powder. It is soluble in organic solvents such as methanol and ethanol but slightly soluble in water and ether. Its pH range is 5.5 - 6.5 based on saturated aqueous solution. It, chemically N-(4-Hydroxyphenyl) acetamide, is derived from the interaction of p-aminophenol and an aqueous solution of acetic anhydride. Paracetamol is available in tablet, capsule, liquid suspension, suppository, intravenous, intramuscular, and effervescent forms. In the present work, solid dispersions of Paracetamol in HPMC were first prepared to enhance its dissolution rate and then the suspensions were incorporated with agar spherules using the meltable disposition method. Agar, a hydrophilic colloidal substance that undergoes swelling and releases the dispersed drug in an aqueous environment act as the reservoir type. The reservoir type agar micro spherules are then encapsulated using ethyl cellulose as coating material to obtain slow release of Paracetamol.

PREPARATION OF SOLID DISPERSIONS:

Solid dispersions of Paracetamol in HPMC were prepared by solvent evaporation method. Drug: carrier ratio of 1:1 was employed. The carrier was first dissolved in chloroform (30 ml) with the help of a magnetic stirrer. Then Paracetamol was transferred into this polymer chloroform solution part by part while stirring. The solvent was removed by evaporation at 40° under vacuum. The mass obtained was dried in a dessicator for 72 hours, crushed, pulverized and shifted through mesh no 80. Preparation of physical mixture of drug: carrier ratio 1:1 was used.

Paracetamol and HPMC were mixed thoroughly in a glass mortar. This was done by geometric dilution technique to ensure a homogenous distribution

DISSOLUTION RATE STUDIES ON SOLID DISPERSIONS:

The dissolution rate of Paracetamol in pure form, solid dispersion and from physical mixture was studied using a USP XXII dissolution rate apparatus employing a paddle stirrer. Solid dispersion equivalent to 100mg of Paracetamol was filled in hard gelatin capsules and externally wound with stainless steel wire as a sink. 900 ml of pH 7.4 buffer solution was used as dissolution media. The temperature was maintained at 37±1°. A 5 ml aliquot of dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with a fresh quantity of dissolution media. The samples were suitably diluted and analyzed for Paracetamol at 248 nm using UV spectrophotometer Shimadzu. Dissolution efficiency (DE%) was also found out as proposed by Khan is defined as the area under the dissolution curve upto a certain time 't' expressed as a % of the area of the rectangle described by 100% dissolution.

D.E. = 0 ò 1 Y.dt X 100 Y.100t

PREPARATION OF AGAR SPHERULES:

Powdered agar-agar 1.5g was dissolved in 75ml of water bath. The colloidal solution was gradually cooled to 55 ° and the solid dispersion of Paracetamol (equivalent to 200g of Paracetamol) was incorporated and mixed thoroughly. Dispersions was then transferred into 200ml liquid paraffin which was maintained at 55±2° in a water bath. The contents were stirred for 5 minutes with a three blade stirrer at 200 rpm to form fine micro spherule. The mixture was cooled in an ice bath to 10° for rigidization of the spherules. The spherules were filtered through a 60 mesh sieve and washed thrice (100ml each) with petroleum ether until the adhering liquid paraffin was totally removed. The micro spherules were dried at room temperature in vacuum dessicator.

ENCAPSULATION OF AGAR MICRO SPHERULES:

Dried agar micro spherules were taken into 100ml hot solution of ethyl cellulose in cyclohexane. The system was stirred at 50 rpm. The contents were slowly cooled to room temperature. The Spherules were then separated through filtration through 60 mesh sieve and

dried in a desiccator. Two different core: coat ratios 2:1 and 1:2 were used, referred as ME1 and ME2.

EVALUATION OF ENCAPSULATED MICROSPHERULES:

DRUG CONTENT UNIFORMITY:

All the batches of uncoated ME1 and ME2 were subjected to drug content analysis. Then encapsulated microspheres equivalent to 200mg of Paracetamol were taken and grounded. This was dissolved and filtered and the Paracetamol was estimated spectrophotometrically at 258nm.

SIZE ANALYSIS: Particle size distribution analysis using method of microscopic measurement for not less than 1000 microspheres were performed.

SHAPE AND TOPOLOGY: Uncoated micro spherules and encapsulated micro spherules were investigated under phase contrast microscope. Uncoated micro spherules were found to be smooth and spherical in the liquid manufacturing vehicle. After drying the surface of the microspheres became rough and spherical. Photomicrograph was taken (Fig.). Encapsulated microspheres were found to be nearly spherical, rough surface and uniform coated with the coating material.

DRUG RELEASE STUDIES ON ENCAPSULATED MICROSPHERULES

Buffer solution of pH 7.4, 900 ml was used as dissolution media. Encapsulated micro spherule (ME1,ME2), equivalent to 200 mg of Paracetamol were filled in hard gelatine capsules and were externally wound with stainless steel wire as sink. Paddle type stirrer was adjusted to 100 rpm. The temperature was maintained at 37±1°. A 5 ml aliquot of dissolution media were withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were suitably diluted and analysed for Paracetamol at 258 nm using UV spectrophotometer, Shimadzu. The percentage of Paracetamol at various times were calculated and plotted against time.

REPORT

Experiment No. 08

COMPUTER SIMULATION IN PHARMACOKINETICS/PHARMACODYNAMICS

AIM: To perform computer simulation in pharmaceutics.

Introduction:

The current scenario is based on the rapid development of technologies and computer simulation is an integral part of the field of pharmacokinetic and pharmacodynamics studies. It helps the rapid development of dosage forms with cheaper prices and by using less manpower. The medical field is still slow in accepting computer simulation models. Simulation can play a major role in the selection of studies to be performed; clinical trial simulation covers many disciplines ir, including pharmacokinetics, pre-clinical pharmacologist, statistician, computer programmer etc: So, all experts can discuss and precede the appropriate research. Understanding the num and objectives of the work is essential for all experts it's a tedious job and the main reason behind the less development of the simulation technique in the field of the medical field.

Computer simulation methods are based on the availability of literature and studies regarding the pharmacokinetic and pharmacodynamics parameters of the selected drugs. The success of computer simulation methods depends on the quality of data inputs available. Previous studies are taken as a reference to predict the simulation, and computer simulations demonstrate the pharmacokinetic parameters (ie, half-lived) of different drugs Computer simulations can give atomic details that are not accessible from experiments and help to elucidate the mechanism of the passive permeation process at a molecular level.

Current Development in Computer Simulation:

All the medicines should undergo development and assessment processes before being launched to the market. The safety of the patient is the main concern for everyone, especially in the case of drugs; so scrutiny and rigorous testing of the product before commercialization is highly essential. Some products fall into potentially harmful substances and repeated

preclinical and clinical studies are harmful to animals and humans; so computer similation can fill the gap and gives better result. Currently computer simulation models are promoted to overcome all these issues, but still this area is under developed and requires more development.

Process of Simulation A System:

- Simulation means mimic any condition and apply computer model using algorithm.
- There is mainly 4 Level of the simulation of pharmacokinetics and pharmacodynamics

I. Level 1: Computer Simulation of the Whole Organ
II. Level 2: Computer Simulation of Isolated Tissues and Organ
III. Level 3: Computer Simulation of the Cell
IV. Level 4 Commuter Simulation of Protein and Genes

Advantages

- Several preparation can be obtained from a single animal
- Relativity small amount of test materials reagents) is required.
- Cheap and less time consuming
- Interferences due to pharmacokinetic
- Compensatory reflexes is avoided

Disadvantages

- Designing a model is an art that requires domain knowledge, training, and experience
- Operations are performed on the system using random numbers, hence difficult to predict the result
- Simulation requires manpower and it is a time-consuming process
- Simulation results are difficult to translate. It requires experts to understand

Experiment No. 09

QUALITY BY DESIGN IN PHARMACEUTICAL DEVELOPMENT

Introduction:

- The pharmaceutical industry looking for ways to ensure and enhance the quality safety and efficacy of pharmaceutical products. However, drug recall, manufacturing failure cost, scale-up issues and improper understanding of processes and products in the recent past suggest otherwise.
- In the traditional QbD approach product quality and performance are predominantly ensured by end-product testing with a limited understanding of process and product parameters. So Regulatory bodies are therefore focusing on implementing QbD.
- **Quality:** The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as identity strength and purity.

Quality by Design:

- QbD concept introduced by ICH Q8 guidelines.
- A systematic approach to development that begins with a predefined objective and emphasizes product and process understanding and process control, based on sound science and quality risk management.
- QbD ensures the better design of the product with fewer problems in manufacturing
- Implementation of the QbD concept is important for all products, including generic and biotechnological products.
- Quality should be built into design rather than testing alone

Aim of pharmaceutical QbD includes:

- Achieving predetermined or targeted product quality specification.
- To reduce the defects and failure of the product by understanding product design and controls.
- Enhance process and product development efficiencies.
- Manage the root cause analysis and post approval management
- International Conference of Harmonization (ICH) instituted three regulatory guidance's(Q8,09.010) ▸

- ICH Q8 aims to design a quality pharmaceutical product and its manufacturing process to achieve the intended product performance.
- ICH Q9 primarily focuses on quality risk management principles,
- ICH Q10 pharmaceutical quality system.

Advantages of QbD:

- A better understanding of all risk involved in the process and product thereby reduced batch failure.
- Minimize deviation and costly investigation.
- Minimized material and process variables to attain consistent quality in manufacturing.
- Enhanced regulatory compliance with less burden of post-approval submission.
- Good marketing and fewer drug recalls from the market.
- The time launch of products by improved yields, lower cost, fewer investigations, reduced testing, etc.
- Allow the continuous improvement over the total product life cycle.

Elements for pharmaceutical development

- QTPP
- COA
- Quality Risk Management
- Design Spaces
- Control Strategies
- Life cycle Management

Quality Target Product Profile

QTPP is defined as a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, safety and efficacy, of a drug product is realized.

Consideration for the QTPP may include,

- Route of administration.
- Dosage form
- Dosage strength
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetics characteristics (e.g. dissolution, aerodynamic performance).
- Drug product quality criteria (e.g. sterility, purity, stability, and drug release) appropriate for the intended marketed product.

Critical Quality Attributes

- COA has been defined as "a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- COA are generally associated with the drug substances, excipient intermediates and products.
- The quality attributes of a drug product may include identity assay, content uniformity, degradation products, residual solvents, drug release, moisture content, and microbial limits.
- Physical attributes such as odour, size, shape, colour, configuration and friability.
- These attributes can be critical or not critical

Risk Assessment

- Risk assessment is a valuable science-based process used in quality risk management that can be aid in identifying which material attributes and process parameters potentially have an effect on product CQAs
- There are many attributes of the drug substances & excipients and process parameters that may impact the CQAs of intermediate and finished drug materials.
- Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.
- They can be overcome by once the significant parameters are identified, they can be further studied to achieve a higher level of process understanding.

Design Space

- The ICH Q8 states that the design space is multi-dimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.
- Product domain knowledge and experiment data are necessary to define the design space, which depends on the Design of Experiment (DoE) that investigates the interactions between the input variables with output material.
- The DoE approach can be used to establish the design space.

Control Strategy

- Control strategy is defined as a planned set of controls derived from the current product and process understanding that assures process performance and product quality.
- The ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and processes controls.
- It is necessary to describe and clarify how raw materials, intermediates, package closure processes, and drag components relate to final product quality and control.

Life cycle management

- QbD system aim to improve efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.
- It focused on building quality into the product and manufacturing processes, as well as continuous process improvement and reduction of variability.

Experiment No. 10

DOE Using Design Expert Software

INTRODUCTION TO DESIGN OF EXPERIMENTS (DOE):

DOE is an essential piece of the reliability program pie: It plays an important role in Design for Reliability (DER) programs, allowing the simultaneous investigation of the effects of various factors and thereby facilitating design optimization.

DOE helps in:

- Identifying relationships between cause and effect.
- Providing an understanding of interactions among causative factors
- Determining the levels at which to set the controllable factors (product dimension, alternative material, alternative designs, etc.) in order to optimize reliability.
- Minimizing experimental error (noise).
- Improving the robustness of the design or process to variation.

INTRODUCTION

Much of our knowledge about products and processes in the engineering and scientific disciplines is derived from experimentation. An experiment is a series of tests conducted in a systematic manner to increase the understanding of an existing process or to explore a new product or process. Design of Experiments, or DOE, is a tool to develop an experimentation strategy that maximizes learning using a minimum of resources. Design of Experiments is widely used in many fields with broad application across all the natural and social sciences. It is extensively used by engineers and scientists involved in the improvement of manufacturing processes to maximize yield and decrease variability. Often times, engineers also work on products or processes where no scientific theory or principles are directly applicable. Experimental design techniques become extremely important in such situations to develop new products and processes in a cost-effective and confident manner.

Stages of DOE:

Designed experiments are usually carried out in five stages planning, screening, optimization, robustness testing and verification

Planning:

It is important to carefully plan for the course of experimentation before embarking upon the process of testing and data collection. A few of the considerations to keep in mind at this stage are a thorough and precise objective identifying the need to conduct the investigation, assessment of time and resources available to achieve the objective and integration of prior knowledge to the experimentation procedure. A team composed of individuals from different disciplines related to the product or process should be used to identify possible factors to investigate and the most appropriate response(s) to measure. A team approach promotes synergy that gives a richer set of factors to study and thus a more complete experiment. Carefully planned experiments always lead to an increased understanding of the product or process. Well-planned experiments are easy to execute and analyze. Botched experiments, on the other hand, may result in data sets that are inconclusive and may be impossible to analyze even when the best statistical tools are available.

Screening:

Screening experiments are used to identify the important factors that affect the process under investigation out of the large pool of potential factors. These experiments are carried out in conjunction with prior knowledge of the process to eliminate unimportant factors and focus attention on the key factors that require further detailed analyses. Screening experiments are usually efficient designs requiring few executions, where the focus is not on interactions but on identifying the vital few factors.

Optimization

Once attention has been narrowed down to the important factors affecting the process, the next step is to determine the best setting of these factors to achieve the desired objective. Depending on the product or process under investigation, this objective may be to either increase yield or decrease variability or to find settings that achieve both at the same time.

Robustness Testing

Once the optimal settings of the factors have been determined, it is important to make the product or process insensitive to variations that are likely to be experienced in the application environment. These variations result from changes in factors that affect the process but are beyond the control of the analyst Such factors (eg. humidity, ambient temperature, variation in material, etc.) are referred to as noise or uncontrollable factors. It is important to identify such sources of vanation and take mest the product or process is made insensitive (or robusty to these factors

Verification

This final stage involves validation of the best settings by conducting a few follow-up experimental runs to confirm that the process functions as desired and all objectives are met

Experiment No. 11

FORMULATION OF DATA ANALYSIS USING DESIGN EXPERT SOFTWARE/EXCEL

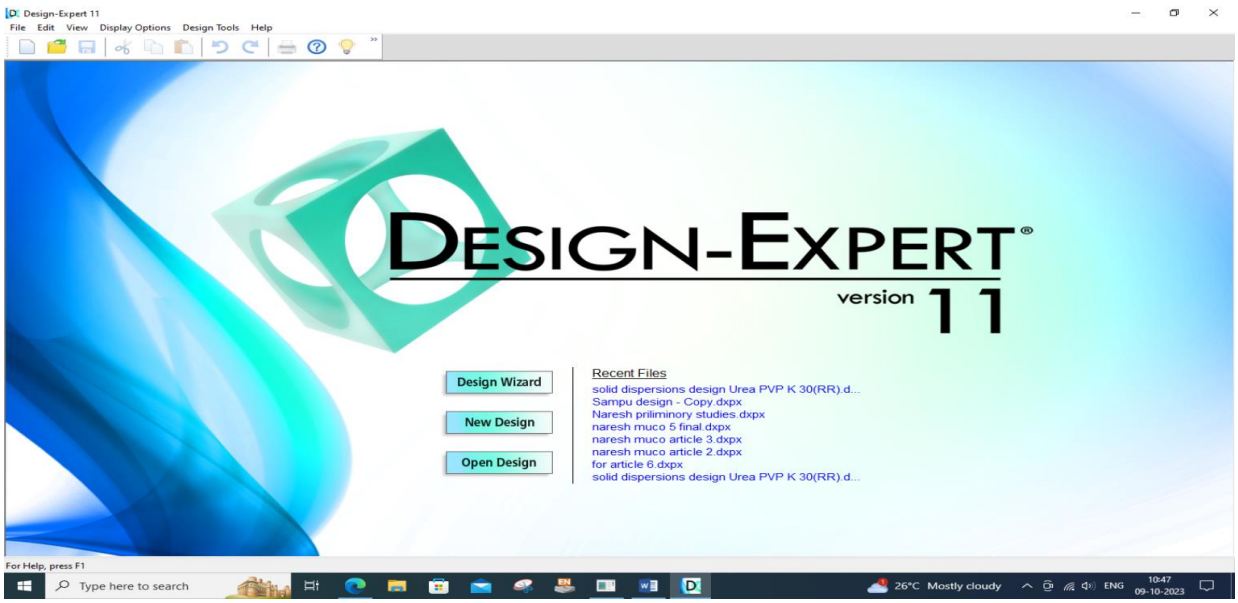
Steps:

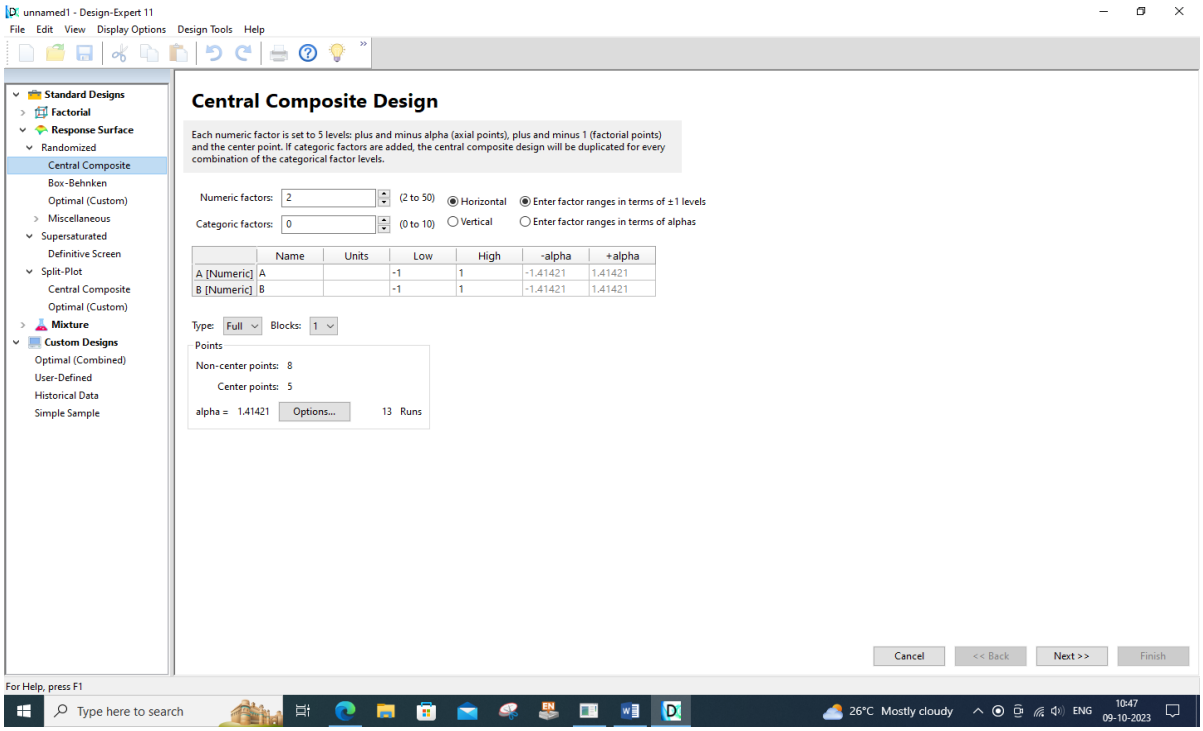
1. Central composite design
2. Fixing inputs (independent variables)
3. Output (dependent variables)

- Hardness
- Weight variation
- Dissolution

4. Analysis

- Plots and Point prediction

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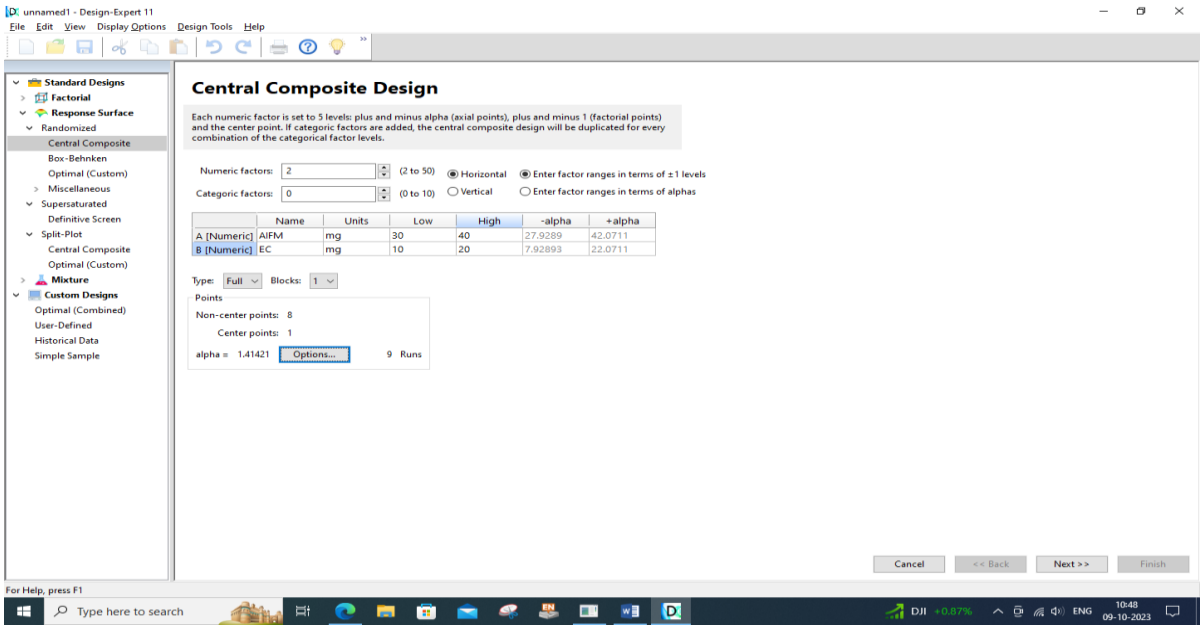
File Edit View Display Options Design Tools Help
Standard Designs
Factorial
Response Surface
Randomized
Central Composite
Box-Behnken
Optimal (Custom)
Miscellaneous
Supersaturated
Definitive Screen
Split-Plot
Central Composite
Optimal (Custom)
Mixture
Custom Designs
Optimal (Combined)
User-Defined
Historical Data
Simple Sample
Central Composite Design
Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categoric factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.
Numeric factors: 2 (2 to 50) Horizontal Enter factor ranges in terms of ±1 levels
Categoric factors: 0 (0 to 10) Vertical Enter factor ranges in terms of alphas
Name Units Low High -alpha +alpha
A [Numeric] A -1 1 -1.41421 1.41421
B [Numeric] B -1 1 -1.41421 1.41421
Type: Full Blocks: 1
Points
Non-center points: 8
Center points: 5
alpha = 1.41421 Options... 13 Runs
Cancel << Back Next >> Finish
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
10:47
09-10-2023


unnamed1 - Design-Expert 11
File Edit View Display Options Design Tools Help
Standard Designs
Factorial
Response Surface
Randomized
Central Composite
Box-Behnken
Optimal (Custom)
Miscellaneous
Supersaturated
Definitive Screen
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Historical Data
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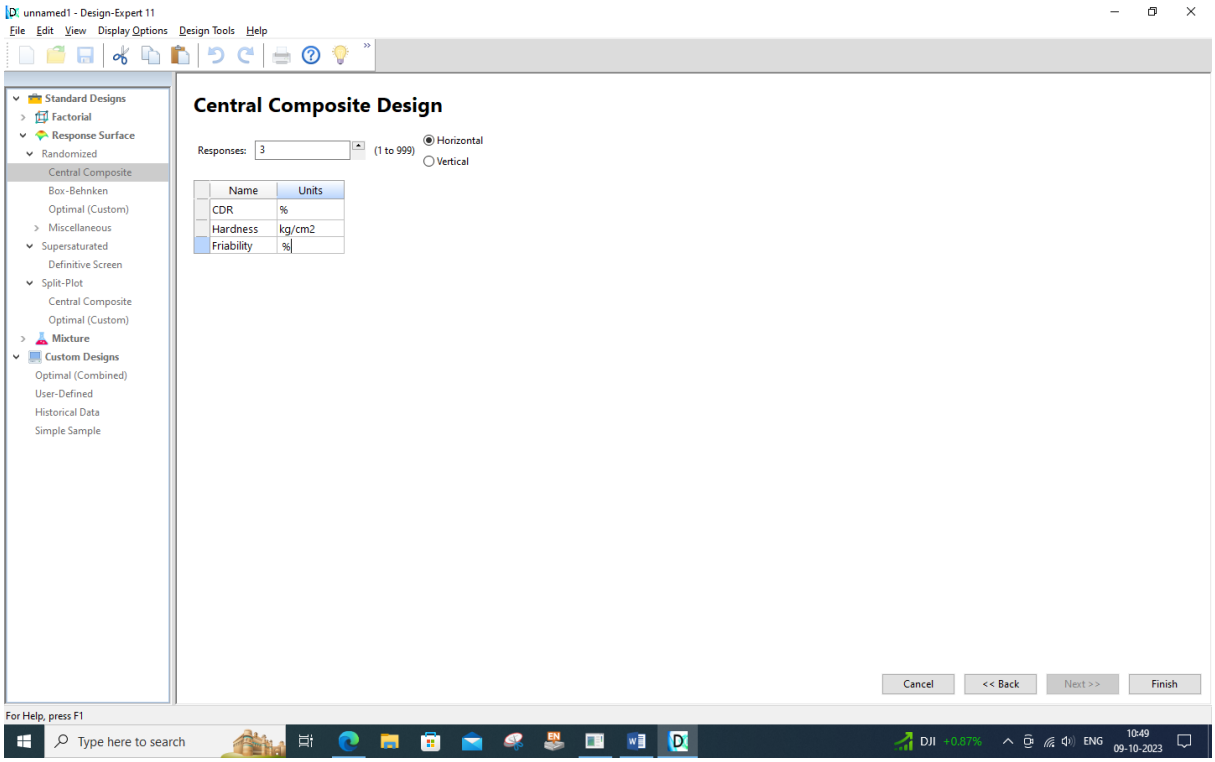
Central Composite Design
Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categoric factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.
Numeric factors: 2 (2 to 50) Horizontal Enter factor ranges in terms of ±1 levels
Categoric factors: 0 (0 to 10) Vertical Enter factor ranges in terms of alphas
Name Units Low High -alpha +alpha
A [Numeric] AIFM mg 30 40 27.9289 42.0711
B [Numeric] EC mg 10 20 7.92893 22.0711
Type: Full Blocks: 1
Points
Non-center points: 8
Center points: 1
alpha = 1.41421 Options... 9 Runs
Cancel << Back Next >> Finish
For Help, press F1
Type here to search
DJI +0.87%
ENG
10:48
09-10-2023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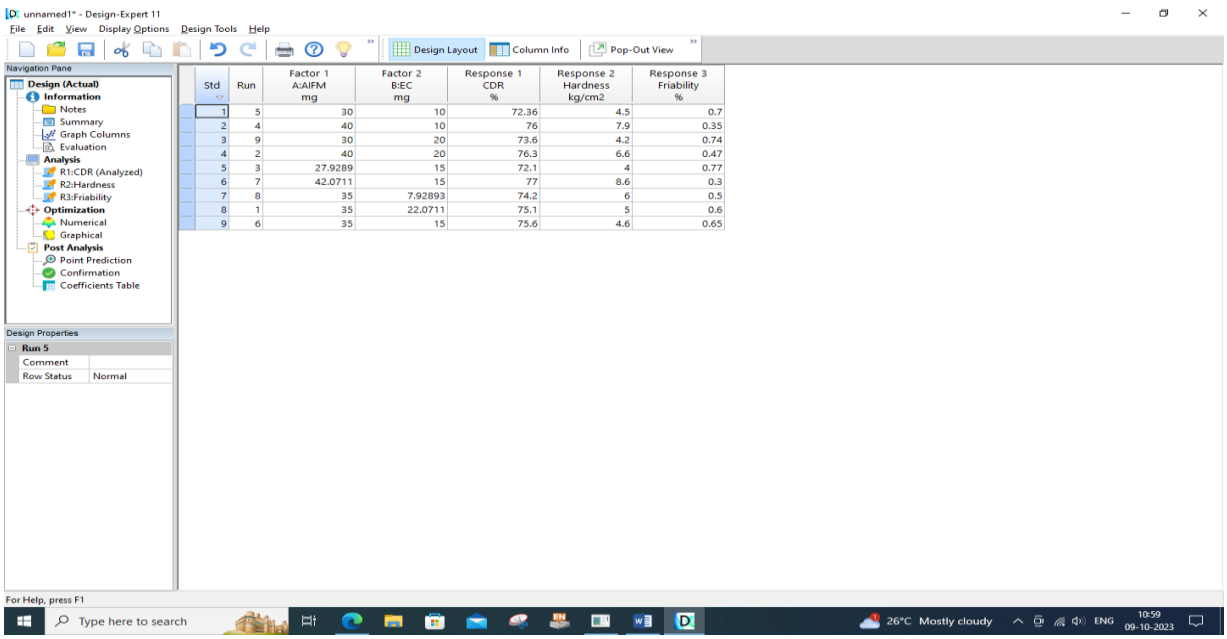
File Edit View Display Options Design Tools Help
Standard Designs
Factorial
Response Surface
Randomized
Central Composite
Box-Behnken
Optimal (Custom)
Miscellaneous
Supersaturated
Definitive Screen
Split-Plot
Central Composite
Optimal (Custom)
Mixture
Custom Designs
Optimal (Combined)
User-Defined
Historical Data
Simple Sample
Central Composite Design
Responses: 3 (1 to 999)
Horizontal
Vertical
Name Units
CDR %
Hardness kg/cm2
Friability %
Cancel
<< Back
Next >>
Finish
For Help, press F1
Type here to search
DJI +0.87%
ENG
10:49
09-10-2023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File Edit View Display Options Design Tools Help
Design Layout
Column Info
Pop-Out View
Navigation Pane
Design (Actual)
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Design Properties
Run 5
Comment
Row Status Normal
Std Run Factor 1 A:AIFM mg Factor 2 B:EC mg Response 1 CDR % Response 2 Hardness kg/cm2 Response 3 Friability %
1 5 30 10 72.36 4.5 0.7
2 4 40 10 76 7.9 0.35
3 9 30 20 73.6 4.2 0.74
4 2 40 20 76.3 6.6 0.47
5 3 27.9289 15 72.1 4 0.77
6 7 42.0711 15 77 8.6 0.3
7 8 35 7.92893 74.2 6 0.5
8 1 35 22.0711 75.1 5 0.6
9 6 35 15 75.6 4.6 0.65
For Help, press F1
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26°C Mostly cloudy
ENG
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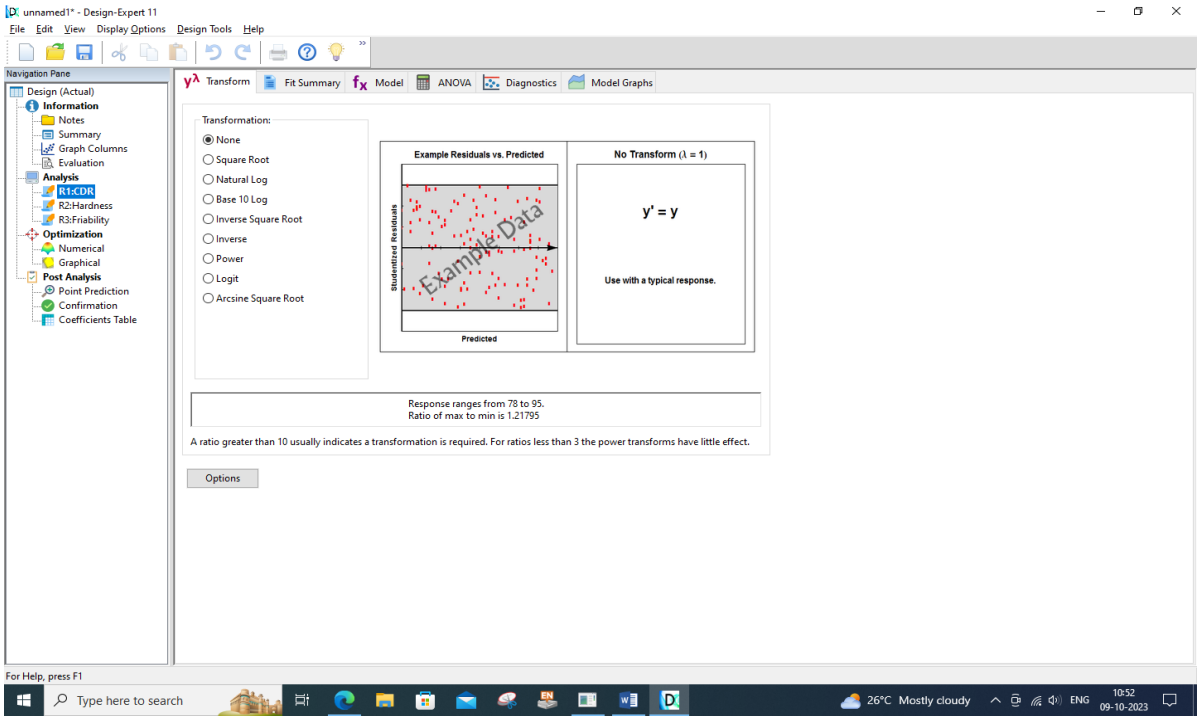
09-10-2023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File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
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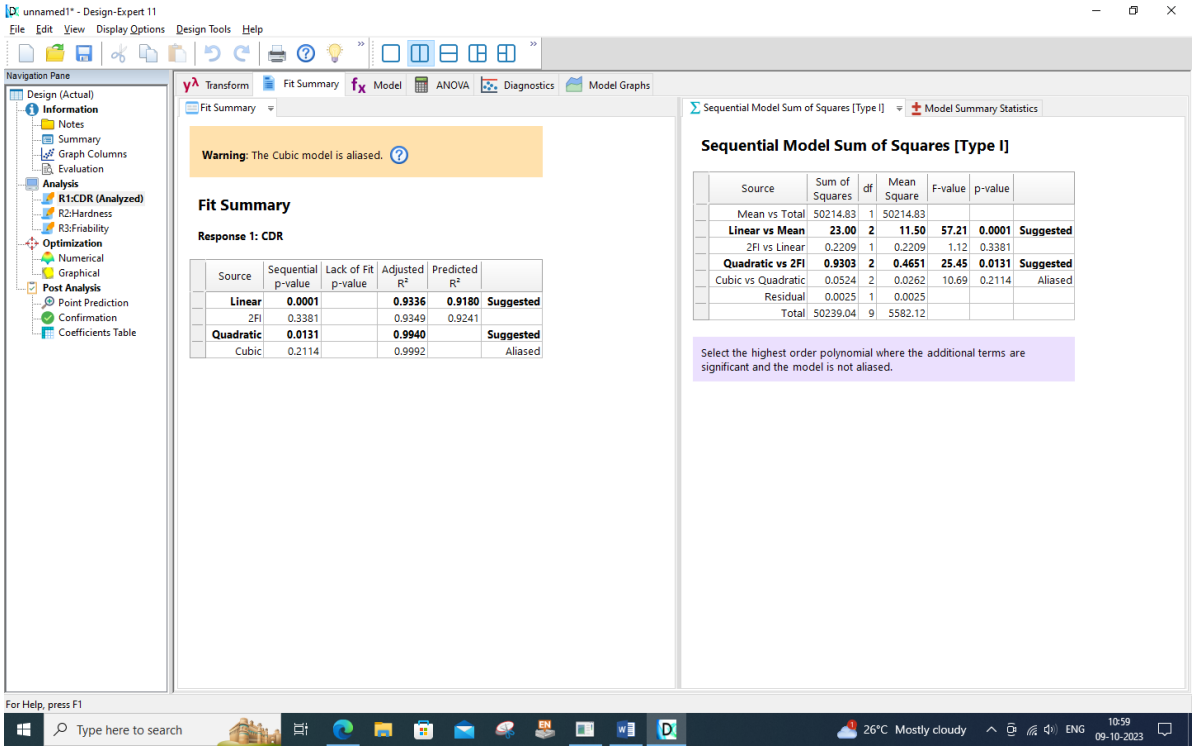
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Transformation:
None
Square Root
Natural Log
Base 10 Log
Inverse Square Root
Inverse
Power
Logit
Arcsine Square Root
Example Residuals vs. Predicted
Studentized Residuals
Predicted
Example Data
No Transform (λ = 1)
y' = y
Use with a typical response.
Response ranges from 78 to 95.
Ratio of max to min is 1.21795
A ratio greater than 10 usually indicates a transformation is required. For ratios less than 3 the power transforms have little effect.
Options
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
10:52
09-10-2023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File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Fit Summary
Sequential Model Sum of Squares [Type I]
Model Summary Statistics
Warning: The Cubic model is aliased.
Fit Summary
Response 1: CDR
Source | Sequential p-value | Lack of Fit p-value | Adjusted R² | Predicted R²
Linear 0.0001 0.9336 0.9180 Suggested
2FI 0.3381 0.9349 0.9241
Quadratic 0.0131 0.9940 Suggested
Cubic 0.2114 0.9992 Aliased
Sequential Model Sum of Squares [Type I]
Source | Sum of Squares | df | Mean Square | F-value | p-value
Mean vs Total 50214.83 1 50214.83
Linear vs Mean 23.00 2 11.50 57.21 0.0001 Suggested
2FI vs Linear 0.2209 1 0.2209 1.12 0.3381
Quadratic vs 2FI 0.9303 2 0.4651 25.45 0.0131 Suggested
Cubic vs Quadratic 0.0524 2 0.0262 10.69 0.2114 Aliased
Residual 0.0025 1 0.0025
Total 50239.04 9 5582.12
Select the highest order polynomial where the additional terms are significant and the model is not aliased.
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
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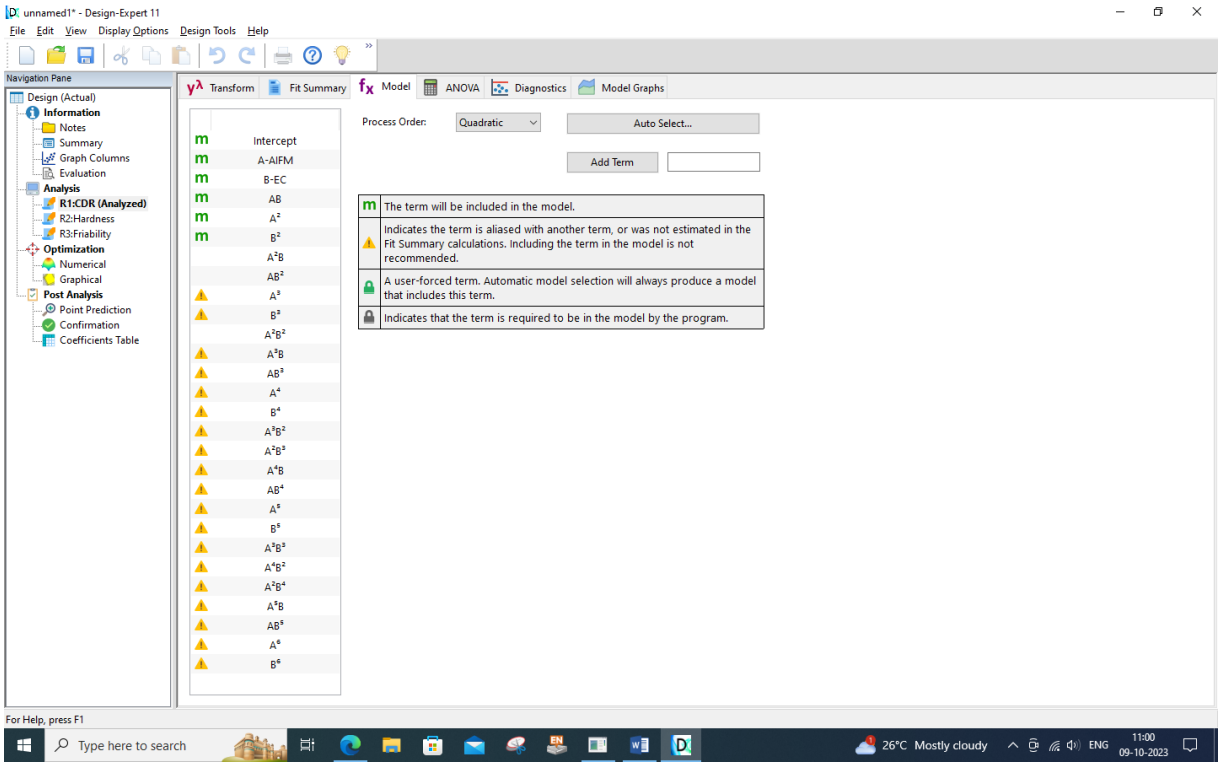
09-10-2023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File Edit View Display Options Design Tools Help
Navigation Pane
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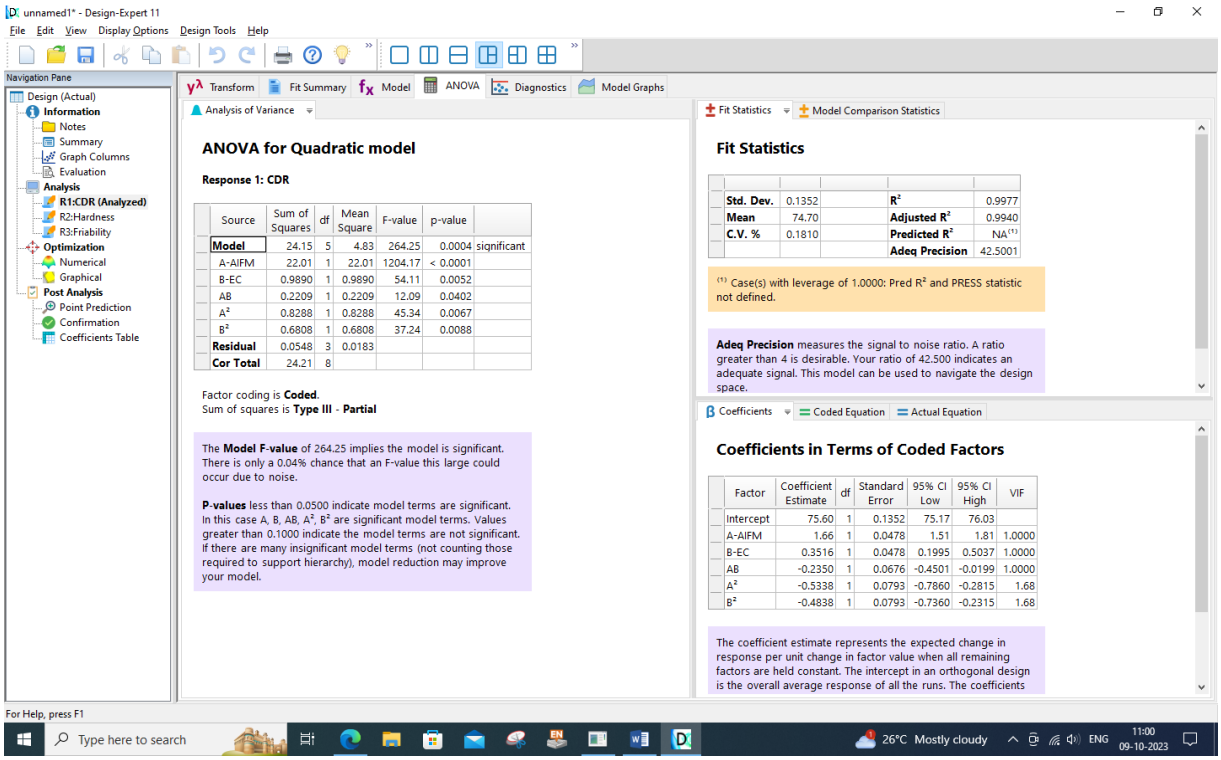
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Process Order:
Quadratic
Auto Select...
Add Term
Intercept
A-AIFM
B-EC
AB
A²
B²
The term will be included in the model.
Indicates the term is aliased with another term, or was not estimated in the Fit Summary calculations. Including the term in the model is not recommended.
A user-forced term. Automatic model selection will always produce a model that includes this term.
Indicates that the term is required to be in the model by the program.
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
11:00
09-10-2023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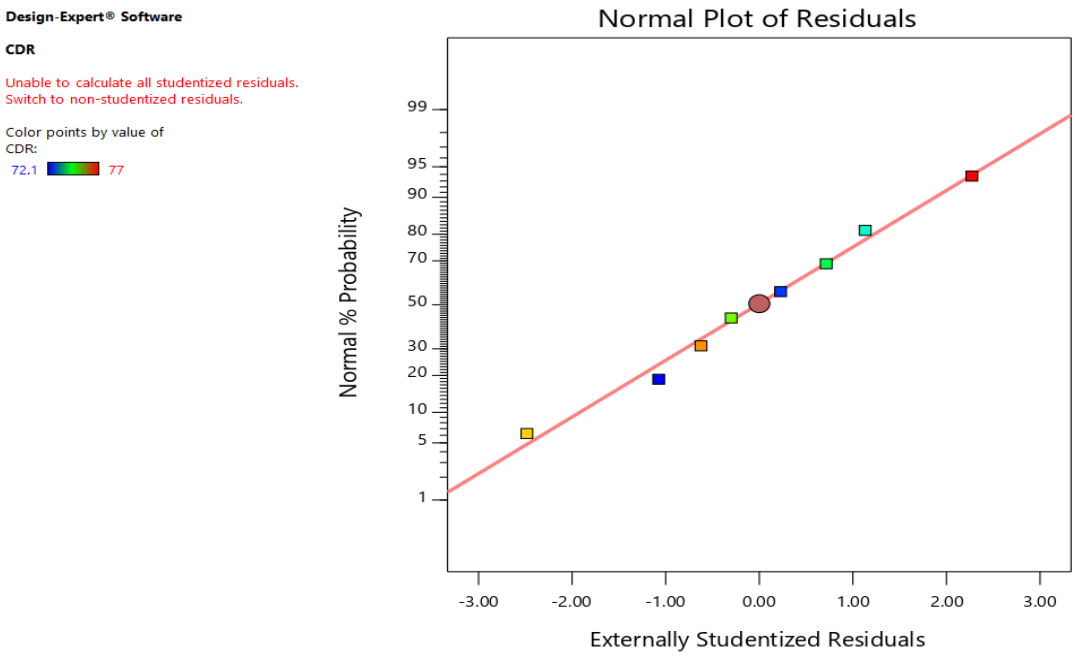
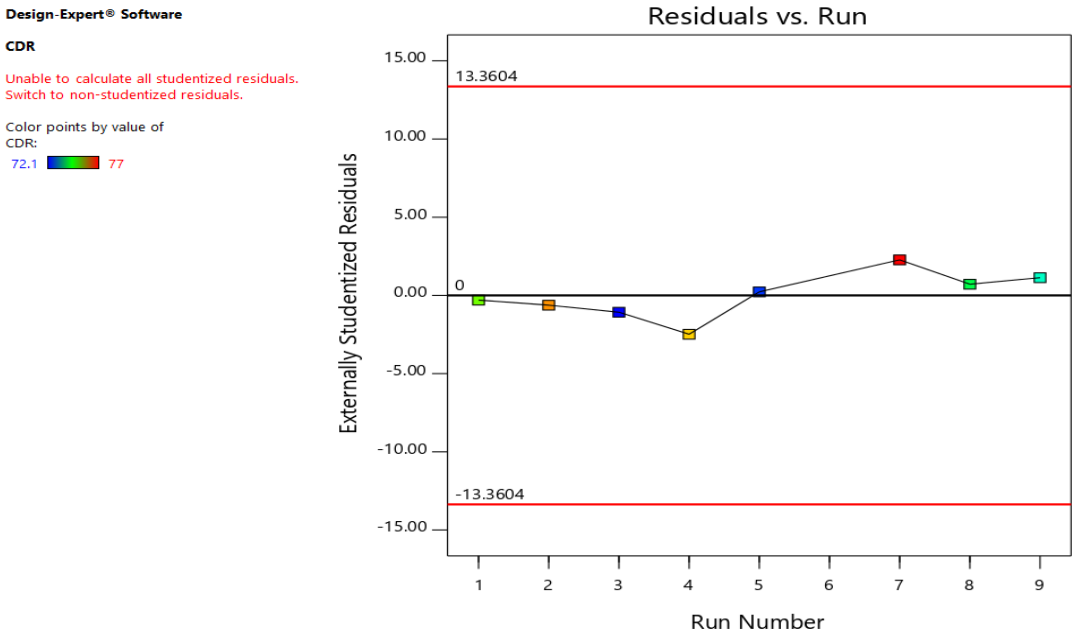
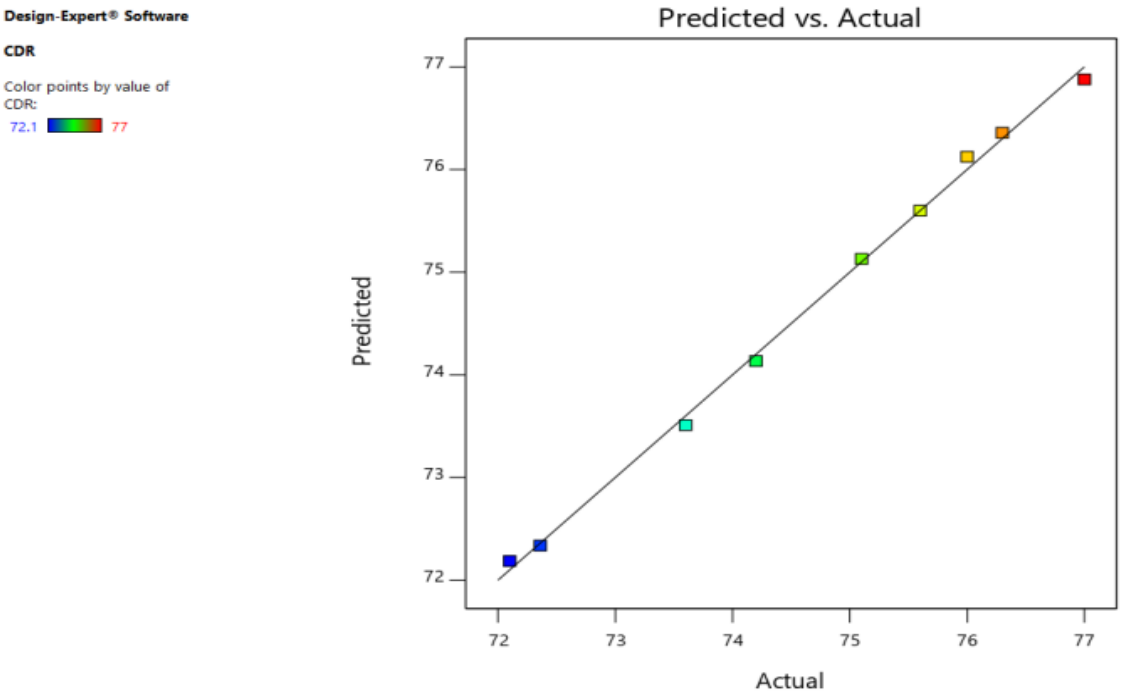
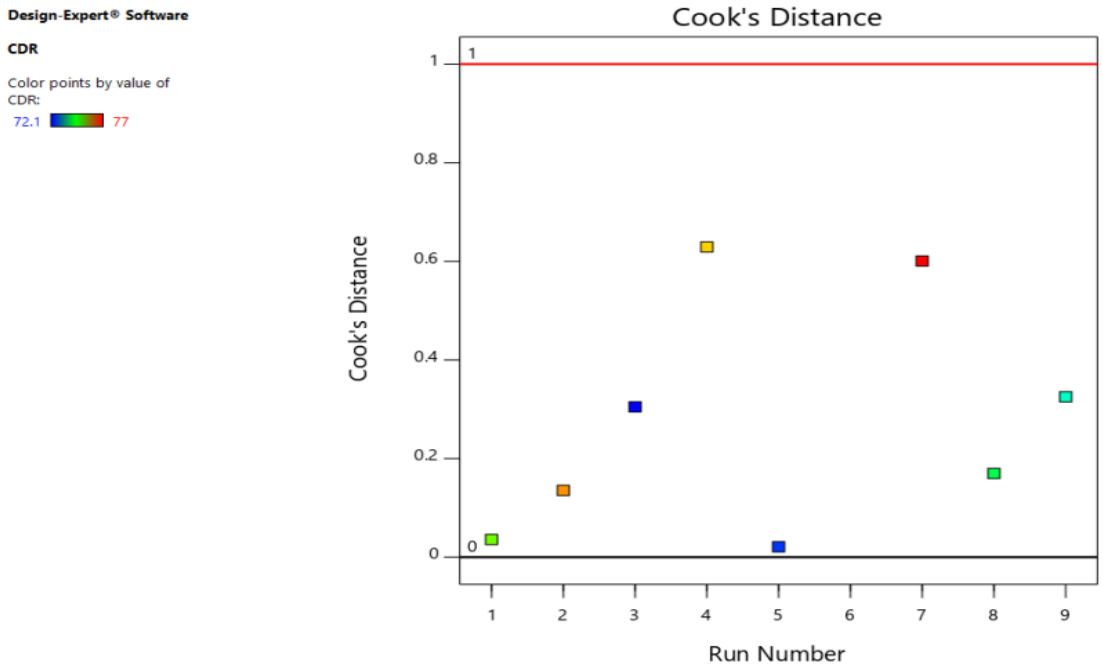
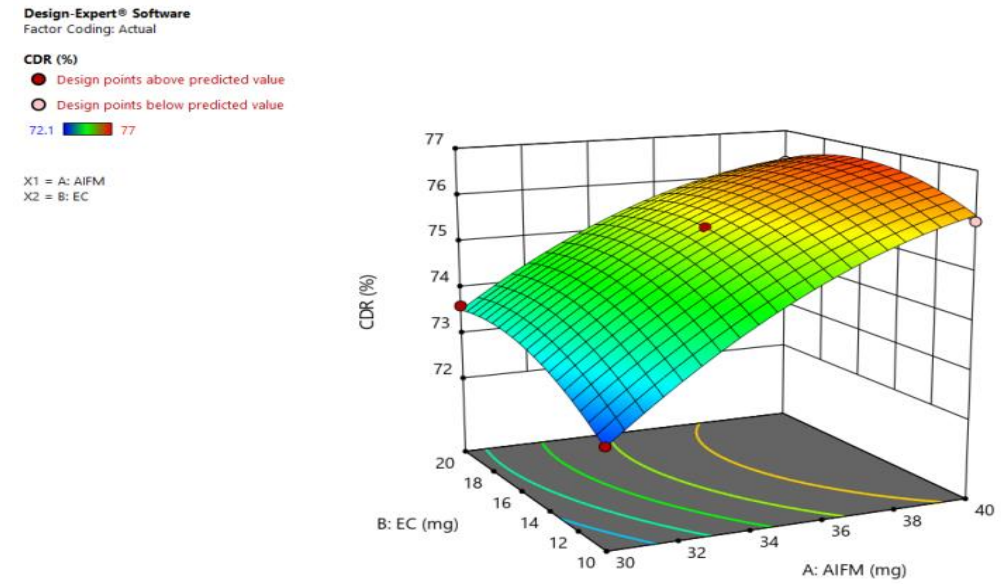
File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Analysis of Variance
ANOVA for Quadratic model
Response 1: CDR
Source | Sum of Squares | df | Mean Square | F-value | p-value
Model | 24.15 | 5 | 4.83 | 264.25 | 0.0004 | significant
A-AIFM | 22.01 | 1 | 22.01 | 1204.17 | < 0.0001
B-EC | 0.9890 | 1 | 0.9890 | 54.11 | 0.0052
AB | 0.2209 | 1 | 0.2209 | 12.09 | 0.0402
A² | 0.8288 | 1 | 0.8288 | 45.34 | 0.0067
B² | 0.6808 | 1 | 0.6808 | 37.24 | 0.0088
Residual | 0.0548 | 3 | 0.0183
Cor Total | 24.21 | 8
Factor coding is Coded.
Sum of squares is Type III - Partial
The Model F-value of 264.25 implies the model is significant. There is only a 0.04% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, A², B² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.
Fit Statistics
Model Comparison Statistics
Fit Statistics
Std. Dev. 0.1352
Mean 74.70
C.V. % 0.1810
R² 0.9977
Adjusted R² 0.9940
Predicted R² NA(1)
Adeq Precision 42.5001
(1) Case(s) with leverage of 1.0000: Pred R² and PRESS statistic not defined.
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 42.500 indicates an adequate signal. This model can be used to navigate the design space.
Coefficients
Coded Equation
Actual Equation
Coefficients in Terms of Coded Factors
Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF
Intercept | 75.60 | 1 | 0.1352 | 75.17 | 76.03
A-AIFM | 1.66 | 1 | 0.0478 | 1.51 | 1.81 | 1.0000
B-EC | 0.3516 | 1 | 0.0478 | 0.1995 | 0.5037 | 1.0000
AB | -0.2350 | 1 | 0.0676 | -0.4501 | -0.0199 | 1.0000
A² | -0.5338 | 1 | 0.0793 | -0.7860 | -0.2815 | 1.68
B² | -0.4838 | 1 | 0.0793 | -0.7360 | -0.2315 | 1.68
The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
11:00
09-10-2023

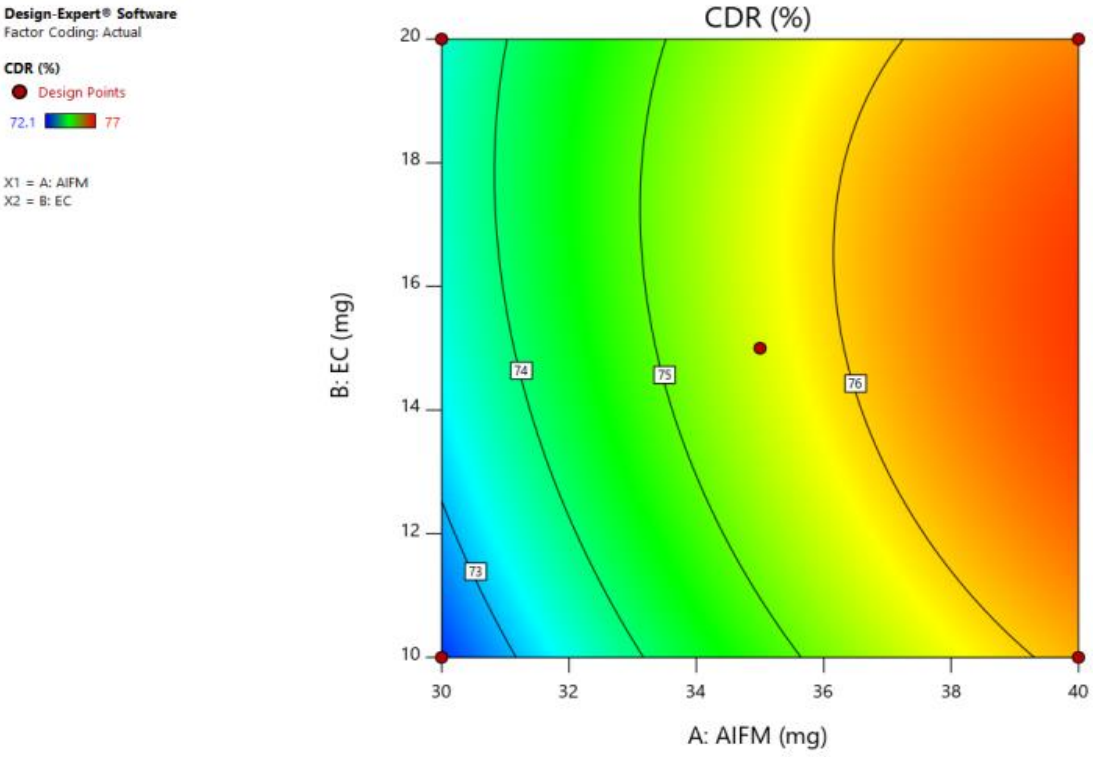

Design-Expert® Software
CDR
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
CDR:
72.1
77
Normal Plot of Residuals
Normal % Probability
99
95
90
80
70
50
30
20
10
5
1
-3.00
-2.00
-1.00
0.00
1.00
2.00
3.00
Externally Studentized Residuals

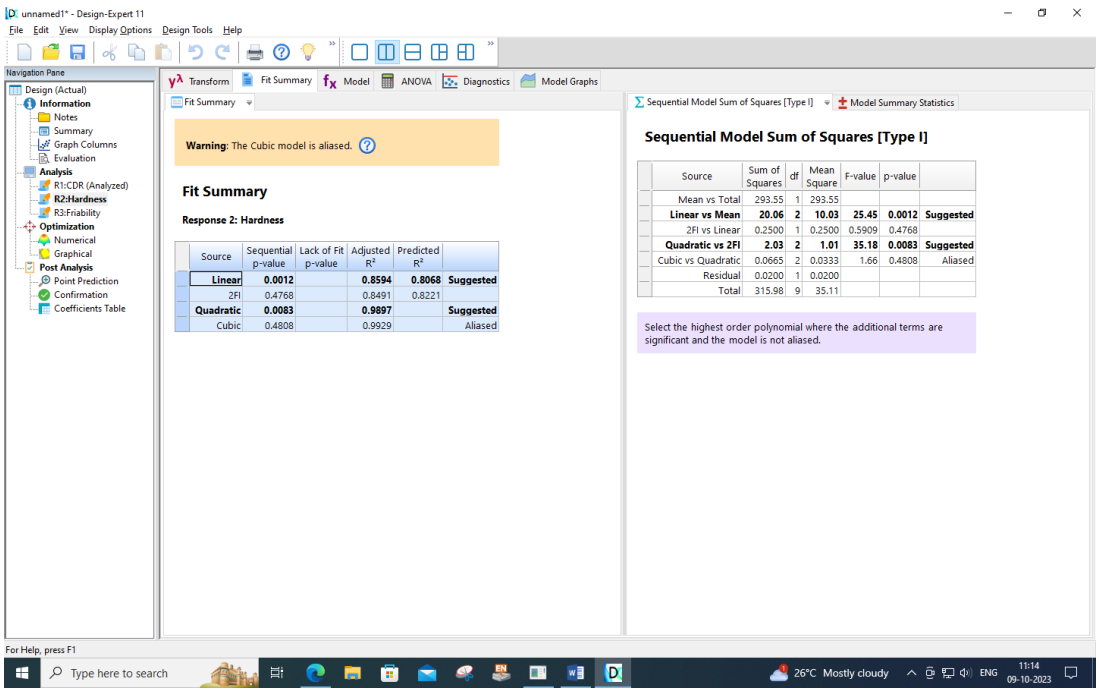

Design-Expert® Software
CDR
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
CDR:
72.1
77
Residuals vs. Run
Externally Studentized Residuals
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
13.3604
0
-13.3604
1
2
3
4
5
6
7
8
9
Run Number


Design-Expert® Software
CDR
Color points by value of CDR:
72.1
77
Predicted vs. Actual
Predicted
Actual
72
73
74
75
76
77


Design-Expert® Software
CDR
Color points by value of CDR:
72.1
77
Cook's Distance
Cook's Distance
Run Number
1
0
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
7
8
9


Design-Expert® Software
Factor Coding: Actual
CDR (%)
Design points above predicted value
Design points below predicted value
72.1
77
X1 = A: AIFM
X2 = B: EC
CDR (%)
77
76
75
74
73
72
B: EC (mg)
20
18
16
14
12
10
A: AIFM (mg)
30
32
34
36
38
40


Design-Expert® Software
Factor Coding: Actual
CDR (%)
Design Points
72.1
77
X1 = A: AIFM
X2 = B: EC
CDR (%)
B: EC (mg)
20
18
16
14
12
10
74
75
76
73
A: AIFM (mg)
30
32
34
36
38
40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File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
Information
Notes
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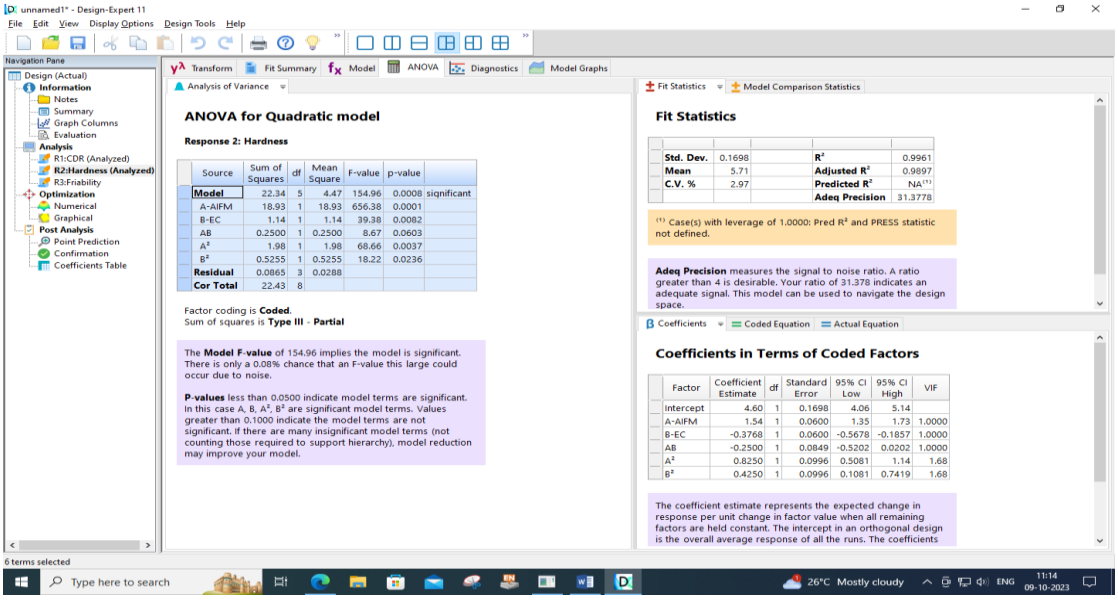
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Fit Summary
Warning: The Cubic model is aliased.
Fit Summary
Response 2: Hardness
Source | Sequential p-value | Lack of Fit p-value | Adjusted R² | Predicted R²
Linear 0.0012 0.8594 0.8068 Suggested
2FI 0.4768 0.8491 0.8221
Quadratic 0.0083 0.9897 Suggested
Cubic 0.4808 0.9929 Aliased
Sequential Model Sum of Squares [Type I]
Model Summary Statistics
Sequential Model Sum of Squares [Type I]
Source | Sum of Squares | df | Mean Square | F-value | p-value
Mean vs Total 293.55 1 293.55
Linear vs Mean 20.06 2 10.03 25.45 0.0012 Suggested
2FI vs Linear 0.2500 1 0.2500 0.5909 0.4768
Quadratic vs 2FI 2.03 2 1.01 35.18 0.0083 Suggested
Cubic vs Quadratic 0.0665 2 0.0333 1.66 0.4808 Aliased
Residual 0.0200 1 0.0200
Total 315.98 9 35.11
Select the highest order polynomial where the additional terms are significant and the model is not aliased.
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
11:14
09-10-2023


unnamed1* - Design-Expert 11
File Edit View Display Options Design Tools Help
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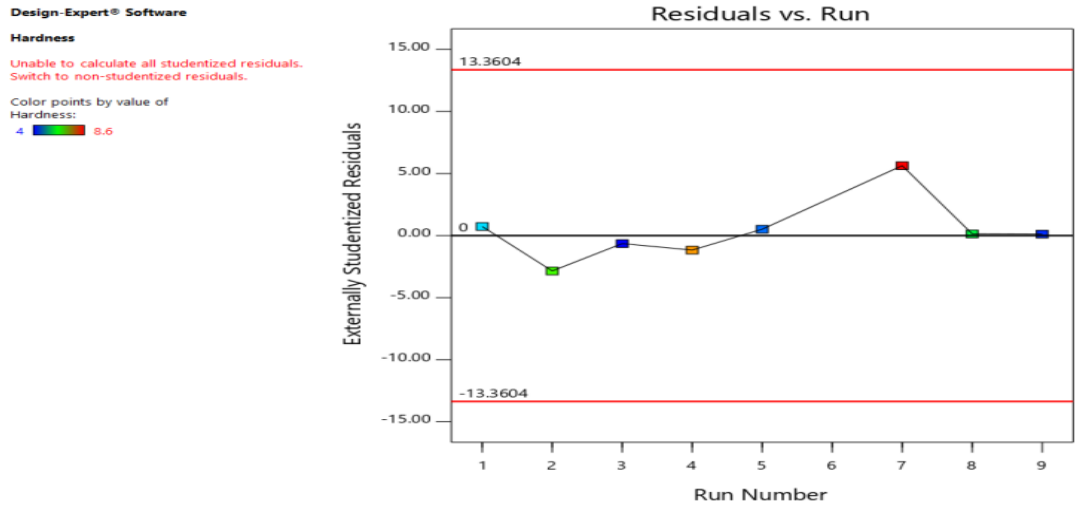
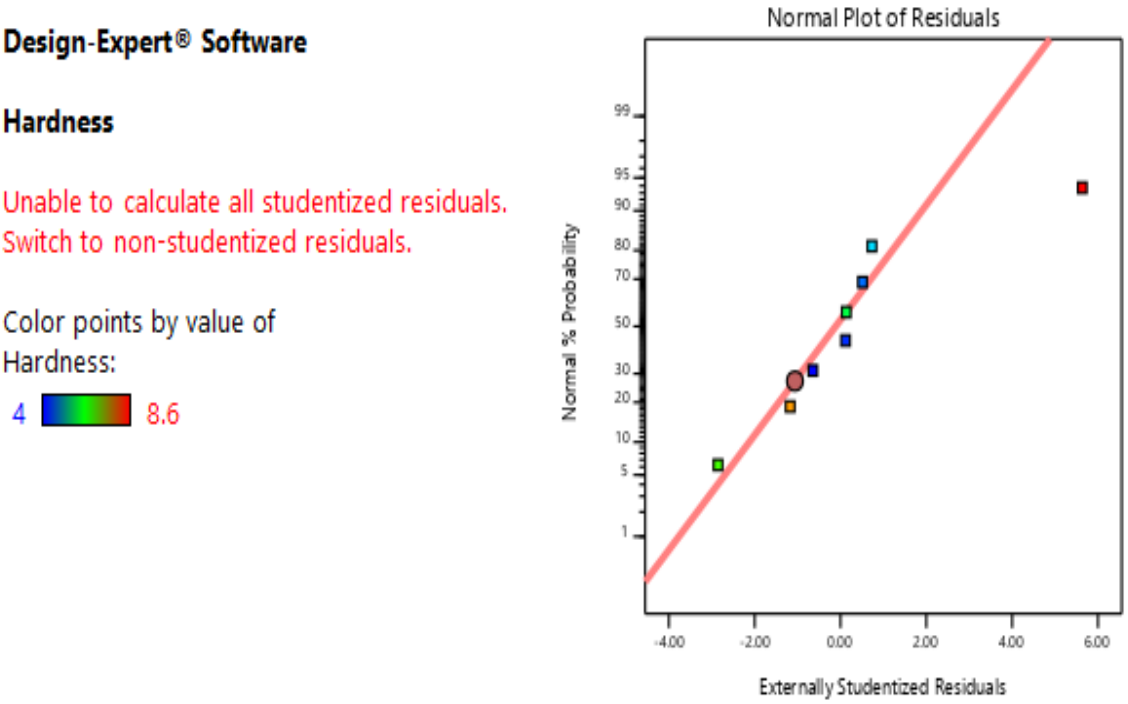
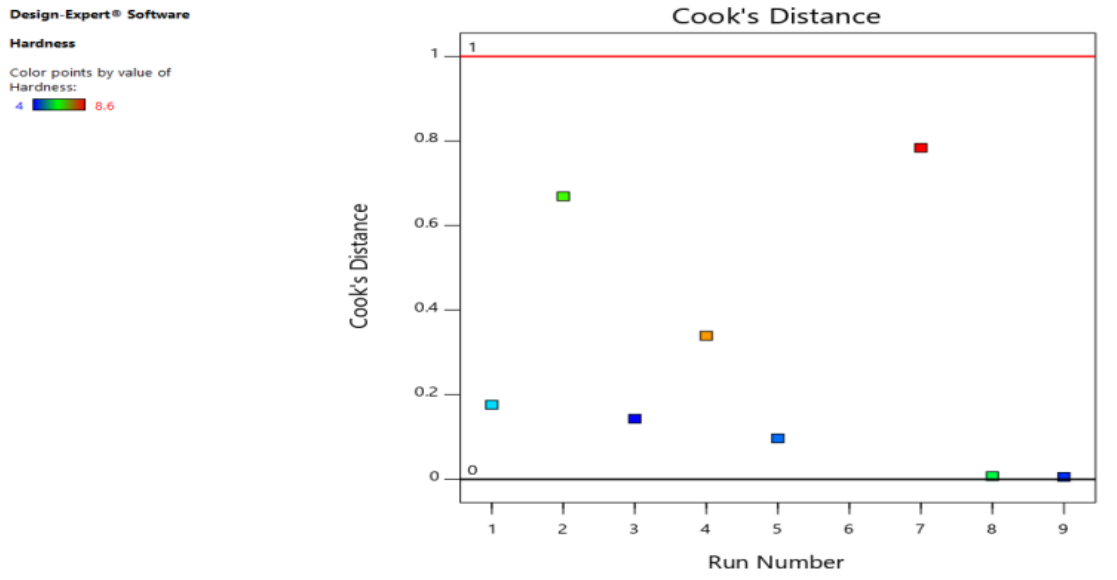
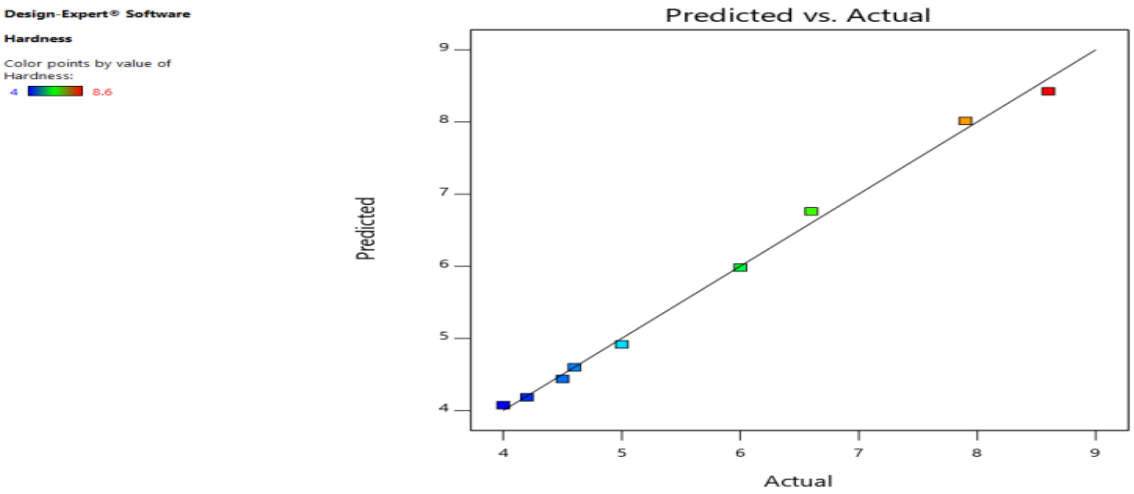
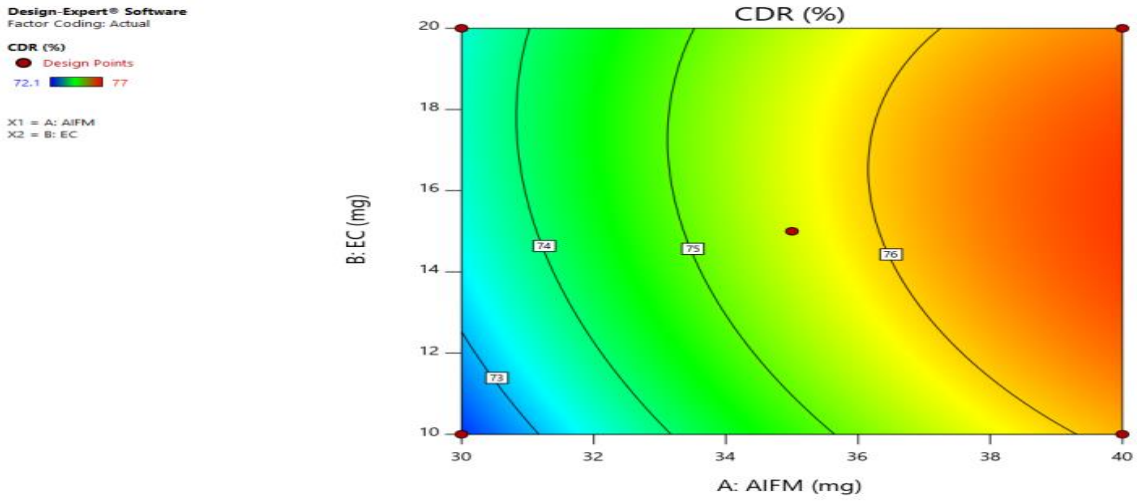
R1:CDR (Analyzed)
R2:Hardness (Analyzed)
R3:Friability
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform
Fit Summary
Model
ANOVA
Diagnostics
Model Graphs
Analysis of Variance
ANOVA for Quadratic model
Response 2: Hardness
Source | Sum of Squares | df | Mean Square | F-value | p-value
Model 22.34 5 4.47 154.96 0.0008 significant
A-AlFM 18.93 1 18.93 656.38 0.0001
B-EC 1.14 1 1.14 39.38 0.0082
AB 0.2500 1 0.2500 8.67 0.0603
A² 1.98 1 1.98 68.66 0.0037
B² 0.5255 1 0.5255 18.22 0.0236
Residual 0.0865 3 0.0288
Cor Total 22.43 8
Factor coding is Coded.
Sum of squares is Type III - Partial
The Model F-value of 154.96 implies the model is significant. There is only a 0.08% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant. In this case A, B, A², B² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.
Fit Statistics
Model Comparison Statistics
Fit Statistics
Std. Dev. 0.1698 R² 0.9961
Mean 5.71 Adjusted R² 0.9897
C.V. % 2.97 Predicted R² NA(1)
Adeq Precision 31.3778
(1) Case(s) with leverage of 1.0000: Pred R² and PRESS statistic not defined.
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 31.378 indicates an adequate signal. This model can be used to navigate the design space.
Coefficients
Coded Equation
Actual Equation
Coefficients in Terms of Coded Factors
Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF
Intercept 4.60 1 0.1698 4.06 5.14
A-AlFM 1.54 1 0.0600 1.35 1.73 1.0000
B-EC -0.3768 1 0.0600 -0.5678 -0.1857 1.0000
AB -0.2500 1 0.0849 -0.5202 0.0202 1.0000
A² 0.8250 1 0.0996 0.5081 1.14 1.68
B² 0.4250 1 0.0996 0.1081 0.7419 1.68
The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients
6 terms selected
Type here to search
26°C Mostly cloudy
ENG
11:14
09-10-2023

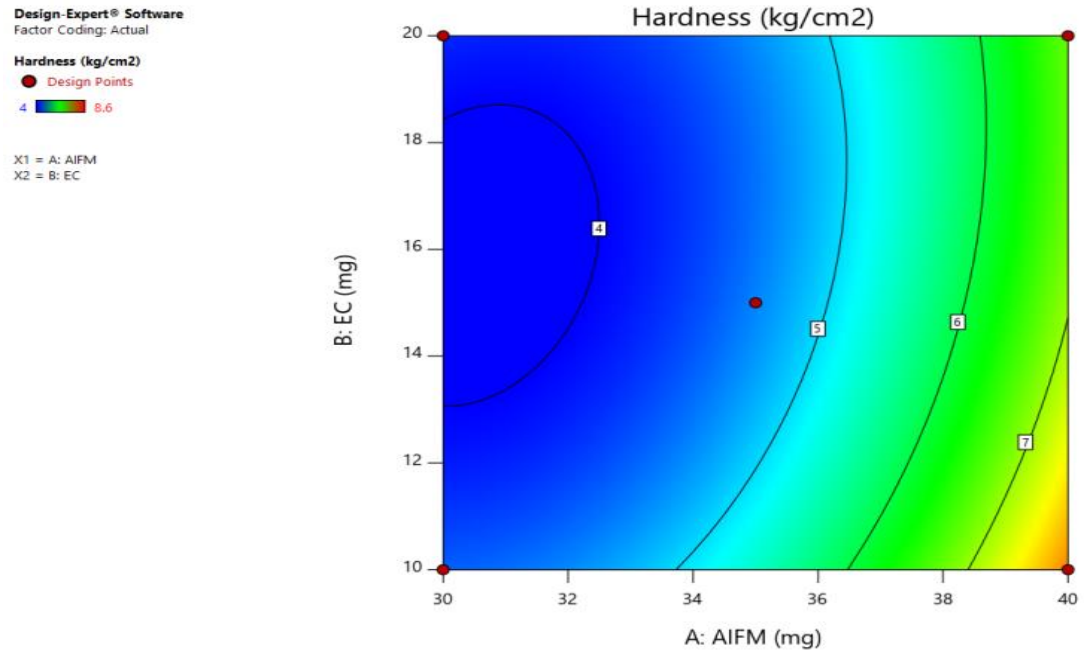

Design-Expert® Software
Hardness
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
Hardness:
4
8.6
Residuals vs. Run
Externally Studentized Residuals
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
13.3604
0
-13.3604
1
2
3
4
5
6
7
8
9
Run Number

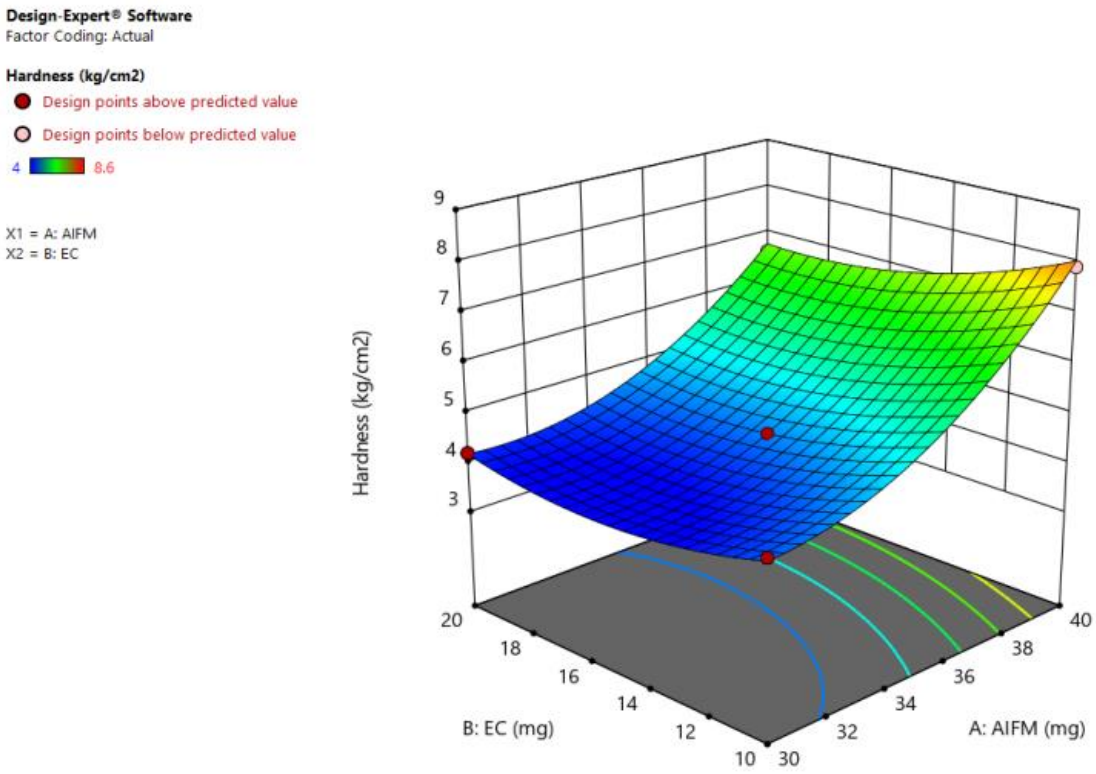

Design-Expert® Software
Hardness
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
Hardness:
4
8.6
Normal Plot of Residuals
Normal % Probability
99
95
90
80
70
50
30
20
10
5
1
-4.00
-2.00
0.00
2.00
4.00
6.00
Externally Studentized Residuals

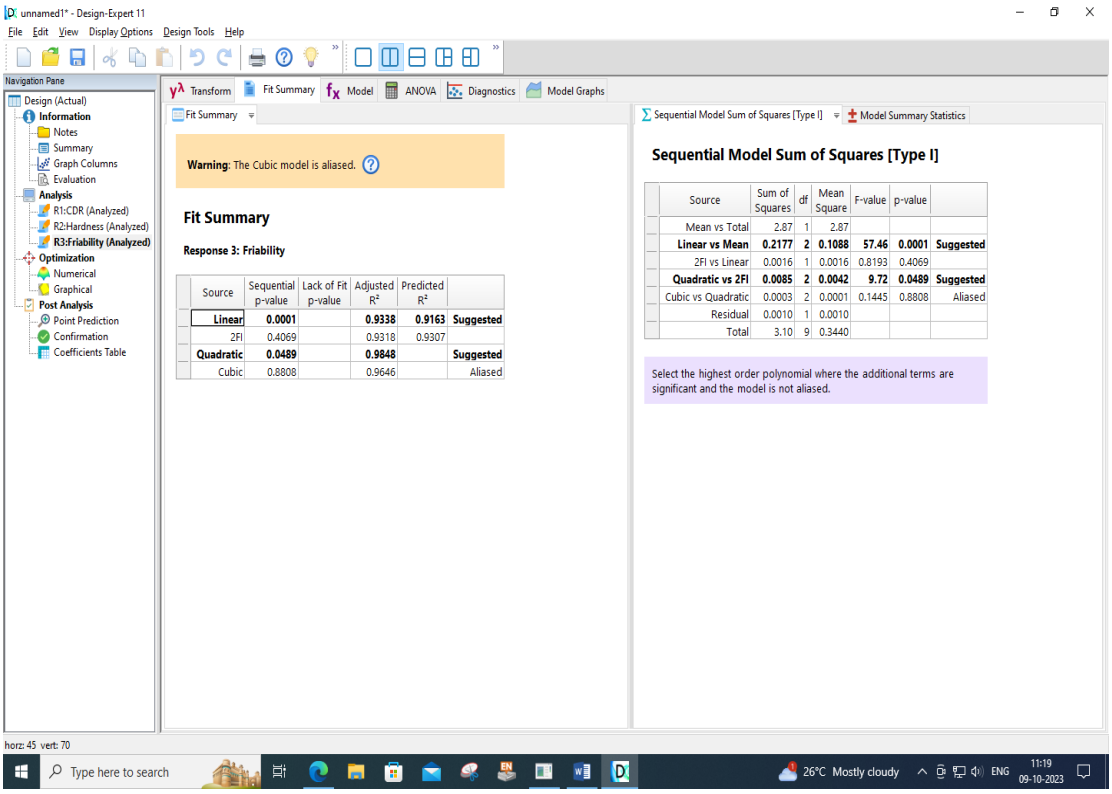

Design-Expert® Software
Hardness
Color points by value of Hardness:
4
8.6
Cook's Distance
Cook's Distance
Run Number
1
0
0
0.2
0.4
0.6
0.8
1
1
2
3
4
5
6
7
8
9

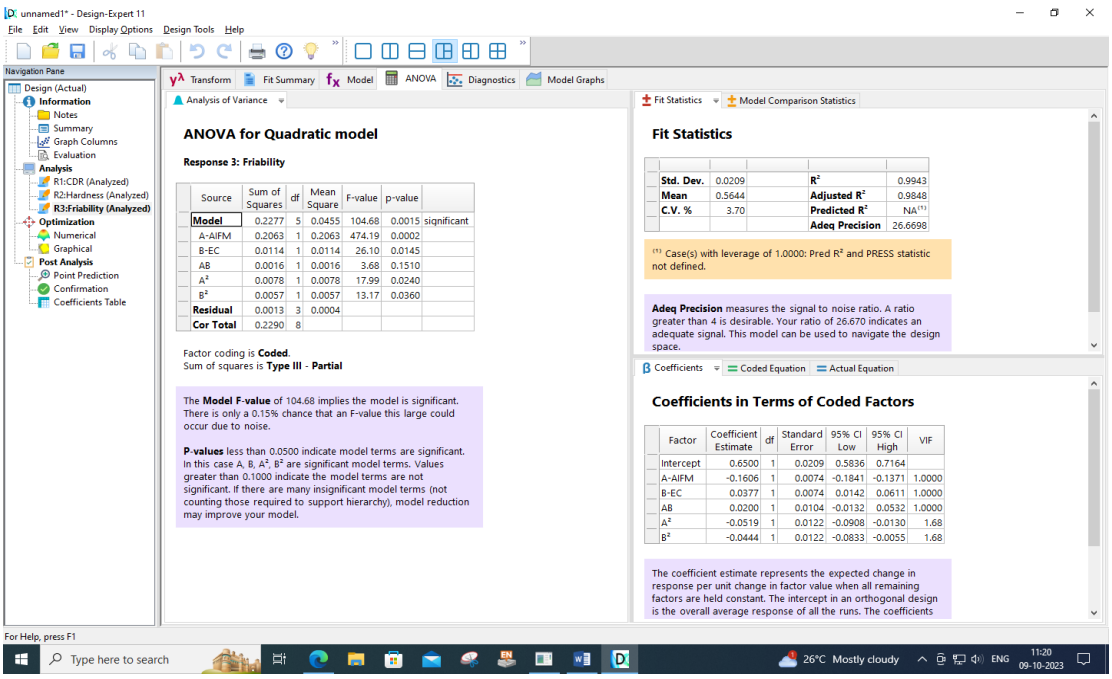

Design-Expert® Software
Hardness
Color points by value of Hardness:
4
8.6
Predicted vs. Actual
Predicted
Actual
4
5
6
7
8
9

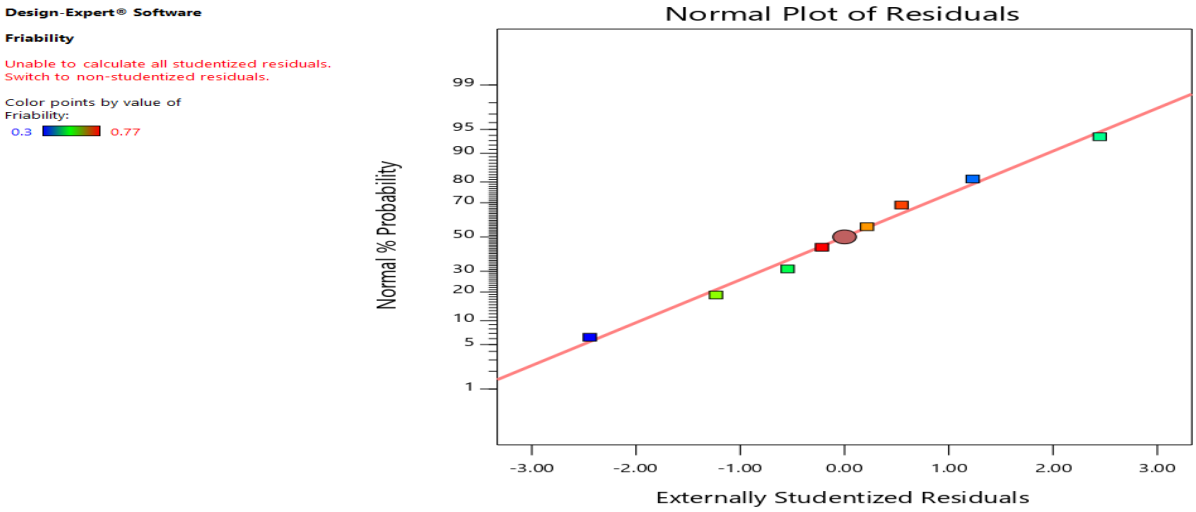

Design-Expert® Software
Factor Coding: Actual
CDR (%)
Design Points
72.1
77
X1 = A: AIFM
X2 = B: EC
CDR (%)
B: EC (mg)
A: AIFM (mg)
73
74
75
76
10
12
14
16
18
20
30
32
34
36
38
40

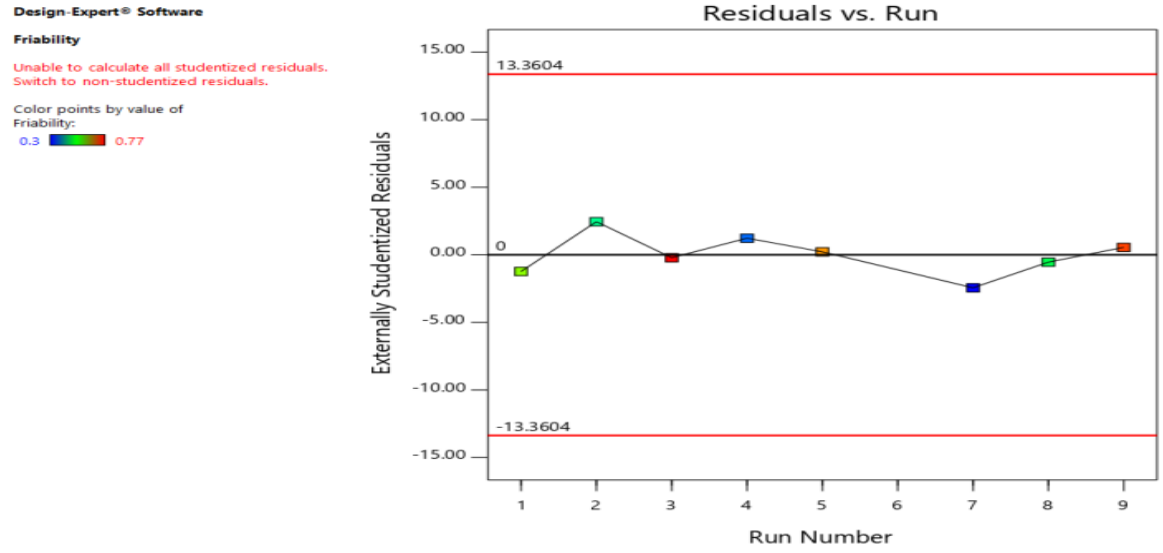

Design-Expert® Software
Factor Coding: Actual
Hardness (kg/cm2)
Design Points
4
8.6
X1 = A: AIFM
X2 = B: EC
Hardness (kg/cm2)
B: EC (mg)
A: AIFM (mg)
20
18
16
14
12
10
30
32
34
36
38
40
4
5
6
7

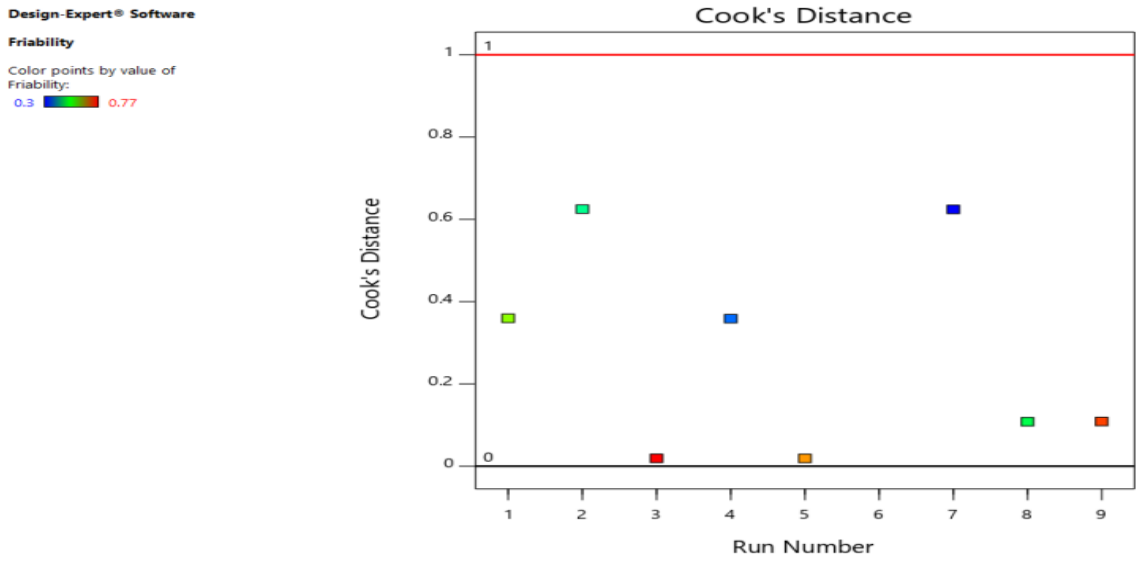

Design-Expert® Software
Factor Coding: Actual
Hardness (kg/cm2)
Design points above predicted value
Design points below predicted value
4
8.6
X1 = A: AIFM
X2 = B: EC
Hardness (kg/cm2)
9
8
7
6
5
4
3
B: EC (mg)
20
18
16
14
12
10
A: AIFM (mg)
30
32
34
36
38
40

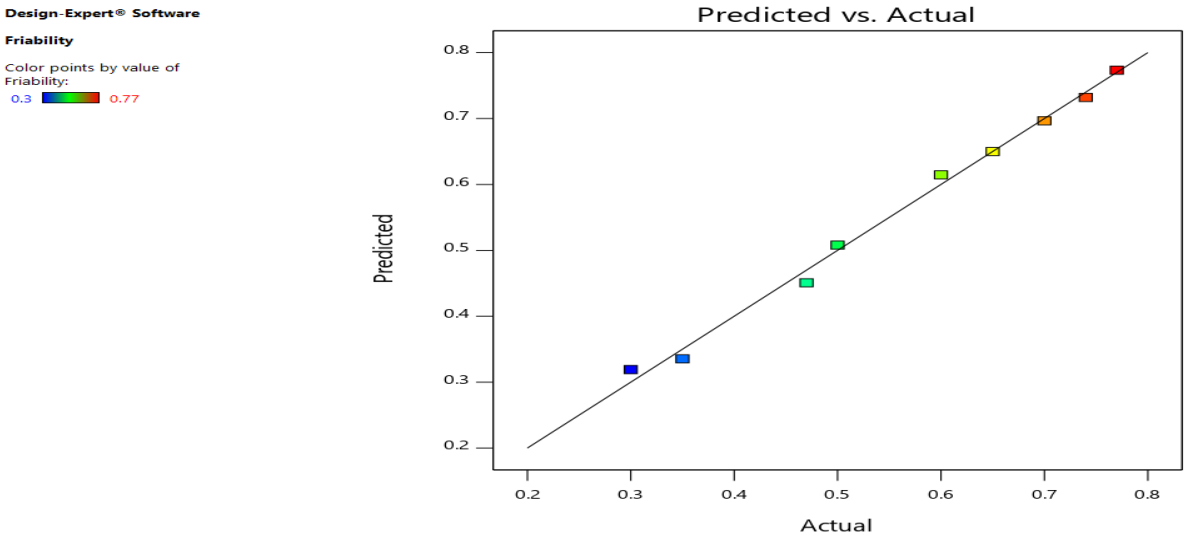

unnamed1* - Design-Expert 11
File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness (Analyzed)
R3:Friability (Analyzed)
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform Fit Summary Model ANOVA Diagnostics Model Graphs
Fit Summary
Warning: The Cubic model is aliased.
Fit Summary
Response 3: Friability
Source | Sequential p-value | Lack of Fit p-value | Adjusted R² | Predicted R²
Linear | 0.0001 | | 0.9338 | 0.9163 | Suggested
2FI | 0.4069 | | 0.9318 | 0.9307
Quadratic | 0.0489 | | 0.9848 | | Suggested
Cubic | 0.8808 | | 0.9646 | | Aliased
Sequential Model Sum of Squares [Type I]
Model Summary Statistics
Sequential Model Sum of Squares [Type I]
Source | Sum of Squares | df | Mean Square | F-value | p-value
Mean vs Total | 2.87 | 1 | 2.87
Linear vs Mean | 0.2177 | 2 | 0.1088 | 57.46 | 0.0001 | Suggested
2FI vs Linear | 0.0016 | 1 | 0.0016 | 0.8193 | 0.4069
Quadratic vs 2FI | 0.0085 | 2 | 0.0042 | 9.72 | 0.0489 | Suggested
Cubic vs Quadratic | 0.0003 | 2 | 0.0001 | 0.1445 | 0.8808 | Aliased
Residual | 0.0010 | 1 | 0.0010
Total | 3.10 | 9 | 0.3440
Select the highest order polynomial where the additional terms are significant and the model is not aliased.
horz: 45 vert: 70
Type here to search
26°C Mostly cloudy
ENG
11:19
09-10-2023

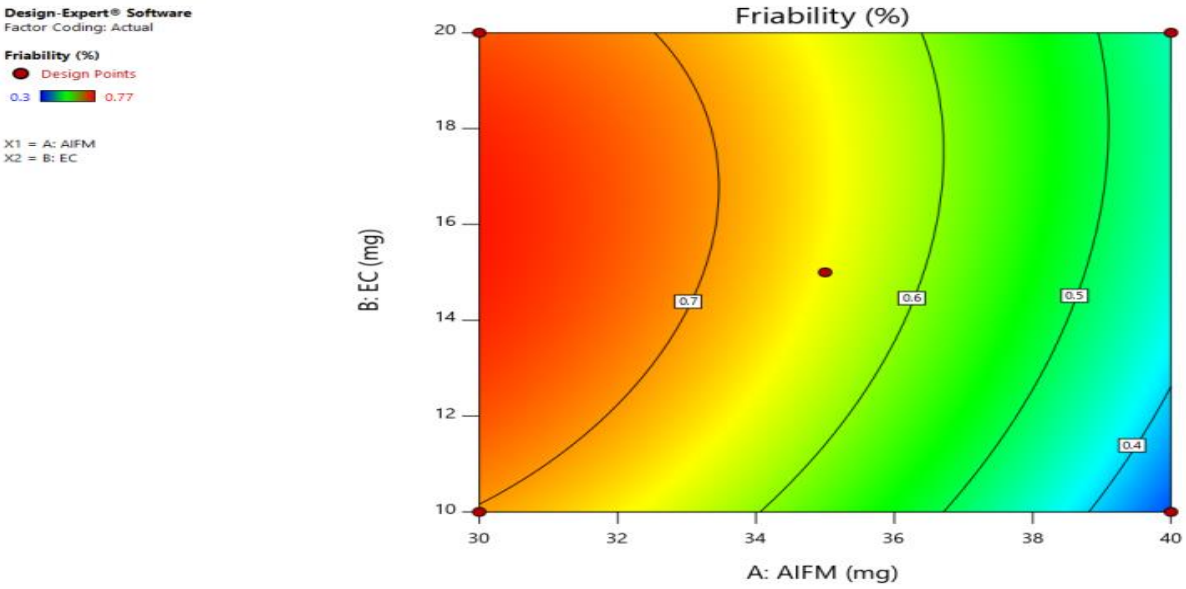

unnamed1* - Design-Expert 11
File Edit View Display Options Design Tools Help
Navigation Pane
Design (Actual)
Information
Notes
Summary
Graph Columns
Evaluation
Analysis
R1:CDR (Analyzed)
R2:Hardness (Analyzed)
R3:Friability (Analyzed)
Optimization
Numerical
Graphical
Post Analysis
Point Prediction
Confirmation
Coefficients Table
Transform Fit Summary Model ANOVA Diagnostics Model Graphs
Analysis of Variance
ANOVA for Quadratic model
Response 3: Friability
Source | Sum of Squares | df | Mean Square | F-value | p-value
Model | 0.2277 | 5 | 0.0455 | 104.68 | 0.0015 | significant
A-AlFM | 0.2063 | 1 | 0.2063 | 474.19 | 0.0002
B-EC | 0.0114 | 1 | 0.0114 | 26.10 | 0.0145
AB | 0.0016 | 1 | 0.0016 | 3.68 | 0.1510
A² | 0.0078 | 1 | 0.0078 | 17.99 | 0.0240
B² | 0.0057 | 1 | 0.0057 | 13.17 | 0.0360
Residual | 0.0013 | 3 | 0.0004
Cor Total | 0.2290 | 8
Factor coding is Coded.
Sum of squares is Type III - Partial
The Model F-value of 104.68 implies the model is significant. There is only a 0.15% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant. In this case A, B, A², B² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.
Fit Statistics
Model Comparison Statistics
Fit Statistics
Std. Dev. 0.0209 | R² 0.9943
Mean 0.5644 | Adjusted R² 0.9848
C.V. % 3.70 | Predicted R² NA(1)
Adeq Precision 26.6698
(1) Case(s) with leverage of 1.0000: Pred R² and PRESS statistic not defined.
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 26.670 indicates an adequate signal. This model can be used to navigate the design space.
Coefficients
Coded Equation
Actual Equation
Coefficients in Terms of Coded Factors
Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF
Intercept 0.6500 | 1 | 0.0209 | 0.5836 | 0.7164
A-AlFM -0.1606 | 1 | 0.0074 | -0.1841 | -0.1371 | 1.0000
B-EC 0.0377 | 1 | 0.0074 | 0.0142 | 0.0611 | 1.0000
AB 0.0200 | 1 | 0.0104 | -0.0132 | 0.0532 | 1.0000
A² -0.0519 | 1 | 0.0122 | -0.0908 | -0.0130 | 1.68
B² -0.0444 | 1 | 0.0122 | -0.0833 | -0.0055 | 1.68
The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients
For Help, press F1
Type here to search
26°C Mostly cloudy
ENG
11:20
09-10-2023

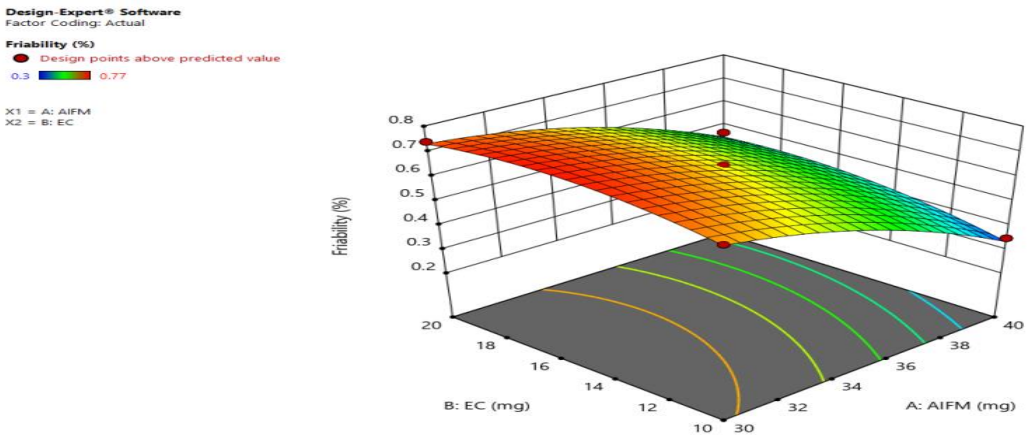

Design-Expert® Software
Friability
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
Friability:
0.3
0.77
Normal Plot of Residuals
Normal % Probability
99
95
90
80
70
50
30
20
10
5
1
-3.00
-2.00
-1.00
0.00
1.00
2.00
3.00
Externally Studentized Residuals


Design-Expert® Software
Friability
Unable to calculate all studentized residuals.
Switch to non-studentized residuals.
Color points by value of
Friability:
0.3
0.77
Residuals vs. Run
Externally Studentized Residuals
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
13.3604
0
-13.3604
1
2
3
4
5
6
7
8
9
Run Number


Design-Expert® Software
Friability
Color points by value of
Friability:
0.3
0.77
Cook's Distance
Cook's Distance
1
0.8
0.6
0.4
0.2
0
1
0
1
2
3
4
5
6
7
8
9
Run Number


Design-Expert® Software
Friability
Color points by value of
Friability:
0.3
0.77
Predicted vs. Actual
Predicted
Actual
0.2
0.3
0.4
0.5
0.6
0.7
0.8


Design-Expert® Software
Factor Coding: Actual
Friability (%)
Design Points
0.3
0.77
X1 = A: AIFM
X2 = B: EC
Friability (%)
B: EC (mg)
A: AIFM (mg)
0.7
0.6
0.5
0.4
10
12
14
16
18
20
30
32
34
36
38
40


Design-Expert® Software
Factor Coding: Actual
Friability (%)
Design points above predicted value
0.3
0.77
X1 = A: AIFM
X2 = B: EC
Friability (%)
B: EC (mg)
A: AIFM (mg)

Final Equation in Terms of Coded Factors

CDR $= +75.60 + 1.66X_1 + 0.3516X_2 - 0.2350X_1X_2 - 0.5338X_1^2 - 0.4838X_2^2$

Hardness $= +4.60 + 1.54X_1 - 0.3768X_2 - 0.2500X_1X_2 + 0.8250\ X_1^2 + 0.4250X_2^2$

Friability $= +0.6500 - 0.1606X_1 + 0.0377X_2 + 0.0200X1X_2 - 0.0519X_1^2 - 0.0444X_2^2$

Vision and Mission of the Institution

Vision

The East Point College of Pharmacy aspires to be a globally acclaimed institution, **recognized** for **excellence in** pharmaceutical education, research and nurturing students for **holistic development.**

Mission

M1	Create pharmacy graduates through **quality education**
M2	Promote innovation, **creativity**, and excellence **in teaching**, learning, and **research**
M3	**Inspire** integrity, teamwork, critical thinking**, personal** development, and ethics in **students** and lay **the** foundation for lifelong learning
M4	**Serve** the **healthcare, technological, scientific**, and **economic** needs of then **society**.