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Design and Optimizing of Metformin and 5-Fluorouracil Co-Loaded Nano Spheres by Box-Behnken Experimental Design for the Treatment of Colorectal Cancer

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ABSTRACT: Aim and objective of the study was to design and optimize metformin and 5-Fluorouracil drug molecules co-loaded with chitosan biodegradable polymer Nano-spheres for effectively targeting colorectal cancer cells in chemically induced colorectal cancer models. The metformin and 5- fluorouracil loaded chitosan nanoparticles were formulated by ionotropic crosslinking method. Experimental design consisted of three independent variables: chitosan, tripolyphosphate and stirring speed and three dependent variables: particle size, entrapment efficiency and drug release using Box-Behnken experimental design. Response surface modelling and the ability to fit to the model were evaluated with Design-Expert® software (Version 12). The optimized formulation by the design software indicated 1.33% of chitosan, 0.715 % of TPP at a Stirring speed of 3383 rpm is recommend to achieve a desirability value of 0.813 to have an acceptable range of 0.8 to 1, suggesting that the formulation quality is acceptable and excellent.

KEY WORDS: Box-Behnken experimental design, Design-Expert® software, Metformin, 5-Fluorouracil, Nano-spheres, Quality by design.

INTRODUCTION

Colorectal cancer (CRC) is the term for unchecked cell division in the colon or rectum. Majority of CRC arises in people above the age of 50, though it is found amongst younger adults also. The incidence had declined in older adults due to early discovery and screening. But the incidence has increased in younger adults below 50 for unknown reasons. Mutation of APC gene results in Familial Adenomatous Polyposis (FAP) can increase CRC risk to 100%. Localized cancers can be totally removed by surgical procedures like hemicolectomy or colectomy with ileorectal anastomosis. Chemotherapy is an option in most of the cases even after surgical resection. 5-fluorouracil (5-FU) is frequently used to treat colorectal cancer. 5-FU inhibits thymidylate synthase (TS) and incorporates its metabolites into RNA and DNA to produce its anticancer effects. (1)

Metformin belongs to the class of biguanides and is the treatment of choice for DM2.Metformin acts by decreasing the blood glucose levels and helps in the improvement of insulin sensitivity. Metformin also has an alternative pathway on the cells which is activation of Adenosine Monophosphate-Activated Protein Kinase (AMPK) which in turn acts on the mammalian target of rapamycin (mTOR) and Fatty acid synthase (FAS) inhibition resulting in decreased protein and fat synthesis which helps in declining the cancer cell progression due to limited availability of proteins and fats for cancer cell division to occur.

Change is predictable in everything; it includes the drug formulations also. Traditional drug formulation though is easily accessible, modification is necessary to meet the changes happening amongst the human population. Complex drug therapies, multiple diseases, comorbidities make the therapeutic decision making a complex process. This results in poor patient compliance, adverse drug reactions, side effects, drug interactions, drug resistance and more. Taking into consideration of different interpersonal and intrapersonal variations in the population, pharmacokinetic and pharmacodynamic changes happen invariably. Novel drug

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delivery system (NDDSs) targets the specific site and increases the drug concentration at a specific site making it a Targeted Drug Delivery System (TDDS), this diminish the systemic toxicity, reduce the dose and the dosing frequency and increase the bioavailability. Novel drug delivery system has an increased attraction for cancer therapy in recent days. Current therapy available for the cancer therapy have poor safety profile, restricted drug delivery to the target site especially for colon cancer, increased drug clearance. Systemic administration can cause CNS toxicity like Pancerebellar syndrome and subacute encephalopathy with sever cognitive impairment including disorientation, confusion, seizures. Repeated administration of certain drugs had also resulted in drug resistance. Moving forward more care has to be exercised towards formulation of drug molecules.

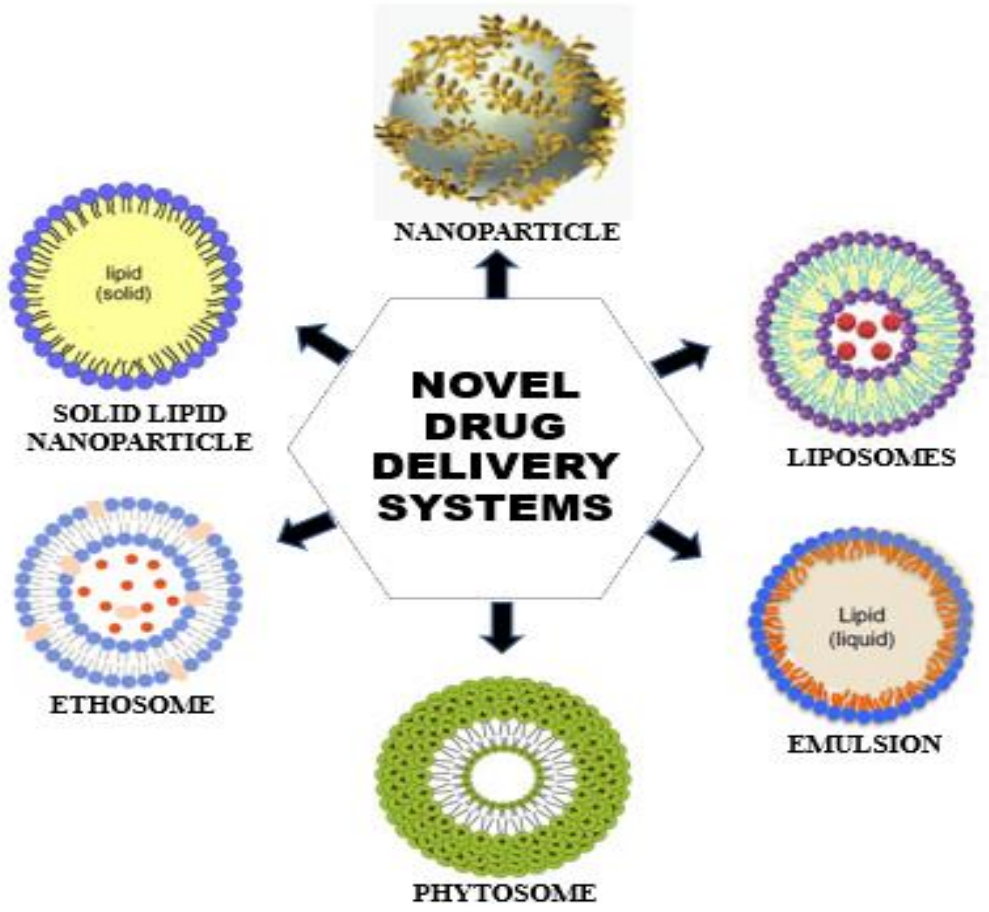

Figure 1. Novel drug delivery systems

Nanoparticles (NPs) are particles ranging in the in the size from 10 to 1000 nm and has a variety of application in various areas like medicine, diagnostics, engineering, environmental remediation, catalysis and more. They have enhanced reactivity, sensitivity and better surface area due to decreased particle size. (2)

Polymeric nanoparticles offer selective targeting, controlled release, drug molecule protection, and the capacity to integrate imaging and therapy. Highly biodegradable and biocompatible polymeric nanoparticles are employed in medication delivery and diagnostic applications. (3)

Nanomaterials are applicable in the field of medicine as nanomedicines, nano drugs, medical devices, tissue engineering, biopolymers, nutraceuticals, nanocapsules, biosensors, weapons, sensory enhancement equipment's and in fields of electronics, agriculture. (4,5)

In this present study, the drug-polymer nanoparticle formulation is enhanced with the help of design expert software and improvement in the surface characteristics and morphology is achieved to an appropriate level expected.

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MATERIALS AND METHODS

Design of Experiment (DOE)

Response surface methodology implemented as the design of experiment and the independent variables were studied with varying concentrations of chitosan, tripolyphosphate and stirring speed with different RPM. Particle size, entrapment efficiency and drug release were considered as dependent variables (Table 1).

Table 1. Box-Behnken experimental design

Independent factors	**Unit**	**Levels**		
		Low	**Medium**	**High**
X_1 = Amount of chitosan	%	0.5	1.25	2
X_2 = Amount of tripolyphosphate	%	0.5	1	1.5
X_3 = Stirring speed	RPM	1000	3000	5000
Responses (dependent factors)				
Y1 = Size	Nanometer			
Y2 = EE of nanoparticles	%			
Y3 = Percentage of MET&FU release	%			

Box-Behnken design (BBD) is the three-factor, three-level statistical screening approach used to optimize the nanoparticles. (6)

Preparation of Metformin and Fluorouracil loaded Chitosan nanoparticles (7)

The MET&FU loaded CH nanoparticles were formulated by ionotropic crosslinking method. MET&FU was added into CH solution, and the mixture was stirred at 3500 rpm for 1 hour. The chitosan/MET&FU solution was added into tripolyphosphate (TPP) (1% w/v) continuously. The MET&FU loaded chitosan nanoparticles were kept in desiccator until further use.

Table 2. Formula of MET&FU loaded chitosan nanoparticles

		Factor 1	**Factor 2**	**Factor 3**	**Response 1**	**Response 2**	**Response 3**
Std	Run	A: Chitosan	B: TPP	C: Stirring speed	PS	EE	DR
		%	%	RPM	nm	%	%
7	1	0.5	1	5000	350	53	76
1	2	0.5	0.5	3000	150	58	62
17	3	1.25	1	3000	270	86	91
11	4	1.25	0.5	5000	190	41	80
14	5	1.25	1	3000	270	86	91
10	6	1.25	1.5	1000	120	72	42
8	7	2	1	5000	240	81	50
2	8	2	0.5	3000	350	90	69
9	9	1.25	0.5	1000	80	32	75
12	10	1.25	1.5	5000	240	64	79
4	11	2	1.5	3000	450	84	71
13	12	1.25	1	3000	270	86	91

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5	13	0.5	1	1000	220	43	61
6	14	2	1	1000	510	70	49
3	15	0.5	1.5	3000	330	59	67
16	16	1.25	1	3000	270	86	91
15	17	1.25	1	3000	270	86	91

Response surface modelling and the ability to fit to the model were evaluated with Design-Expert® software (Version 12).

RESULTS AND DISCUSSION

Optimization study (8)

Concentration of chitosan, TPP and stirring speed influenced the particle size (nm), EE (%) and release (%) of the prepared MET&FU entrapped chitosan nanoparticles under optimal assay conditions. The following polynomial equation was used to optimize the parameters.

$$Y = \alpha_0 + \alpha_1X_1 + \alpha_2X_2 + \alpha_3X_3 + \alpha_4X_1X_2 + \alpha_5X_2X_3 + \alpha_6X_1X_3 + \alpha_7X_1^2 + \alpha_8X_2^2 + \alpha_9X_3^2$$

The figure 2. a, b and c depicts the three dimensional (3D) response plots showing the impact of three variables on the response – Particle size

Particle size (PS)

The particle size ranged from 120 nm to 510 nm. Higher chitosan and TPP concentrations tended to increase particle size. Higher stirring speeds resulted in smaller particle sizes, as seen in runs 6, 14, and 16.

Entrapment Efficiency (EE)

EE ranged from 32% to 90%. Higher chitosan concentrations generally led to higher EE, except for run 9, which had low EE possibly due to lower chitosan and TPP concentrations. Higher TPP concentrations sometimes resulted in lower EE, as seen in runs 2 and 8.

Drug Release (DR)

Drug release ranged from 42% to 91%. Higher chitosan concentrations generally resulted in higher drug release, as observed in runs 10, 12, and 15. Higher TPP concentrations tended to decrease drug release, as seen in runs 2, 5, and 6.

Particle size (PS)

Figure 2. a, b and c: 3D response plots showing the impacts of three variables on particle size.

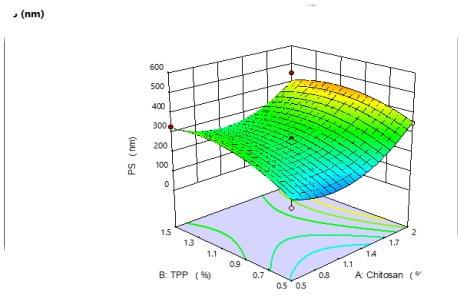

Figure 2.(a) Impact of polymer and cross-linker on size of nanoparticles (nm)

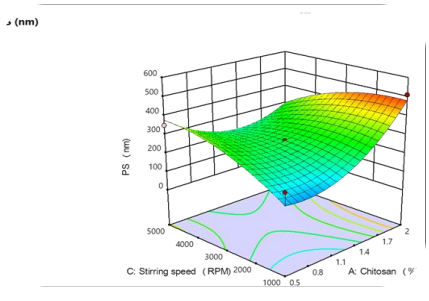

Figure 2 (b) Impact of polymer and stirring speed on size of nanoparticles (nm)

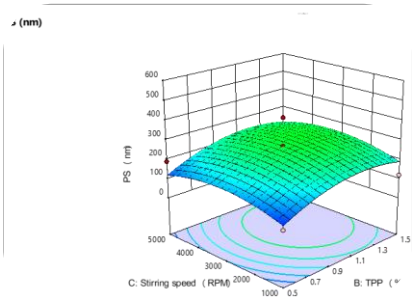

Figure 2 (c) Effect of TPP concentration and stirring speed (rpm) on size of nanoparticles (nm)

The figure 2. (a) illustrates the impact of varying concentrations of chitosan (A) and tripolyphosphate (TPP) (B) on the particle size of the nanoparticles.

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As the concentration of chitosan increases, the size of the nanoparticles tends to increase. This is evident from the trend observed in the graph. Conversely, lower amounts of TPP tends to increase the size of the nanoparticles which is indicated by the increase in particle size observed when TPP concentration is at its lowest level.

Figure 2 (b) illustrates the influence of varying concentrations of chitosan (A) and stirring speed (C) on the particle size of the nanoparticles. An increase in the concentration of chitosan leads to an increase in the particle size of the nanoparticles. This observation aligns with the understanding that chitosan serves as a major component in the formation of nanoparticles. Increasing the stirring speed leads to a decrease in the particle size of the nanoparticles. This inverse relationship between stirring speed and particle size is commonly observed in nanoparticle synthesis processes. Higher stirring speeds facilitate better dispersion and homogenization of the components in the solution, resulting in more uniform and smaller particle sizes. Increased agitation promotes the breakup of larger aggregates and enhances the nucleation and growth of smaller nanoparticles.

Figure 2 (c), represents the varying concentration of tripolyphosphate (TPP) (B) and stirring speed (C) on particle size. Decreased levels of TPP, has an effect of increasing the particle size of the nanoparticles. Higher concentrations of TPP may facilitate stronger cross-linking between chitosan molecules, resulting in more compact and smaller nanoparticles. Conversely, lower concentrations of TPP may lead to weaker cross-linking, allowing for larger and less compact nanoparticles to form.

Entrapment Efficiency (EE)

Figure 3. a, b and c: 3D response plots showing the impacts of three variables on entrapment efficiency.

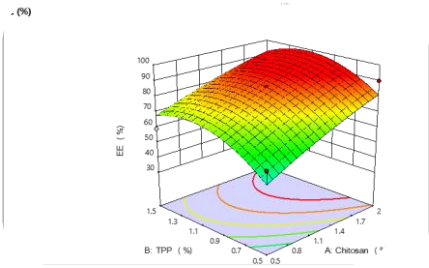

Figure 3 (a) Impact of polymer and cross-linker on entrapment efficiency (%) of nanoparticles

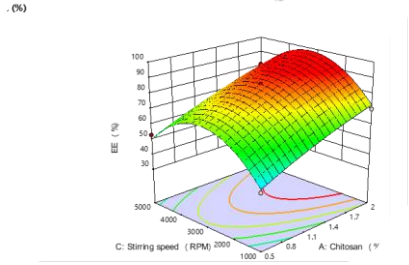

Figure 3 (b) Impact of concentration of polymer and stirring speed (rpm) on entrapment efficiency (%) of the formulation

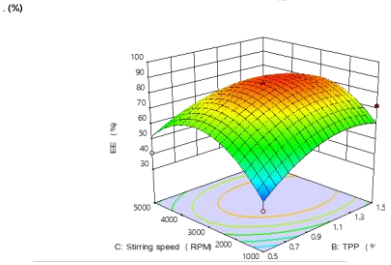

Figure 3 (b) Impact of concentration of polymer and stirring speed (rpm) on entrapment efficiency (%) of the formulation

In Figure 3 (a), the term AB represents the interactive effects of chitosan concentration (A) and tripolyphosphate (TPP) concentration (B) on the entrapment efficiency of nanoparticles.

Decreasing the concentration of chitosan leads to a reduction in entrapment efficiency. This observation suggests that chitosan concentration plays a crucial role in determining the encapsulation of Metformin and Fluorouracil (MET&FU) within the nanoparticles. Higher concentrations of chitosan likely provide more polymer chains available for cross-linking with TPP, resulting in more efficient entrapment of the drug molecules.

Increasing the concentration of TPP leads to a decrease in entrapment efficiency. This trend suggests that higher concentrations of TPP might negatively impact the encapsulation of MET&FU within the nanoparticles.

Figure 3 (b), the term AC represents the interactive effects of chitosan concentration (A) and stirring speed (C) on the entrapment efficiency of nanoparticles. Increasing the concentration of chitosan leads to an increase in entrapment efficiency. Increasing the stirring speed leads to an increase in entrapment efficiency. This observation suggests that higher stirring speeds during nanoparticle formulation result in higher entrapment efficiency.

Figure 3 (c), the term BC represents the interactive effects of TPP concentration (B) and stirring speed (C) on the entrapment efficiency of nanoparticles. Increasing the concentration of TPP leads to a decrease in entrapment efficiency. This trend suggests that higher concentrations of TPP negatively impact the encapsulation of MET&FU within the nanoparticles. An increase in the stirring speed leads to an increase in entrapment efficiency. Higher stirring speeds promote better mixing and distribution of chitosan and drug molecules within the solution, leading to more uniform encapsulation within the nanoparticles.

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Drug Release (DR)

Figure 4. a, b and c: 3D response plots showing the impacts of three variables on drug release.

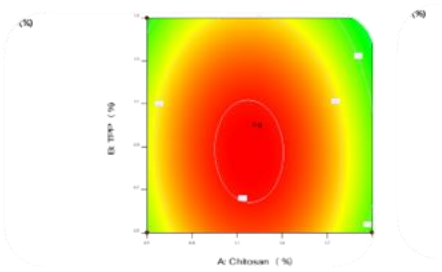

Figure 4 (a). Impact of polymer and cross-linker on MET&FU release

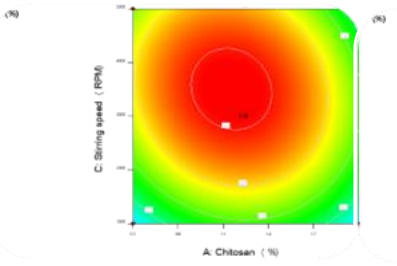

Figure 4 (b) Impact of polymer concentrations and stirring speed (rpm) on MET&FU releases.

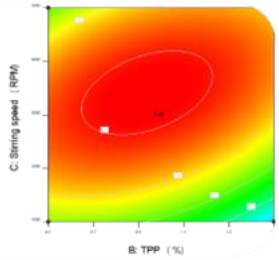

Figure 4 (c). Impact of cross-linking agent and stirring speed (rpm) on MET&FU release

Figure 4 (a), the term AB represents the interactive effects of chitosan concentration (A) and TPP concentration (B) on the drug release from the nanoparticles.

Increasing the concentration of chitosan leads to an increase in drug release. Higher chitosan concentrations may result in the formation of larger nanoparticles or alterations in the structure of the nanoparticles, affecting drug release kinetics. Higher chitosan concentrations can potentially lead to looser cross-linking and a more porous structure, allowing for faster diffusion of the drug molecules out of the nanoparticles, thus increasing drug release Higher TPP concentrations promote stronger cross-linking with chitosan, resulting in the formation of larger and more densely packed nanoparticles with reduced porosity. The tighter cross-linking restricts the diffusion of drug molecules out of the nanoparticles, leading to slower drug release kinetics. Conversely, decreasing the concentration of TPP leads to an increase in drug release. Lower TPP concentrations result in weaker cross-linking and the formation of smaller nanoparticles with higher porosity. The increased porosity facilitates the diffusion of drug molecules out of the nanoparticles, resulting in faster drug release.

In Figure 4 (b), the term AC represents the interactive effects of chitosan concentration (A) and stirring speed (C) on drug release from the nanoparticles. Increasing the concentration of chitosan leads to an increase in drug release. Increasing the stirring speed leads to an increase in drug release. Higher stirring speeds during nanoparticle preparation can influence the size, shape, and porosity of the nanoparticles. Increased stirring speed promotes more efficient mixing of chitosan and TPP solutions, resulting in the formation of smaller nanoparticles with higher surface area-to-volume ratios and potentially increased porosity

The figure 4 (c) shows the term BC where B is the TPP and C is the stirring speed. Increasing the concentration of TPP leads to a decrease in drug release. This phenomenon can be attributed to the increased cross-linking density between chitosan and TPP molecules at higher TPP concentrations. A denser cross-linked network results in reduced pore size and decreased drug diffusion rates, leading to slower drug release kinetics. Conversely, decreasing the concentration of TPP results in increased drug release. Lower TPP concentrations lead to weaker cross-linking, resulting in larger pore sizes and enhanced drug diffusion rates, thereby facilitating faster drug release. The effect of stirring speed on drug release has been discussed previously.

ANOVA for BBD

Table 3. Response model and statistical parameters obtained from ANOVA for BBD

Responses	Adjusted R^2	Predicted R^2	Model P value	Adequate precision	%CV
Particle size	0.9070	0.9488	<0.0004	15.57	11.03
Entrapment efficiency	0.9555	0.9345	<0.0005	18.78	5.59
Drug release	0.9713	0.7992.	<0.0001	22.15	3.31

Table 03 represents the statistical parameters such as adjusted R^2, predicted R^2, model P values, adequate precision and %CV.

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Adjusted R^2 and Predicted R^2

The adjusted R^2 values for particle size, entrapment efficiency, and drug release (0.9070, 0.9555, and 0.9713, respectively) indicate the proportion of variance in the response variables explained by the independent variables in the regression model. The high adjusted R^2 values suggest that the regression models are well-fitted to the experimental data, and they provide a good representation of the variability in the responses.

Model P Value

The model P value represents the statistical significance of the regression model. A low model P value (<0.05) indicates that the regression model is statistically significant, implying that the independent variables have a significant effect on the response variables.

Adequate Precision

Adequate precision measures the signal-to-noise ratio in the model. Higher adequate precision values (15.57, 18.78, and 22.15 for particle size, entrapment efficiency, and drug release, respectively) indicate better model reliability.

%CV (Coefficient of Variation)

The %CV provides information about the precision of the model estimates. Lower %CV values (11.03, 5.59, and 3.31 for particle size, entrapment efficiency, and drug release, respectively) suggest higher precision in the model estimates. The Table 3 confirms the robustness and reliability of the regression models for predicting particle size, entrapment efficiency, and drug release, and it highlights the significance of the independent variables in influencing these responses in the Box-Behnken experimental design.

Polynomial model equations

Table 4. Polynomial model equations

Polynomial model	
Particle size (Y1)	+258+70.36*A-25.75*B-50.00*C-7.75*AB+59.75*AC-26.75*BC+81.63*A^2-91.88*B^2+33.12*C^2
Entrapment efficiency (Y2)	+81.12+18.12*A-6.88*B+6.00*C+4.32*AB-1.98*AC+2.02*BC-7.88*A^2-6.07*B^2
Drug release (Y3)	+95.2+2.88*A-10.63*B-2.31*C-10.25*AB-0.500*AC+5.50*BC-11.13*A^2-9.63*B^2

The responses of Y1, Y2 and Y3 are equated

These polynomial model equations represent mathematical relationships between the independent variables (factors) and the response variables (particle size, entrapment efficiency, and drug release) in the form of quadratic equations. Each equation consists of terms corresponding to the main effects of the factors (A, B, and C), as well as interaction terms (AB, AC, BC), and quadratic terms (A2, B2, C2). Let's break down each equation:

Particle Size (Y1):

The equation for particle size (PS) is:

PS = +258 + 70.36A - 25.75B - 50.00C - 7.75AB + 59.75AC - 26.75BC + 81.63A2 - 91.88B2 + 33.12*C2

This equation indicates that particle size is influenced by the main effects of factors A, B, and C, as well as their interactions and quadratic effects. The positive coefficient for factor A (chitosan) suggests that increasing the concentration of chitosan tends to increase particle size. Similarly, the negative coefficient for factor B (tripolyphosphate) suggests that increasing its concentration tends to decrease particle size. Interaction terms such as AB, AC, and BC indicate how the combined effect of two factors influences particle size. For instance, the negative coefficient for AB suggests that the interaction between chitosan and tripolyphosphate affects particle size. Quadratic terms (A2, B2, C2) account for non-linear effects of the factors on particle size, allowing for curvature in the response surface.

Entrapment Efficiency (Y2)

The equation for entrapment efficiency (EE) is:

EE = +81.12 + 18.12A - 6.88B + 6.00C + 4.32AB - 1.98AC + 2.02BC - 7.88A2 - 6.07B2

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Similar to the particle size equation, this equation includes main effects, interaction terms, and quadratic terms for factors A, B, and C. The positive coefficient for factor A suggests that increasing the concentration of chitosan tends to increase entrapment efficiency, while the negative coefficient for factor B suggests the opposite effect. Interaction terms and quadratic terms in this equation also influence entrapment efficiency, capturing the combined and non-linear effects of the factors.

Drug Release (Y3)

The equation for drug release (DR) is:

DR = +95.2 + 2.88A - 10.63B - 2.31C - 10.25AB - 0.500AC + 5.50BC - 11.13A2 - 9.63B2

Similarly, this equation accounts for the main effects, interaction terms, and quadratic terms of factors A, B, and C on drug release. Interpretation of coefficients in this equation follows the same logic as for particle size and entrapment efficiency. For instance, the positive coefficient for factor A suggests that increasing the concentration of chitosan tends to increase drug release, while the negative coefficient for factor B suggests the opposite effect. Interaction and quadratic terms further refine the understanding of how these factors influence drug release. These polynomial equations provide a mathematical representation of the relationships between the independent variables and the responses, enabling prediction and optimization of the formulation parameters for desired particle size, entrapment efficiency, and drug release characteristics.

Table 5. Optimum formulation derived by BBD

Factor	Chitosan (%)	TPP (%)	Stirring speed (rpm)	Desirability
Optimum formulation	1.33	0.715	3383	0.813

Table 5. Presents the optimal formulation derived from the Box-Behnken design (BBD)

Optimized formula for MET&FU loaded chitosan nanoparticles was identified as chitosan at 1.33%, TPP at 0.715% and a stirring speed of 3383 rpm was appropriate. The desirability value was 0.813, indicating that it falls within the range of 0.8 to 1, which suggests that the formulation quality is acceptable and excellent.

Predicted and observed values

Table 6. Value of responses under optimal assay conditions for nanoparticles

Point Prediction	Particle size (nm)	Entrapment efficiency (%)	Drug release (%)
Predicted	231.04±1.32	80.06±0.56	89.99±0.44
Observed	220.68±0.96	78.72±0.38	92.2±1.41
% error	4.48	1.67	-2.45

Table 6 provides the predicted and observed values of responses under optimal assay conditions for MET&FU loaded chitosan nanoparticles, along with the corresponding percentage error

% error = (observed value-predicted value)/predicted value x 100

The observed particle size is 220.68 nm, which is 4.48% lower than the predicted value of 231.04 nm. The observed entrapment efficiency is 78.72%, which is 1.67% lower than the predicted value of 80.06%. The observed drug release is 92.2%, *which* is 2.45% higher than the predicted value of 89.99%. These percentage errors provide insights into the accuracy of the predicted values compared to the observed values, allowing for an assessment of the reliability of the optimization process (Figure 5).

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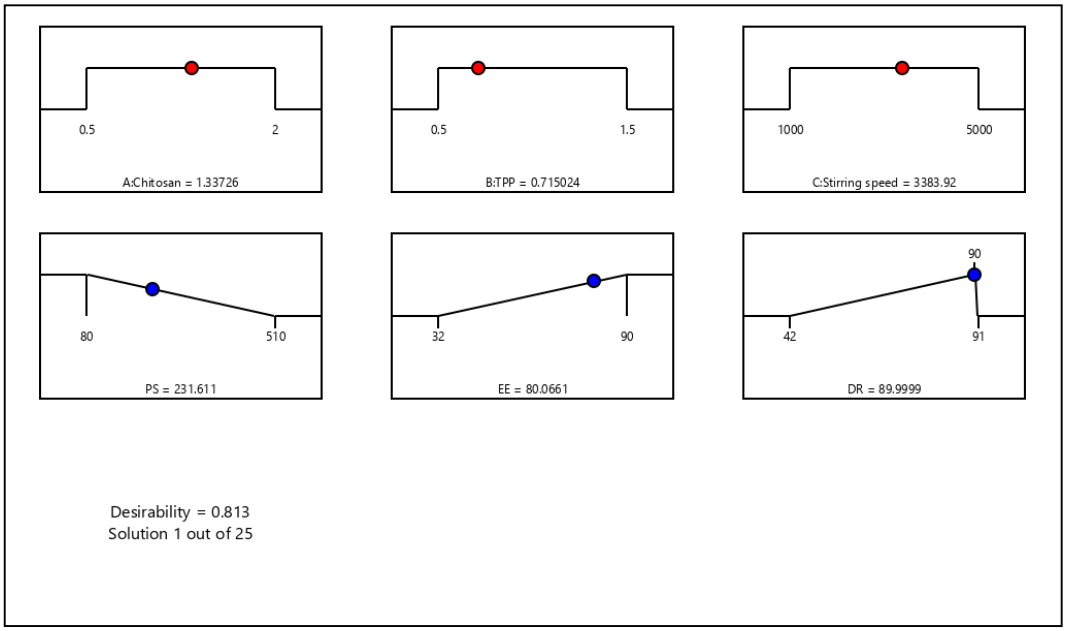
Figure 5. Desirability graph of MET&FU loaded CH nanoparticles



CONCLUSION

Box and Behnken study design adopted from design software was effective in optimizing and designing the right quantity of polymer, binding agent to be used and fixing the right speed of rotation to obtain the desirable formulation with excellent surface morphology and release kinetics though this study. Metformin, 5-Fluorouracil co-loaded with chitosan biodegradable polymer nanoparticles had a particle size of 230.04 nm, entrapment efficacy of 80.06 % and drug release of 89.99% respectively with a desirability of 0.813, indicated the formulation quality was acceptable and excellent.

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All authors contributed to the concept study and design. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of C. L. Baid Metha College of Pharmacy (Date 12.10.2018/No07/321/PO/RE/S/01/CPCSEA).

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