Application of quality by design (QbD) in drug layering of rifaximin colon specific pellets

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ABSTRACT:

This study's main goal was to find out how the coating polymers Eudragit S100 and HPMC K100M, as well as coating level conditions, affected the quality characteristics of pellets formulated using a quality by design (QbD) methodology.The drug pellets of rifaximinwere developed by powder layering technology. The time it took for 90% of the drug to be released from the coated pellets was assessed together with the rate of drug release of rifaximin.Additionally, differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy were used to examine the thermal and spectroscopic properties, as well as the

surface features (FTIR).In a coating pan, drug stacking and polymer coating over the pellets were carried out. Thermal and infrared analysis findings indicated that there were no significant interactions between the coated polymers and the medication.To foretell the impact of dependent variables, the regression model was created (drug release at time 2 h, 4 h and Q90). According to the findings, the polymer ratio and coating level had the biggest impacts on all of the response variables. Following a failure probability analysis, the design space was constructed using the medication release rate as a guide. The outcomes made clear how crucial it is to optimize the process variables using the QbD technique in order to produce pharmaceutical coating process and pellets of consistently excellent quality.

Keywords: pellets, powder layering, QbD, coating, rifaximin.

INTRODUCTION:

Spherical agglomerates having favorable flow properties, whether they are in powder or granule form. Depending on the preparation method, the resulting pellets typically have particle sizes between 0.5 and 1.5 mm.Pellets decrease the amount of drug needed, lessen gastrointestinal discomfort, control drug release, and improve the active ingredient's absorption[1].Pellet formulations provide substantially higher repeatability of the release properties than single-unit dosage forms. Due to the low surface area-to-volume ratios, they are appropriate systems for film coating. These dosage forms' resilience to environmental components like moisture, air, and light are among their finest qualities[2].To enhance the absorption ofpolypeptideor proteinbased drugs or to treat local illnesses including colon cancer and inflammatory bowel disease, colon specific drug delivery systems (CSDDS) have been developed. Several methods, together with pH-dependent polymer coating, microbial enzyme triggering and time controlled release, have been employed to achieve colon-specific medication delivery. One of the purposes of colon-specific medication administration must include to carefully regulatingrelease of drug before colon keeping enough susceptibility to prompt release at the proximal colon[3].

The outer Eudragit S100 coating dissolves rapidly in the distal small intestine when the lumen has a pH value higher than seven, protecting the device against gastrointestinal settings with typical pH values higher than. Once the exterior pH-sensitive polymer dissolves, the polysaccharide layer is revealed, and it begins to take up water and expand to generate gel, delaying the release of the medication for a certain amount of time. The loaded medications are

subsequently released when the swollen pellets reach the proximal colon and are broken down by microbial enzymes[4,5].

The formulation and manufacturing process can be improved by employing the systematic, effective, risk-controlled, and knowledge-based QbD technique, which places a strong emphasis on preliminary design. The following procedures may be used in QbD-based techniques for pharmaceutical development: definition of quality target product profiles (QTPP), identification of critical quality characteristics (CQA), and preliminary risk assessment. Finding the impact of material qualities and process parameters on CQAs is the fundamental goal of risk assessment. A statistical approach called design of experiment (DoE) can be employed for the screening and optimization of material qualities and process parameters. A statistical technique that is frequently used for the optimization of formulation and process variables with desired attributes is the Box Behnken design (BBD) [6-7].

Rifaximin (RFX) inhibits bacterial RNA synthesis. This is achieved by the action on beta subunit of the DNA (Deoxyribonucleic Acid) dependent RNA (Ribonucleic Acid) polymerase enzyme. RFX is widely used in the treatment of irritable bowel syndrome (IBS) and other associated diseases[8].

The main objective of this study was to evaluate the potential of HPMC as a film-coating material and its potential use in CSDDS in conjunction with an outer Eudragit S100 coating. Pellet form CSDDS was chosen because multi-unit systems were statistically more reliable than single-unit systems.

MATERIALS:

Rifaximin was received as a gift sample from Ankur Drugs and Pharma Ltd., Baddi, Himachal Pradesh. EudragitS100 and HPMC K100M were procured as a gift sample from Evonik Degussa Pvt. Ltd., Mumbai. All other reagents and chemicals used were of analytical grade.

METHOD:

Experimental design and fitted model[9-10]

The impacts of the design variables plasticizer concentration (x_1), polymer ratio (x_2), and coating level (x_3) as independent variables were examined using a modified Box Behnken design (BBD) with three factors and three levels. Drug release within two hours, four hours, and the time to release 90% of the drug concentration were the dependent variables. Table 1 displays the experimental plan for 13 runs for the three criteria that were assessed. Based on the results of the

exploratory trials, low, medium, and high amounts of control factors were chosen. Design expert® software, version 10.0.1, was used for the statistical analysis and optimization of the coating process.

Preparation of drug pellets by powder layering:[11-12]

During the drug loading process, 530 g of micronized rifaximinwas continuously mixed with 6% w/w PVP solution in isopropyl alcohol to generate a dispersion. Drug-loaded pellets were produced by piling the drug/binder combination onto non-pareil beads (1000 g) in a coating pan (Instacoat R & D Coater, Ideal Cures Pvt. Ltd., Mumbai, India). use a spray gun with a 4 atm pressure and a 20 rpm coating pan. The conditions for drug stacking were as listed in Table 2.

Inner Film Coating with HPMC K100M[13-14]

A coating pan was used to apply a layer of the release retardant polymer HPMC K100M high viscosity over the drug-layered pellets in order to limit the rate of release. The necessary amount of HPMC was progressively added to the isopropyl alcohol with constant stirring to create the HPMC non-aqueous coating solution. Propylene glycol was used as a plasticizer after a little amount of Methylene chloride was applied to solubilize the polymer. After stacking, the pellets were dried for 30 minutes at 50°C in a hot air oven.

Outer Film Coating with Eudragit S100[15]

The solvent mixture of, isopropyl alcohol, acetone and water is added while vigorously stirring with a magnetic stirrer to create the Eudragit S100 coating solution. The solution was then stirred briefly before the required amount of triethyl citrate, a plasticizer, was added.

The proportion of HPMC K100M and Eudragit S100 coating and the coating level of these polymers are the two factors that have the biggest impact on the release of rifaximin from pellets, according to preliminary research. The amounts of these components were determined using preliminary analysis and observations. The coating parameters are given in table 2.

Table 1: Experimental design: Independent and dependent variables and the levels used for factorial design

Factors (independent variables)	**Levels used**			**Responses (dependent variables)**
	-1	0	+1	
X1: plasticizer concentration (%)	10	20	30	Y1= Drug release at 2 hrs Y2= Drug release at 4 hrs
X2 = polymers ratio (Eudragit	2:1	4:1	6:1	Y3= Q90 (time to release 90%

S100/HPMCK1000)				of drug)
X3: Coating level	5	10	15	

Table 2:Coating parameters required during coating

Conditions	**Preheating**	**Coating**	**Drying**
Inlet air temperature(°C)	50-60	60-70	50
Product temperature(°C)	38-45	50-55	40-45
Outlet air temperature(°C)	35-40	40-45	40-45
Spray rate (ml/min)	-	3-4	-
Atomizing air pressure(psi)	-	20	-
Pan speed (rpm)	34-40	35-37	35-37

EVALUATION OF DRUG LAYERED PELLETS:[16-20]

Surface morphology of coated pellets

The morphology of the coated pellets' surfaces and cross sections pre and post compression was compared using scanning electron microscopy (SEM). With the help of an auto fine coater (JSM-7610FPlus ,JEOL-JFC 1600, Japan), platinum was applied to the dried samples, which were subsequently examined under various magnifications by an analytical scanning electron microscope.

Differential scanning calorimetry (DSC):

Using DSC, thermal characteristics were assessed (DSC60+ Shimadzu, Japan). The samples were hermetically packed in metal pans after being precisely weighed. As a reference, an empty aluminium pan was used. Under nitrogen gas, the samples were heated at a scanning rate of 10°C/min from 50 to 350°C.

Drug content

Before being dissolved in ethanol, rifaximin pellets (400 mg) targeted for the colon were first triturated. Serial dilutions were made furtherby the addition of 6.8pH phosphate buffer solutions.

UV spectrophotometer method was employed, at 274 nm, for thedetermination of drug content (Shimadzu, Japan).

In vitro drug release

Drug release pattern from the uncoated pellets was performed using basket type (USP XXIII dissolution)apparatus (100 rpm and 37 ± 0.5 ºC) in 900 ml pH 1.2 buffer solution for the first 2 h, then dissolution was continued in phosphate buffer pH 6.8 up to the time to release 90% 0f drug. At the definite intervals of time, 5 ml of sample were withdrawn for testing. The withdrawn sample solution was replaced by same volume of fresh dissolution medium. The sample was thereafter filtered, suitably diluted and analyzed by UV spectrophotometer at the λmax247 nm. The absorbance was recorded to determine the % drug release. All the measurements were performed in triplicates.

RESULTS AND DISCUSSION

SEM photographs revealed that the rough surface of core pellets was almost getting covered after coating with improved surface texture and smoothness. The deformities like cracks and pores generally get formed during the pelletization process and are unavoidable. The coated pellets were larger in size as compared to uncoated pellets with about 0.639-0.913 mm of diameters. The average coating thickness estimated from SEM analysis was 68.89±2.0 μm.

Evaluation of physical mixture

DSC was used to obtain the thermograms of the model drug and its physical mixture. At 226.63°C, the melting point of rifaximin was evident as a prominent endothermic peak. The physical mixture's melting point was 224.9°C, which is a little lower than the drug's actual melting point. The DSC peak has reportedly shifted as a result of contaminants, according to several investigations.

In addition, DSC thermogram of Rifaximin presented a sharp endothermic peak at 217.75ºC indicating the melting point of the drug existing form. Similar sharp endothermic peal but with low intensity was observed at 217.59ºC in Rifaximin-excipients mixture depicting no interaction between the API and the selected excipients.

The drug content was found satisfactory, indicate homogeneity of finished formulations. Drugcontent of the formulation was ranging from 32.12 to 32.85 mg per 100 mg functional coated rifaximin pellets.

Initial risk assessment[21]

QTPP is regarded as one of the core components of the QbD strategy by the International Council for Harmonization (ICH) Q8 (R2) standards. Early in the product development process, it is necessary to define the implications of CMAs and CPPs on CQAs. Table 2 provides the QTPP for coated rifaximin pellets with controlled release. The initial risk assessment was done to determine how the CQAs were affected by the formulation and process factors.Drug release at 2 h, 4 h and Q90 was identified for the assessment as a subset of CQAs that may be affected by dosage form and process factors and should be thoroughly considered for upcoming formulation and process development.The preparatory experiments, prior knowledge, experience, details regarding polymers, and information about the process conditions from published articles served as the foundation for the risk assessment. As indicated in Table 3, the quantitative risk priority numbers were divided into three categories for the initial assessments: high, medium, and low. While low risk variables just need a cursory examination, variables of high risk should be explored as control factors and described in depth.

Table 3. Initial risk assessment for formulation and process development of coated pellets

CQA	**Formulation and process variables**					
	Plasticizer conc.	**Polymer ratio**	**Coating level**	**Spray rate**	**Atomizing air pressure**	**Inlet temp**
Drug release at 2h and 4h	Low	High	High	Low	Low	Low
Q90 (Time to release 90%drug)	Low	High	High	Low	Low	Low
Drug Content uniformity	Low	Low	Low	Low	Low	Low
Appearance	High	Medium	Medium	Low	Low	Medium
Pellets density	High	Low	Low	Low	Low	Low

Low	Broadly acceptable risk. No investigation is further required
Medium	Risk is acceptable. Further investigation may be needed in ordered to reduce the risk
High	Risk is unacceptable. Further investigation is required for reduction

	of risk

Experimental design and Models of fitting[22]

Table 3 lists the experimental runs along the independent variables and the reflected outcomes for the thirteen formulations put to the test. By adding statistically significant coefficients (p 0.05), the initial regression model was improved. An antagonistic effect is indicated by a minus sign before the coefficients, whereas a synergistic effect is indicated by a plus sign. Whereas coefficients with a single factor term reflect a linear relationship between the factor and response, coefficients with multiple factors or higher order terms in the regression equations indicate an interaction or quadratic relationship.

Table 3: Experimental design parameters

Run	**Independent variables**			**Dependent variables (Mean ± S.D.)**			
	X1	X2	X3	Y1	Y2	Y3	Y4
	Plasticizer conc.	Polymer ratio	Coating level	Drug release at 2 hr (%), n=3	Drug release at 4 hr (%), n=3	Q90 (90% of drug release) n=3	Pellet Density (g/cm3), n=5
1	10	2:1	10	20.39± 0.8	48.33±1.1	5±0.3	1.3791 ± 0.0012
2	10	4:1	15	2.08±0.2	11.09±0.9	9±0.9	1.4001 ± 0.0006
3	30	4:1	15	1.99±0.6	10.38±1.7	12±1.3	1.3987 ± 0.0006
4	30	2:1	10	16.87±0.4	40.18±0.6	7±0.8	1.4008 ± 0.0004
5	20	6:1	15	1.80±0.2	11.79±0.3	18±0.2	1.4299 ± 0.0007
6	10	6:1	10	1.80±0.3	26.02±1.1	14±0.7	1.4024 ± 0.0012
7	20	2:1	5	29.38±0.8	41.32±1.4	5±1.8	1.4296 ± 0.0004
8	30	4:1	5	3.81±1.2	25.43±0.7	7±1.5	1.4343 ±

							0.0007
9	20	6:1	5	1.99±0.6	25.86±0.2	10±0.7	1.4101 ± 0.0008
10	10	4:1	5	8.37±0.8	26.08±0.6	6±0.3	1.4001 ± 0.0007
11	20	2:1	15	17.8±1.4	30.12±1.3	10±1.2	1.4330 ± 0.0010
12	30	6:1	10	1.42±0.6	24.43±1.1	17±0.9	1.3901 ± 0.0008
13	20	4:1	10	3.71±1.8	18.77±0.8	11±0.6	1.4017 ± 0.0008

Control factors' effects on drug release profiles

The findings of the several trial runs for dissolution are provided in table 3.The regression analysis was utilized to create simplified quadratic models in the coded terms indicated in Eqs. (2)–(5) using the control parameters that influenced the drug release rate.

$y1$ = 40.58-2.98*A-15.67*B-14.66*C+2.39AB+1.05AC+1.98BC------- (2)

$y2$ = 55.92 − 3.76*A-21.11*B-15.66*C-0.36AB-0.27AC-3.47BC-------(3)

$y3$ = 10.0+1.12*A+4*B+2.36*C+0.25AB-0.50AC-0.75BC--------(4)

$y4$ = 1.40 +0.012*A+0.029*B+1.002*C+0.09AB-0.07AC-0.05BC--------(5)

According to Table 4, the data was fitted well in the model as evidenced by the modest residual sum of squares (SS) and mean squares (MS), significant F value, and p values less than 0.05. Table 4 shows that the actual model R^2, adjusted R^2, and anticipated R^2 for y_1, y_2 and $y_3$were all close to 1. These values' similarity was indicative of the goodness of fit. The accompanying p values for the factors are shown in Table 5 along with the coefficient terms of the factors that relate to the drug release responses (y1-y3). An impact on the responses that is more significant is indicated by a greater coefficient value.The equation also suggests that a greater Eudragit S100:HPMC ratio (X_2) reduced the release profile, albeit to a lesser extent than would be the case if the plasticizer concentration was increased.

Contour plots can show the effect of each control component on the release ofdrug (Fig. 2). The graphs demonstrate that decreasing the drug release rate and raising the level of coating and polymer ratio. The drug release at 2 h and 4 h and Q_{90} was negatively impacted by the linear terms of the control factors, indicating that the coating level and polymer ratio slowed the drug

release rate. Larger coefficients for the coating level in particular showed that the coating polymer ratio had a considerable impact on the drug release rate.

The coating polymers on the drug-layered pellets served as a barrier to stop water from penetrating the pellet, dissolving the drug inside, and letting the drug diffuse into the surrounding medium. The barrier layer's thickness increased with increasing coating level, which ultimately lengthened the drug's diffusion path. Since the coating layer serves as a physical barrier between the drug and the dissolving media, higher coating levels may result in a slower drug release rate because of the lengthened diffusional path.

The coating level had a negative effect on the drug release, i.e., the drug release rate was slowed down with an increase in level of coating, as demonstrated in the regression model described by Eq. (2) - (5) and Table 5. Further coalescence between the polymer particles may be to blame for the decrease in release rate, making the polymer barrier less permeable to water and the drug.Large standard deviations were seen in low coating (5%w/w) compared to high coating level (15%w/w), suggesting that uniform coating distribution at high coating level formed a more homogenous coating layer, which ultimately resulted in more consistent drug release compared to thin coating (Table 1 and Fig. 1).

Table4: Analysis of variance (ANOVA) of dependent variables for the experimental design

Responses	**Values**	**Sum of Squares**	**Mean Square**	**F value**	**p value**	**R square**	**Adjusted R square**	**Predicted R square**
Y1	Cor Total	5532.78				0.9804	0.9568	0.8870
	Regression	5424.23	904.04	41.65	0.0004			
	Residual	108.54	21.71					
Y2	Cor Total	7305.45				0.9937	0.9862	0.9639
	Regression	7259.68	1209.95	132.16	0.0001			
	Residual	45.78	9.16					
Y3	Cor Total	173.06				0.9520	0.8943	0.7233
	Regression	164.75	27.46	16.52	0.0037			
	Residual	8.31	1.66					

Table 5: p-values for significant coefficients of dependent variables

Responses	Source	Coefficients	Standard error	p value
Y1	Model	42.08	1.34	< 0.0001
	A-Plasticizer concn	-10.48	1.65	< 0.0001
	B-polymers ratio	-10.67	1.65	<0.0013
	C-Coating level	-21.16	1.65	< 0.0001
	AB	-0.11	2.3bn n 3	0.9642
	AC	3.05	2.33	0.2477
	BC	1.98	2.33	0.4347
Y2	Model	55.92	0.87	< 0.0001
	A-Plasticizer concn	-11.89	1.07	0.0001
	B-polymers ratio	-15.61	1.07	< 0.0001
	C-Coating level	-22.79	1.07	< 0.0001
	AB	-0.11	1.51	0.9449
	AC	-1.27	1.51	0.4412
	BC	-2.22	1.51	0.2026
Y3	Model	9.13	0.37	0.0037
	A-Plasticizer concn	2.56	0.46	0.0025
	B-polymers ratio	2.87	0.46	0.0015
	C-Coating level	2.19	0.46	0.0049
	AB	1.25	0.64	0.1102
	AC	-0.38	0.64	0.5860
	BC	-0.50	0.64	0.4731

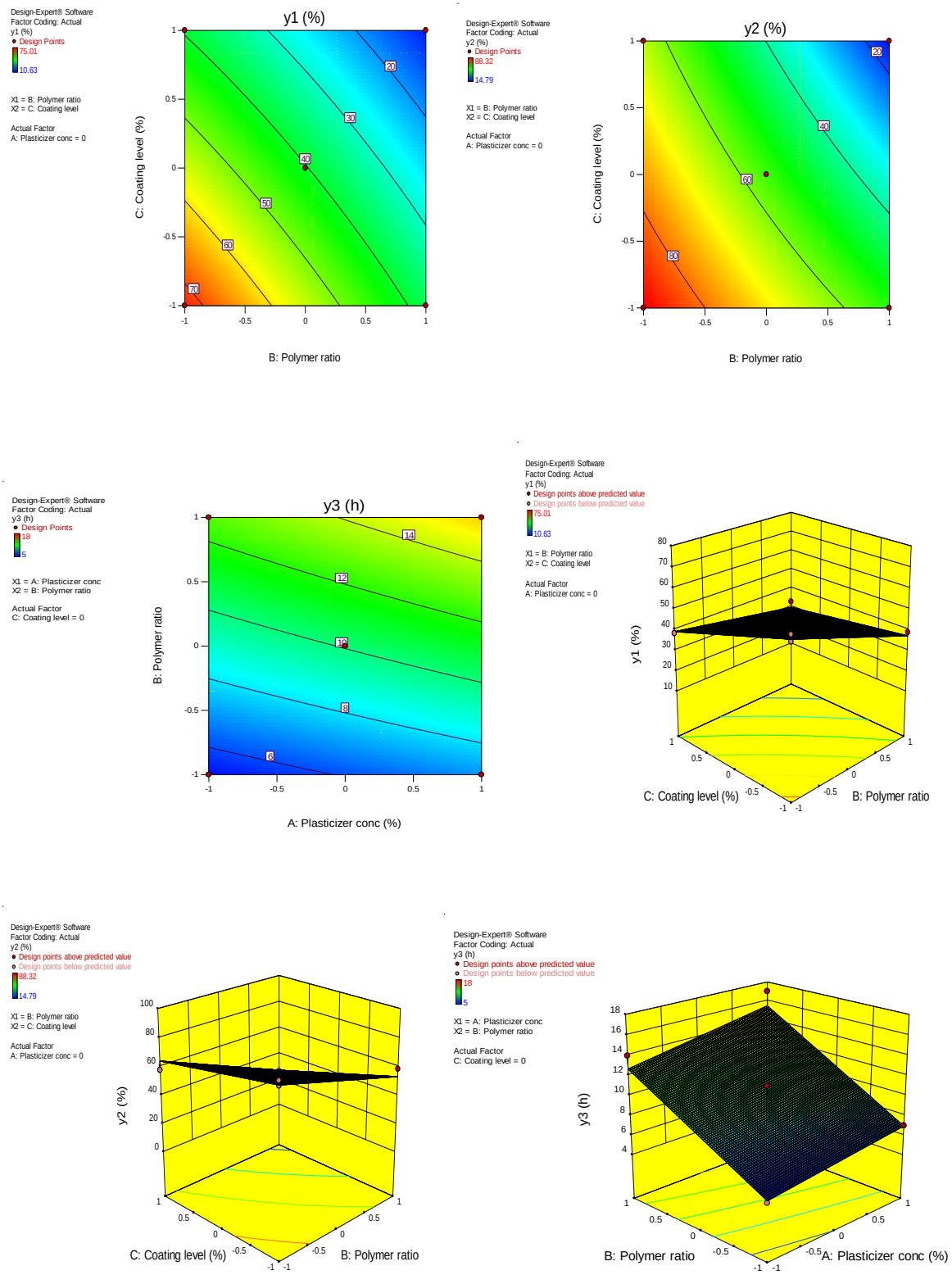


Fig.1: Contour plot (a,b,c) and Response surface (3D) plot (d,e,f) of the effects of variables on the drug release

Table 6:QTPP of pellets.

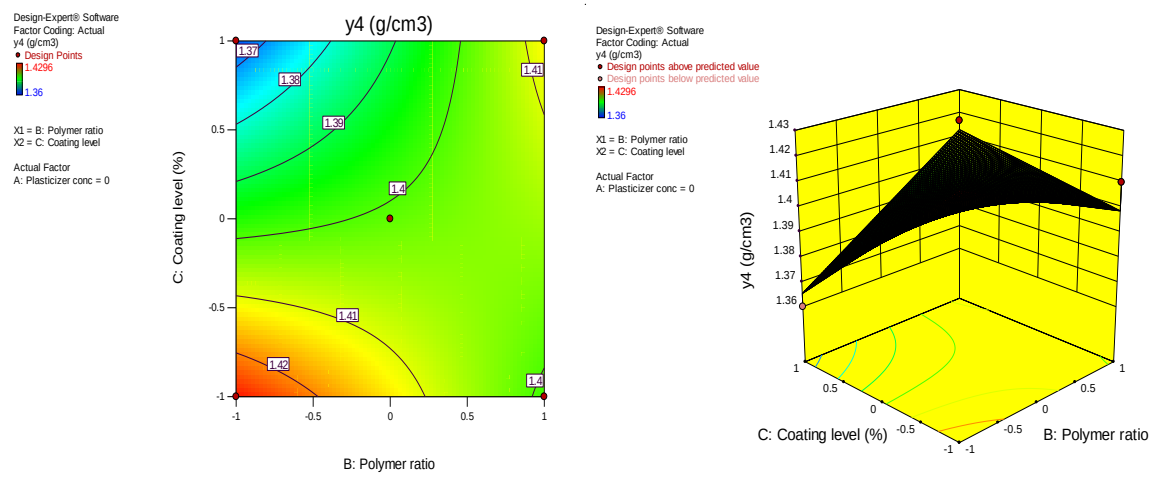
QTPP	Target	Justification
Dosage design	Sustained release pellets	Highly water soluble with short half- life. Minimize risk of dose dumping.
Route of administration	Oral, Patient compliance	Ease of administration
Dose strength	100 mg	Commonly accepted strength.
Dissolution Drug release at 2h Drug release at 4 h 90% Drug release(Q90)	 12-22% 45-60% 8hrs	Release the 90% of drug in the specified time. Failure to meet the dissolution specification can impact onbioavailability. Both process andformulation variables affect the drug dissolution profiles.
Physical attributes	Smooth coating	No physical defectsobserved(like improper coating andchipping etc.)

Effect on density of coated pellets

For various testing runs, coated pellet densities ranged from 1.3799 to 1.4031 g/cm3. Actual model R2, R2 adjusted model R2, and anticipated model R2 were, in that order, 0.998, 0.993, and 0.970. Eq.6 provides the simplified regression model for the coated pellets' actual density.

$y6 = 1.401 - 0.0264A + 0.006AB$……..(6)

As can be seen in Table 4, the data was fitted well in the model as evidenced by the tiny residual SS and MS, big F value, and p 0.05. The relevant p values for the factors are shown in Table 4 along with the coefficients for the coated pellets. A more significant impact on the replies was indicated by a greater coefficient value. The density was significantly impacted negatively by the coating level and the quadratic factors. The actual densities of the pellets were 1.4660 g/cm3and the values were consistent with earlier findings.The contour map **(Fig. 3)** depicts how the control factors affected the density, and only the coating level had an influence.



a) b)

Fig.2: Contour plot (a) and Response surface (3D) plot (b) of the effects of variables on the drug release

Design space and optimization of drug release response[23-26]

The goal of optimization is to maximize the range of input variables for achieving a goal. The achievement of proper response functions for both dependences and independences is a crucial step in optimization.The design space (DS) method aids in determining the range of control variables within which reliable results can be obtained. DS was investigated in the current study. The desired criteria for the release rate of drug were: 2 h (12 - 22%, target, 15%), 4 h (25 -40%) and Q90 (8-12hrs). This allowed for the release of rifaximin from coated pellets to longer period of time as per the need of dosage form. Overall, a good working environment to achieve the desired drug release was attained by selecting polymer ratio for coating of pellets4:1 (Eudragit S100:HPMC) and coating levels over 10%. To assess the variation in coating polymers ratio and coating level, a normal distribution with a 95% confidence level was chosen. Given the likelihood of failure, it was not advised to attempt to safely achieve the anticipated response at a lower polymer ratio. The chance of failure was less than 1% at higher polymer ratio (6:1) and greater coating levels (above 10%), showing the right DS for the intended drug release rate. Two further trials were conducted to confirm the DS. The probabilities of failure, drug release responses, and control factor validation results are displayed in Table 7 respectively. The likelihood of failure for both studies (P1 and P2), which were both inside the DS, was 0.5% and 2.0%, respectively. This may provide potential strategy for optimization of pharmaceutical coating process.

Table 7: Validated experiments of the design space

Experiments	Control factors X1(%)/X2(ratio)/X3(%)	Probability of failure	Responses: Y1/Y2 (% drug release)and Y3(Q90)	If meet specification
P1	20/4:1/10	0.5 %	36.03/58.61/11	Yes
P2	20/6:1/5	2.0%	47.12/59.77/10	Yes

Drug release kinetics[27]

In order to comprehend the release kinetics of the model drug from the coated pellets, in vitro dissolution profiles were fit to various kinetic models.The models used were the Higuchi model, first order and zero order (Eq 7-9).

$C_t = k_0 t$ (7)

$logC_0 - logC_t = k_1 t/2.303$ (8)

$C_t = k_H \sqrt{t}$ (9)

In the above equations, t is the time, $C_t$is the amount of drug released at time t, $C_0$is the initial amount of the drug,$k_0$is the zero order rate constant, $k_1$is the first order rate constant, and $k_H$is the Higuchi constant.

High R^2 denotes a strong connection between the fitted values and the model. Overall, the dissolution data suited the Higuchi and first order models the best. The drug release by diffusion through a polymer membrane is described by the Higuchi model. The concentration gradient served as the primary propulsion in this situation. The model medicine rapidly diffuses out from the pellets since it is freely soluble in water, which causes its contents to gradually diminish over time. The drug release in the first order release kinetic is influenced by the drug concentration in the pellets. R^2 was 0.5957 to 0.9471 for the zero order release kinetics.

The R^2 value showed a weak association between the fitted values at a lower coating level. However, the drug release followed zero order kinetics with greater R^2 as the coating layer thickness grew. This suggests that when the barrier thickness rises, the drug release is independent of drug concentration. Drug release is consistent throughout time with zero order kinetics, regardless of formulation or environmental factors. The medication release is regulated via diffusion through the intact polymeric layer because HPMC is a polymer that is insoluble in water.

4. Conclusion

Rifaximin appeared to be evenly distributed across the pellets, according to Raman imaging. Additionally, negligible interaction between the medication and polymer was confirmed by DSC and FTIR. Using an optimization experimental method, the effects of coating level and curing condition on the drug release rate and mechanical strength of pellets were investigated. The drug release from pellets with various coating level showed that thicker coatings slowed down drug release. It was also possible to draw the conclusion that diffusion served as the main hydrophilic drug release mechanism at higher coating levels. Zero order was released, nevertheless, as the coating level rose. Additionally, the formulation development with aqueous polymer dispersion and the curing procedure were equally crucial.Diffusion through the intact polymeric membrane was the main factor controlling how much medication was released from the pellets. A smooth, uniform layer was created at higher plasticizer concentration, according to the SEM images.

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REFERENCES:

1. Gandhi R, LalKaul C, Panchagnula R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharm SciTechnolo Today 1999; 2:160e170.
2. Frenning, G.; Tuno´N, A.; Alderborn, G. Modeling of drug release from coated granular pellets. *J. Control. Rel.*, v.92, p.113-123, 2003.
3. Guo Y, Zong S, Pu Y, Xu B, Zhang T, Wang B. Advances in pharmaceutical strategies enhancing the efficiencies of oral colon targeted delivery systems in inflammatory bowel disease. Molecules. 2018;23.
4. Rodriguez, M., J.L. Vila-Jato and D. Torres, 1998. Design of a new multiparticulate system for potential site specific and controlled drug delivery to the colonic region. J. Control. Release, 55: 67-77.

5. D.M. Gaber, N. Nafee, O.Y. Abdallah, Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs, Int. J. Pharm. 488 (2015) 86-94.

6. Lawrence XY. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm
Res 2008; 25:781e791.

7. Guideline ICH. Pharmaceutical development Q8 (R2). Annex to pharmaceutical development, Step; 2009. p. 4.

8. Mohammed Saadi and Richard W. McCallum. Rifaximin in irritable bowel syndrome: rationale, evidence and clinical use. TherAdv Chronic Dis. 2013 Mar; 4(2): 71–75.

9. Ragonese R, Macka M, Hughes J, et al. The use of the BoxeBehnken experimental design in the optimization and robustness testing of a capillary electrophoresis method for the analysis of ethambutol hydrochloride in a pharmaceutical formulation. J Pharm Biomed Anal 2002; 27:995e1007.

10. Tiwari R, Agarwal SK, Tiwari S. Formulation and multivariate optimization of microcrystalline cellulose pellets of highly water soluble drug. Int J Drug Deliv. 2013;5:206–13.

11. J. Goole, P. Deleuze, F. Vanderbist, K. Amighi, New levodopa sustained-release floating minitablets coated with insoluble acrylic polymer, Eur. J. Pharm. Biopharm. 68 (2008) 310-318. M Subhabrota, R Souvik, and C Subhadeep. Preparation and gamma scintigraphic evaluation of colon specific pellets of ketoprofen prepared by powder layering technology. Daru. 2011; 19(1): 47–56.

12. C Nastruzzi, R Cortesi, E Esposito, A Genovesi, A Spadoni, C Vecchio, E Menegatti. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS PharmSciTech. 2000 May 6;1(2):E9.

13. Youness Karrout, Christel Neut, Daniel Wils, Florence Siepmann. Novel polymeric film coatings for colon targeting: Drug release from coated pellets. European Journal of Pharmaceutical Sciences. Volume 37, Issues 3–4, 28 June 2009, Pages 427-433

14. Gupta, V.K., Assmus, M.W., Beckert, T.E. and Price, J.C. (2001b). A Novel pH- and Time-based Multi-unit Potential Colonic Drug Delivery System. II. Optimization of Multiple Response Variables, Int. J. Pharm., 213(1–2): 93–102.

15. Khan, M.A., Dib, J., Reddy, I.K., 1996. Statistical optimization of Ketoprofen-Eudragit® S100 coprecipitates to obtain controlled release tablets. Drug Dev. Ind. Pharm. 22, 135–141.

16. NikolettKállai, Oliver Luhn, JuditDredán, KristófKovács, MilénaLengyel. Evaluation of Drug Release From Coated Pellets Based on Isomalt, Sugar, and Microcrystalline Cellulose Inert Cores AAPS PharmSciTech. 2010 Mar; 11(1): 383–391.

17. Pengpong T, Sangvanich P, Sirilertmukul K, Muangsin N. Design, synthesis and in vitro evaluation of mucoadhesive p-coumaratethiolated-chitosan as a hydrophobic drug carrier. Eur J Pharm Biopharm. 2014;86:487–97.

18. Akhgari A, Garekani HA, Sadeghi F, Azimaie M. Statistical optimization of indomethacin pellets coated with pH-dependent methacrylic polymers for possible colonic drug delivery. Int J Pharm 2005;305:22-30.

19. Sinha A, Ball DJ, Connor AL, Nightingale J, Wilding IR. Intestinal performance of two mesalamine formulations in patients with active ulcerative colitis as assessed by gamma scintigraphy. *Practgastroenterol.* 2003;27:56–69.

20. Kwakye KO, Fell JT, Sharma HL, Smith AM. Gamma scintigraphic evaluation of film-coated tablets intended for colonic or biphasic release. *Int J Pharm.* 2004;270:307–313.

21. ShulingKan, Jing Lu, Jianping Liu, Junlin Wang, Yi Zhao. A quality by design (QbD) case study on enteric coated pellets: Screening of critical variables and establishment of design space at laboratory scale. Asian Journal of Pharmaceutical Sciences 9 (2014) 268e 278.

22. PrakashThapa, RituThapa, Du Hyung Choi, SeongHoonJeong. Effects of pharmaceutical processes on the quality of ethylcellulose coated pellets: Quality by design approach. *Powder Technology*, doi:10.1016/j.powtec.2018.08.002.

23. Wang, C.C., Zhang, G., Shah, N.H., et al., 1997. Influence of plasticizers on the mechanical properties of pellets containing Eudragit® RS 30 D. Int. J. Pharm. 152, 153–163.

24. Singh, S.K., Dodge, J., Durrani, J.M., 1995. Optimisation and characterization of controlled release pellets coated with an experimental latex. Int. J. Pharm. 125, 243–255.

25. Pandey S., Swamy S.V., Gupta A., Koli A., Patel S., Maulvi F., Vyas B. Multiple response optimization of processing and formulation parameters of pH sensitive sustained release pellets of capecitabine for targeting colon. *J. Microencapsul.* 2018:1–13.

26. Lijun S, Liping L, Xiaoying S, Honglang C, Shumin Z and Wenchang Z: Optimizing pH-sensitive and time-dependent polymer formula of colonic pH-responsive pellets to achieve precise drug release. Asian J Pharm Sci 2019; 14: 413-22.

27. E N Griffin, P J Niebergall, Release kinetics of a controlled-release multiparticulate dosage form prepared using a hot-melt fluid bed coating method. Pharm Dev Technol. 1999 Jan;4(1):117-24.