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Combinational Drug Therapy Based Isoniazid And Fluoxetine Loaded Muco-Adhesive Tablet For The Management Of Gastrointestinal Tuberculosis

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Abstract

Background: *The present study involved the formulation design and modification of muco-adhesive tablet of isoniazid and fluoxetine. Isoniazid is a first line medication to treat tuberculosis but its efficacy is compromised by multi drug resistance. Its efficacy can be enhanced by combining it with fluoxetine, an antidepressant drug (selective serotonine reuptake inhibitor). One study reported in combination of fluoxetine with isoniazid reduce the MIC of isoniazid by 128th times. Furthermore, the effect of both drugs was sustained by formulating them in muco-adhesive tablet form.*

Methods: *The mucoadhesive tablet was prepared by direct compression method and optmizwd by box behnken design. We used three levels to evaluate the effects of three independent variables—the concentrations of chitosan, microcrystalline cellulose (MCC), and HPMCK15M—on three dependent variables. Muco-adhesion strength, swelling index, and percentage of drug release at 20 hours were the dependent variables that were chosen in comparison to the independent factors.*

Results: *The improved formulation F8 (180.71%) showed a high swelling index and a robust muco-adhesion strength of 45.87 grams.*

This formulation also exhibited a good % drug release(84.23%) at 20th hrs. The optimized formulation also exhibited the controlled drug release over 24 hrs as it follows the zero order drug release kinetics. Since there was no discernible change in the drug content over the course of 90 days, the stability experiments showed that all of the formulations were stable.

Conclusion: According to these results, a good therapeutic delivery method for the successful treatment of gastric TB is the muco-adhesive tablet containing isoniazid and fluoxetine.

Keywords: *DoE, Isoniazid, Fluoxetine, QbD, muco-adhesive tablet*

INTRODUCTION

While pulmonary TB is widely recognized and prioritized in public health programs, its extra pulmonary manifestations, including Gastrointestinal Tuberculosis (GIT TB), often go undetected. [1, 2] GIT TB occurs when *Mycobacterium tuberculosis* infects the gastrointestinal tract, leading to a range of complications that can be life-threatening if not diagnosed early. [3] Unlike pulmonary TB, which presents with classic respiratory symptoms, GIT TB manifests with nonspecific gastrointestinal complaints, making it one of the most challenging forms of TB to diagnose. [4]

The incidence of GIT TB is highest in TB-endemic regions, particularly inSouth Asia and sub-Saharan Africa, but it is also on the rise in developed countries due to increased migration, immunosuppressive therapy use, and HIV co-infection. [5] The ileocecal region is the most frequently impacted area, while the disease can impact any part of the gastrointestinal tract, including the esophagus, stomach, intestines, peritoneum, and hepatobiliary system.

Patients with GIT TB often present with abdominal pain, weight loss, prolonged diarrhea, fever, and anorexia, symptoms that closely resemble other gastrointestinal disorders such as Crohn's disease, intestinal malignancies, and irritable bowel syndrome. This clinical similarity frequently leads to misdiagnosis and delayed treatment, increasing the risk of complications like intestinal strictures, perforation, fistula formation, and peritonitis [6, 7].

One of the biggest hurdles in managing GIT TB is its diagnostic complexity. Unlike pulmonary TB, where sputum examination and chest radiography provide a straightforward approach, diagnosing GIT TB requires invasive methodslikeendoscopic biopsies, laparoscopic evaluation, and imaging studies. The paucibacillary nature of GIT TB makes conventional diagnostic tests, such as acid-fast bacilli (AFB) staining and mycobacterial culture, unreliable [10]. However, recent advances in molecular diagnostics, including GeneXpert MTB/RIF, polymerase chain reaction (PCR), and interferon-gamma release assays (IGRA), have significantly improved detection rates[3]. In order to distinguish GIT TB from other gastrointestinal disorders, imaging methods like CT scans, MRIs, and endoscopies are also essential for diagnosis.

Despite its severity, GIT TB is entirely curable if diagnosed early**.** Anti-tubercular therapy (ATT) remains the mainstay of treatment, typically involving a six-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE)**.** In severe cases with complications such as bowel obstruction, perforation, or abscess formation, surgical intervention may be necessary. [8] However, the rise in multidrug-resistant tuberculosis (MDR-TB) has made treatment more challenging, necessitating longer treatment durations and second-line medications. The issue of multidrug resistance

Additionally, a new obstacle to positive patient outcomes is brought about by the development of drug resistance. Patients suffering from tuberculosis are facing an increasing burden due to drug resistance. Therefore, one of the most important strategies for managing the condition is the development of new therapies with novel targets. An antidepressant medication called fluoxetine can increase the anti-tubercular action of isoniazid by up to 128 times, according to the literature review. [9, 10]

Additionally, the combination of two medications in a mucoadhesive pill improved the treatment's effectiveness. The benefits of long-term, localized drug delivery are offered by the mucoadhesive tablet. [11, 12]

In order to effectively treat gastric TB, we created and refined a muco-adhesive tablet for the co-administration of isoniazid and fluoxetine.

MATERIALS AND METHODS

Isoniazid was purchased from VLD Pharma Tech (India Pvt. Ltd.), Hydrabad, Telengana and Fluoxetine was obtained from Tokyo Chemical Industry, Tokyo, Japan. Chitosan was purchased from Yarrow Chem Product, Mumbai, India. Mannitol, magnesium stearate, and talc were procured from S D Fine Chem Limited, Mumbai, India. Microcrystalline cellulose and HPMCK15M were purchased from LobaChemie, Mumbai, India. All the chemicals used were of analytical grade.

Methods

Preformulation studies

The UV-Visible Spectrophotometry FTIR spectroscopy, along with determination of solubility, partition coefficient, and melting point were used to identify the drugs. Additionally, the medications' compatibility with one another and with excipients in a 1:1 ratio was examined. [13, 14]

Method of Preparation of mucoadhesive tablet

The direct compression method was used to prepare the muco-adhesive tablets and each tablet contained 20 mg of isoniazid and 10 mg fluoxetine. Chitosan MCC, HPMCK15M and the drugs were accurately weighed and sifted through sieve no. 30. After that, the mixture was thoroughly blended for five minutes in a polybag and lubricated for 3 minutes with magnesium stearate and talc. The powder blend was subsequently formed into tablets via the direct compression method with a single-punch tablet compression machine (utilizing 7.0 mm standard concave punches). [15, 16]

Preparation of coating solution

The coating solution was prepared by adding cellulose acetate phthalate (CAP) and polyethylene glycol (PEG) 400 (in ratio 5:1) to a mixture of acetone and IPA in ratio 1:1. The mixture was stirred until the formulation of clear solution. CAP was utilized as semipermeable membrane provider and PEG 400 was used as plasticizer. [17]

Coating of tablets

Conventional coating pan was employed to coat the core tablets with coating solution. All the parameters of coating process i.e. pan speed, coating inlet air, temperature, atomizing air pressure and spray rate were optimized. The weight gain was monitored periodically by checking the average weight of tablets. In a traditional pan coater, the stacked tablets were dried at 50°C for 30 minutes at 1-2. [18]

Box–Behnken Design (BBD) Experiment for optimization:

Box-Behnken design used a response surface approach (Design-Expert® Software Version 12) to optimize the mucoadhesive tablet.

The independent variables included the concentrations of chitosan (X1), MCC (X2), and HPMCK15M (X3) at three different levels: low, medium, and high. As shown in Table 1, these responses were evaluated on three dependent variables: muco-adhesion strength (Y1), percentage of swelling index (Y2), and percentage of drug release after 20 hours (Y3). Additionally, contour plots and 3D response surface graphs were drawn to ascertain how the predefined parameters affected the measured responses. [19, 20]

Table 1: Independent variables in Box–Behnken design used for the optimization of the muco-adhesive tablet

Factor	Independent variables	Unit	Low	Medium	High
X1	Chitosan	mg	30	50	60
X2	MCC	mg	20	30	40
X3	HPMCK15M	mg	40	50	60

Using the following non-linear quadratic model expression, where Y is the dependent variable, b0 is the arithmetic mean, and Y1–Y123 are regression coefficients of acceptable variables, the impact of independent factors on dependent variables at three levels was evaluated. The factors X1, X2, and X3 show how the various parameters interact with one another.

$$Y=b0+Y_1X_1+ Y_2X_2+ Y_3X_3+ Y_1Y_2X_1X_2+ Y_1Y_3X_1X_3+Y_2Y_3X_2X_3+ Y_1^2X_1^2+Y_2^2X_2^2+Y_3^2X_3^2$$

Equation- 1

Evaluation of formulated tablet

General appearance and shape

It includes morphological features of tablets such as shape, color and size. [21]

Thickness

The thickness of precoated tablet was measured with a vernier caliper. The average thickness was then calculated. [21]

Hardness

The hardness was assessed using a Monsanto hardness tester. The pressure needed to split the tablet diametrically was measured while the tablet was held between the two plunger ends. The unit of hardness was kg/cm^2. [22]

Weight uniformity

Twenty tablets were accurately weighed,individually and collectively and the average weight was computed by dividing the total weight by the number of tablets. [23]

Friability

The Roche friabilator was used to calculate the produced tablets' percentage friability. The tablets were subjected to rolling and replacement shocks after being dropped from a height of six inches within the device.

The tablets were removed, cleaned, and weighed again after one hundred revolutions (25 revolutions per minute) had been completed. Friability was assessed using the % decrease in tablet weight. [24, 25]

Swelling study

Each tablet was weighed separately (W1) and put in a glass beaker with 200 mL of pH 6.8 phosphate buffer, which was then incubated at 37 ± 0.5 °C. The pills were taken out of the beaker at regular intervals of one hour until ten hours had passed, and the excess liquid on the surface was gently scraped off with paper. After reweighing the swollen tablets (W2), the swelling index (SI) was computed using the formula below. [26, 27]

$SI= (W_2-W_1)/W_1$

Mucoadhesive strength and mucoadhesive time

A modified balance was used to test the mucoadhesive strength where the left pan of the balance was substituted with a weight to which a tablet was fixed, and weights were used to equalize both sides. Porcine gastric mucosa, characterized by a thick layer of mucus, was affixed to a rubber cork. This cork was previously secured at the bottom of a beaker containing the relevant medium, with the medium level just above the mucosa. [28]

The tablet that came into contact with the pig mucosa had a weight attached to it. Before the pan was raised, this arrangement was left in place for five minutes. The mucoadhesive strength was determined by adding weights to the right-side pan in small increments over time. The weight at which the tablet separated from the mucosa was recorded. [29]

A 10-gram weight was put on the right-side pan to measure the mucoadhesion time after raising it, and the detachment time was noted. The term "mucoadhesion time" describes how long the tablet remained attached to the mucosa.

***In vitro* dissolution studies**

USP II (paddle with sinker) was used to conduct in vitro drug release study of different formulations at 100 rpm in 900 mL of pH 6.8 phosphate buffer medium kept at 37 ± 0.5 °C. After that, 1 mL of the sample was taken out at definedintervals for 12 hours, and replaced with equal amount of dissolution medium. A UV-visible spectrophotometer was used to assess the samples at 262 nm for isoniazid and 224 nm for fluoxetine. [30]

Stability Studies

According to ICH guidelines, the formulation was stored for 90 days at two different temperatures (25°C/60% RH and 40°C/75% RH) in an airtight container. The amount of drug in the samples was measured after 15, 30, 45, 60, and 90 days. The initial drug content was considered to be100%.

RESULTS AND DISCUSSION

Pre-formulation profiling:

The drugs were identified by several analytical techniques including the UV spectroscopy and FTIR spectroscopy. All of the parameters were confirmed to be within acceptable limits and the official compendia specifications.

Solubility of drug:

The solubility studies indicated thatthe drugs are is poorly soluble in water and freely soluble in ethanol, propylene glycol, and phosphate buffer.

Drug excipient compatibility study:

Both medications were found to be with each other and with every excipient included in the formulations, according to the findings of the physical and chemical compatibility studies.

Box Behnken design optimization of mucoadhesive tablet

Mucoadhesive tablets prepared by the direct compression method were optimized using the Box-Behnken design. All fifteen formulations and the actual values of each independent and dependent variable are listed in Table 2. Every independent variable was analyzed at three levels, together with its polynomial effects and binary interactions

Table 2: Actual value of Independent and dependent variables

Formulation code	**A:Chitosan**	**B:MCC**	**C:HPMCK15M**	**Mucoadhesion Strength**	**Swelling index**	**drug Release at 20^{th}hr (isoniazid)**
	Mg	mg	mg	g	%	%
F1	30	20	50	28.34	126.93	64.72
F2	70	20	50	41.78	163.56	75.51
F3	30	40	50	27.97	120.67	61.37
F4	70	40	50	44.87	170.65	78.67
F5	30	30	40	25.78	112.86	59.86
F6	70	30	40	40.34	160.76	76.63
F7	30	30	60	34.88	151.98	72.54
F8	**70**	**30**	**60**	**45.87**	**180.71**	**84.23**
F9	50	20	40	33.89	149.67	71.93
F10	50	40	40	30.56	130.78	67.49
F11	50	20	60	37.86	154.36	74.72
F12	50	40	60	40.56	159.54	73.53
F13	50	30	50	32.78	144.13	69.13
F14	50	30	50	32.67	144.54	68.13
F15	50	30	50	32.98	145.87	68.96

Fitting data to the model

The impact of independent variables was examined on the chosen dependent variables. The best-fitting models for the swelling index, mucoadhesion strength, and percentage of drug release were determined by fitting the observed data into an ANOVA. It was noted that the correlation coefficients, which were computed using the experimental values, adequately accounted for the data. Tables 3, 4, and 5 display the values of R^2, corrected R^2, and predicted R^2. A high F value and a small p-value (less than 0.005) suggested that independent variables have a significant influence on dependent variables.

Table 3:- ANOVA of the fitted equation for the muco-adhesion time

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	536.45	9	59.61	68.13	0.0001	significant
A-Chitosan	390.46	1	390.46	446.27	< 0.0001	
B-MCC	0.5460	1	0.5460	0.6241	0.4653	
C-HPMCK15M	102.25	1	102.25	116.86	0.0001	
Residual	4.37	5	0.8749			
Lack of Fit	4.33	3	1.44	58.37	0.0169	significant
St. Deviation	0.93					
R2	0.99					
Adjusted R2	0.97					
Predicted R2	0.81					
Model	Quadratic					

$Y_1=32.81+6.99X_1+0.26X_2+3.58X_3+0.86X_1X_2-0.89X_1X_3+1.51X_2X_3+1.97X_1^2+0.96X_2^2+1.94X_3^2$

Equation 2

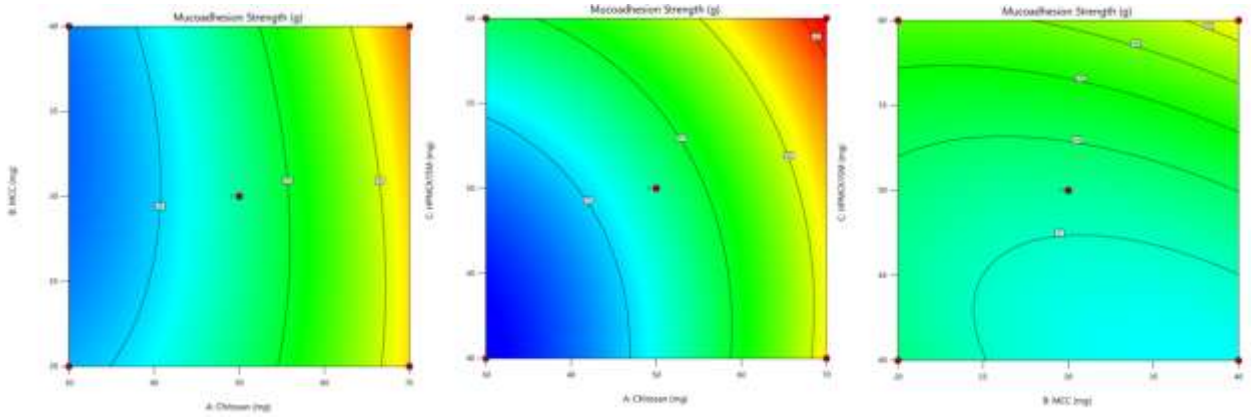

Figure 1: Contour plots showing the effect of independent variables on mucoadhesion strength

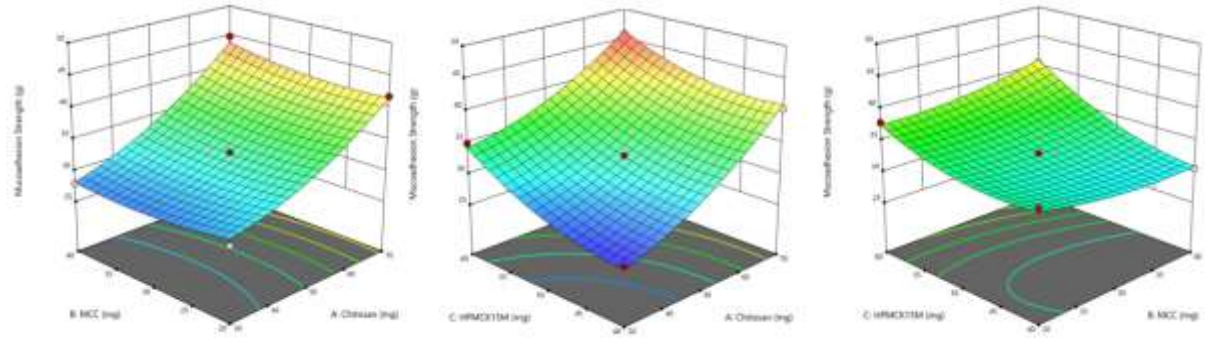

Figure 2: 3D surface plots showing the effect of independent variables on mucoadhesion strength

Table 4:- ANOVA of the fitted equation for the Swelling index

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	4810.68	9	534.52	41.80	0.0017	significant
A-Chitosan	3330.91	1	3330.91	135.87	< 0.0001	
B-MCC	20.74	1	20.74	0.8459	0.3999	
C-HPMCK15M	1069.99	1	1069.99	43.64	0.0012	
Residual	122.58	5	24.52			
Lack of Fit	120.92	3	40.31	48.71	0.0202	significant
St. Deviation	4.95					
R2	0.97					
Adjusted R2	0.93					
Predicted R2	0.87					
Model	Quadratic					

$Y_2=144.85+20.40X_1-1.61X_2+11.57X_3+3.34X_1X_2-4.79X_1X_3+6.02X_2X_3+1.80X_1^2-1.19X_2^2+4.93X_3^2$

Equation 3

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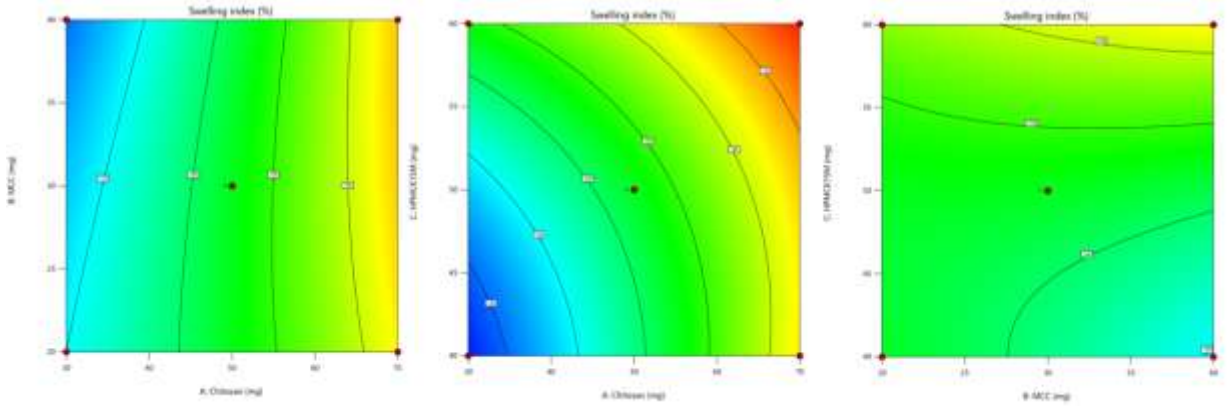

Figure 3: Contour plots showing the effect of independent variables on swelling index

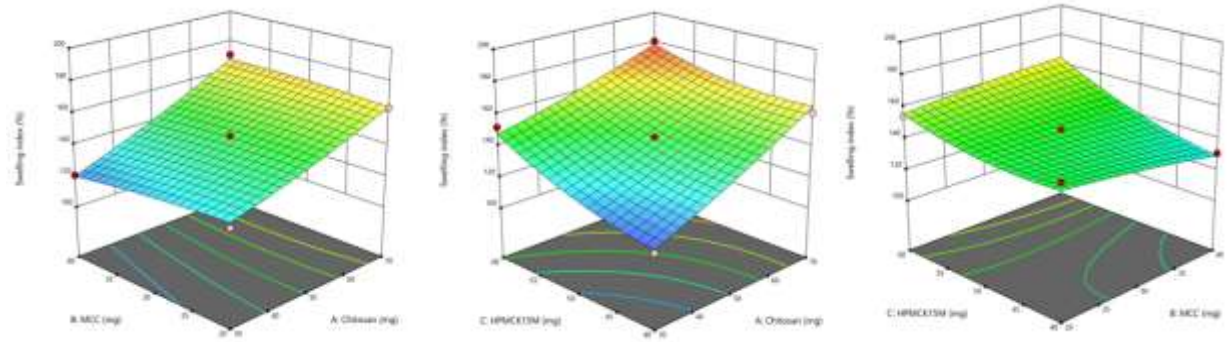

Figure 4: 3D surface plots showing the effect of independent variables on swelling index

Table 5:- ANOVA of the fitted equation for the drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	473.97	9	52.66	31.67	0.0017	significant
A-Chitosan	332.18	1	332.18	136.68	< 0.0001	
B-MCC	4.23	1	4.23	1.74	0.2441	
C-HPMCK15M	72.66	1	72.66	29.90	0.0028	
Residual	12.15	5	2.43			
Lack of Fit	101.58	3	33.7	45.43	0.0287	significant
St. Deviation	1.56					
R2	0.97					
Adjusted R2	0.98					
Predicted R2	0.971					
Model	Quadratic					

$$Y_3=68.74+6.44X_1-0.72X_2+3.01X_3+1.63X_1X_2-2.52X_1X_3+0.81X_2X_3+0.73X_1^2+0.59X_2^2+2.59X_3^2$$

Equation 4

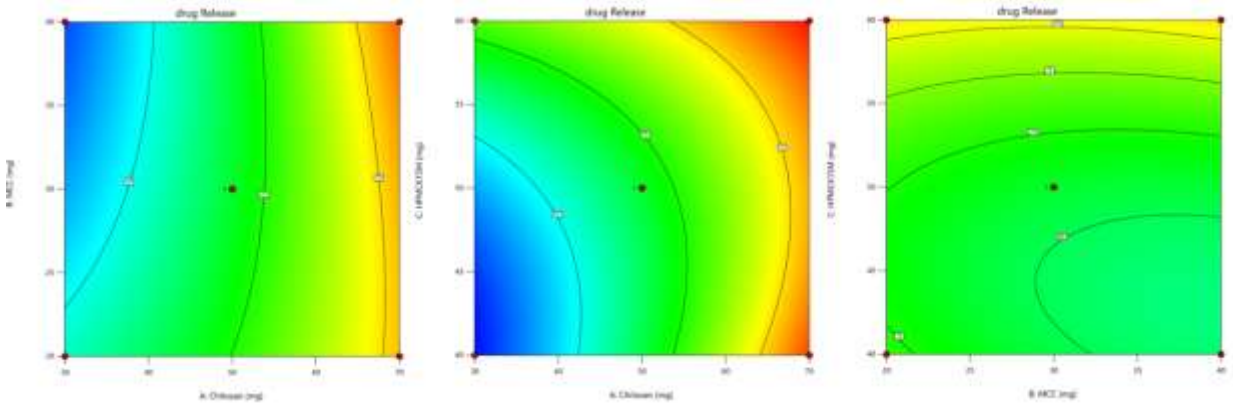

Figure 5: Contour plots showing the effect of independent variables on drug release

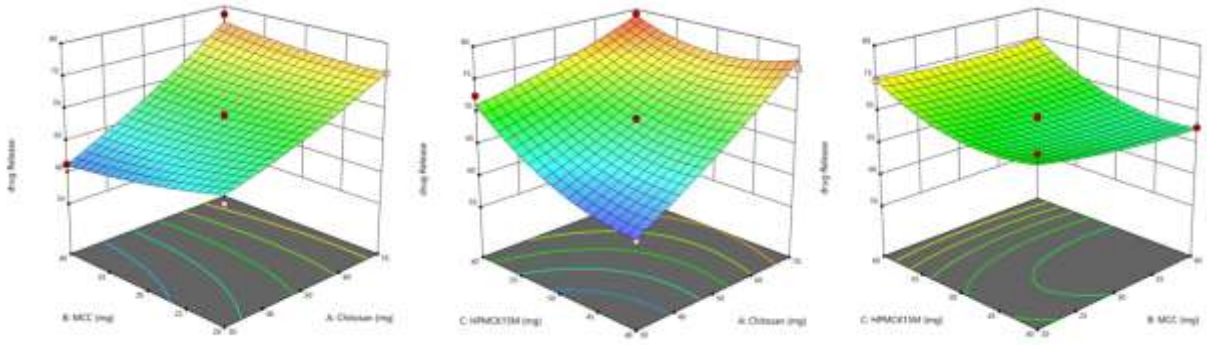

Figure 6: 3D surface plots showing the effect of independent variables on drug release

The findings show that the mucoadhesion time, percentage swelling index, and percentage drug release increase the concentration of chitosan, MCC, and HPMCK15M.

Characterization of mucoadhesive tablets

Pre-Compression Parameters

Powder evaluation:

The bulk density, tapped density, angle of repose, and Hausner's ratio were among the characteristics used to assess the powder of formulations F1–F15. Table 6 lists the specifics for each of these characteristics. It was notedthat the bulk density value falls between 0.359 and 0.517 gm/ml. The tapped density and Hausner ratio was found to be between 0.445 and 0.615 gm/ml, and1.09 and 1.34, respectively. All of the formulations exhibited good flow properties, as reflected by Hausner's ratio and angle of repose value.

Table 6: Pre-formulation characterization of formulations

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Angle of repose
F1	0.513	0.612	1.19	27.97
F2	0.509	0.598	1.17	26.36
F3	0.517	0.593	1.14	25.64
F4	0.415	0.519	1.25	31.85
F5	0.482	0.592	1.22	30.23
F6	0.511	0.599	1.17	26.34
F7	0.359	0.445	1.23	32.24
F8	0.502	0.615	1.22	31.13

F9	0.386	0.467	1.20	30.12
F10	0.498	0.597	1.19	28.98
F11	0.457	0.547	1.19	29.35
F12	0.515	0.613	1.19	29.77
F13	0.497	0.545	1.09	24.97
F14	0.380	0.512	1.34	35.97
F15	0.495	0.587	1.18	27.89

All the values were mean ± S.D. (n=3).

Post-Compression Parameters for mucoadhesive tablets

Morphological Properties

All of the tablets were round in shape with smooth texture and without any imperfections.

Average Weight

The average weight all tablet formulations are mentioned in **table 7.**

Swelling Study

Swelling studies of mucoadhesive tablets are very important in ensuring their performance and proper drug release. This study evaluates the degree of swelling of the tablet when in contact with a fluid, which is crucial for successful drug delivery. All the results are mentioned in **table 7.**

Table 7: *In-vitro* characterization of formulations

Formulation Code	Average Weight (mg)	Swelling Index	Hardness kg/cm^2	Mucoadhesion time (hrs)	Mucoadhesive Strength(gms)
F1	199.29±0.24	126.93±0.87	5.75±0.25	20.97	28.34±89
F2	201.13±0.15	163.56±0.24	5.12±0.27	23.98	41.78±0.56
F3	198.27±0.82	120.67±0.61	6.87±0.73	20.24	27.97±0.75
F4	202.94±0.26	170.65±0.72	6.34±0.82	25.56	44.87±0.18
F5	199.26±0.13	112.86±0.28	7.05±0.64	19.63	25.78±0.97
F6	200.92±0.59	160.76±0.24	5.98±0.41	22.94	40.34±0.34
F7	200.19±0.91	151.98±0.14	6.35±0.82	21.92	34.88±0.29
F8	**199.18±0.61**	**180.71±0.82**	**5.94±0.93**	**25.91**	**45.87±0.85**
F9	200.10±0.85	149.67±0.14	6.66±0.47	21.86	33.89±0.45
F10	201.27±0.57	130.78±0.83	5.35±0.18	20.81	30.56±0.92
F11	199.86±0.91	154.36±0.56	6.93±0.14	22.91	37.86±0.67
F12	201.28±0.23	159.54±0.73	7.65±0.03	24.75	40.56±0.84
F13	200.17±0.98	144.13±0.49	5.24±0.87	21.67	32.78±0.46
F14	202.96±0.17	144.54±0.39	6.25±0.45	22.86	32.67±0.96
F15	198.94±0.57	145.87±0.82	5.84±0.49	21.46	32.98±0.49

Thickness of Tablets

The thickness of all the formulation was found in the range when compared upon of 7 mm punches. Then the ranges could be 5to7mm **table 6.**

Hardness

Tablets were found to hardness in the range of 5.24-7.65 kg/cm^2. This hardness ensures adequate mechanical strength for handling and storage while also being soft enough to adhere to the mucosal surface. The results are mentioned in **Table 7.**

Mucoadhesion Time

The outcome shows that the mucoadhesion time increases in tandem with the concentration of chitosan and polymer. Every outcome is mentioned in **Table 7.**

Mucoadhesive Strength

Mucoadhesive strength in tablets refers to the force required to detach from the mucosal surface of the tablet, and it's influenced by factors like polymer concentration and type. The optimized mucoadhesive tablets exhibit good adhesion and sustained drug release, with strengths ranging from 45.87 g to 25.78 gm. All the results are mentioned in **table 7.**

In vitro percentage release of isoniazid and fluoxetine from mucoadhesive formulation

In vitro drug release of both drugs from optimized formulationis presented in **figure 7.**

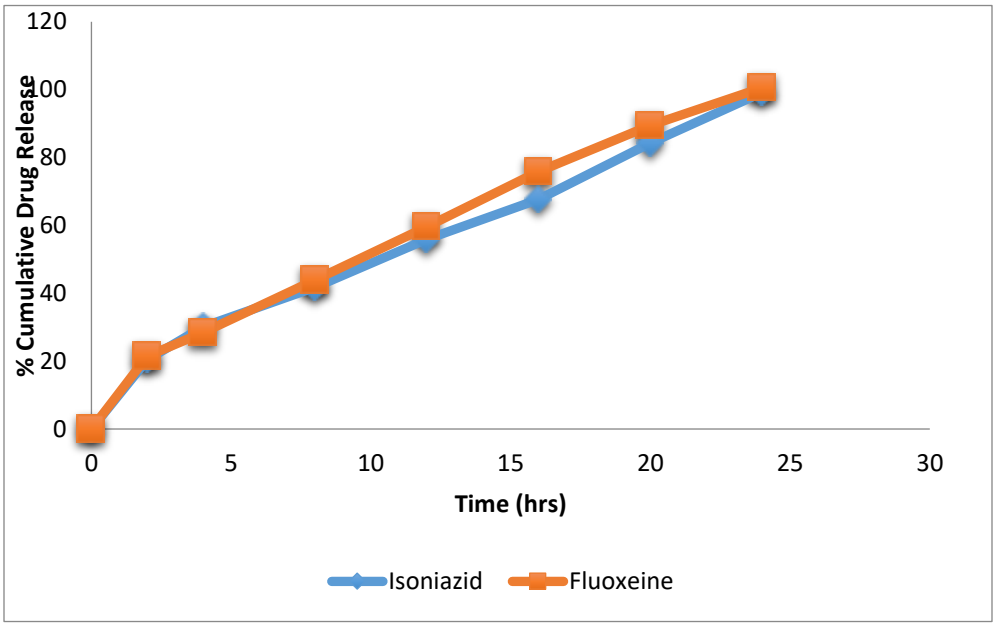

Figure 7: Graph showing percentage drug release of both drugs from optimized formulation (F8)

Stability studies

The stability studies carried out under specified storage conditions (25±°C/60±5 RH, 40±°C/ 75±5 RH) exhibited good stability of the formulation.

CONCLUSION

The present study focused on developing mucoadhesion tablets containing isoniazide and fluoxetine combinational drug delivery system for effective treatment of GITB. The combination of these two medications demonstrated encouraging outcomes, as isoniazid's MIC was significantly lowered, increasing its effectiveness against Mycobacterium tuberculosis. Following zero-order kinetics, the developed formulation (F8) showed a high swelling index, increased muco-adhesion strength, and controlled drug release over a 24-hour duration.

The formulation was found to be stable.

With increased efficacy, patient compliance, and decreased frequency the results imply that the developed muco-adhesive tablet containing isoniazid and fluoxetine could be a promising therapeutic delivery method for the successful treatment of gastrointestinal tuberculosis.

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