RESEARCH ARTICLE

Ibuprofen Release from Poly(L-Lactic Acid)/Cellulose Blend Tablets: Box-Behnken Design for Optimization of the Influenced Parameters

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ABSTRACT

According to the literature, blending PLA with cellulose, a natural polymer, can improve their use in the field of drug delivery systems. This work aimed to prepare a ternary mixture of ibuprofen, poly(L-lactic acid) (PLLA), and cellulose by the physical mixing method and to determine the effect of three selected factors (PLLA/cellulose blend ratio, percentage of the blend, and time of contact) on the amount of IBF released as a function of time. A Box-Behnken experimental design created using Minitab 17 software was used to study and optimize the selected factors. The percentage of IBF released significantly decreased with increasing PLLA/cellulose blend ratio (X_1) and percentage of blend (X_2). No significant interactions between the three factors were observed for Y_1 (30 minutes), Y_2 (60 minutes), and Y_3 (120 minutes). A significant interaction between the PLLA/cellulose ratio and the percentage of the blend was observed only for Y_4 (180 minutes). ANOVA revealed that the refined mathematical model equations for Y_1, Y_3, and Y_4 were more adequate than Y_2 to explain the investigated total variations.

Keywords: Poly(lactic acid), Ibuprofen, Polymeric drug delivery system, Experimental design, Tablet, Sustained release.

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INTRODUCTION

Polymer materials are commonly employed as carriers in drug delivery systems.[1] Among these materials, natural and synthetic biodegradable polymers have been widely studied. Poly(lactic acid) (PLA) is one of the most important synthetic biodegradable polymers for academic research and industrial applications. PLA, coming from renewable sources, is an aliphatic polyester synthesized using different polymerization routes, especially ring-opening polymerization and polycondensation.[2,3] PLA has several advantages, including biodegradability, bioresorbability, biocompatibility, compostability, recyclability, and improved processability. PLA is used in many fields, such as resorbable prosthetic devices for the repair and reconstruction of traumatic wounds, drug delivery systems, and tissue engineering.[4,5] Despite this, PLA has certain disadvantages that limit its use, such as low degradation in natural soil, fragility (or inherent brittleness), narrow temperature range of processing, and power toughness.[5,6]

One of the methods widely used to overcome the drawbacks of PLA is mixing it with other polymers (the formation of blends).[5,7] This method is a cost-effective and convenient approach for generating new polymeric materials that combine the benefits of various current polymers. Blending synthetic polymers with natural polymers leads to the formation of blends (called bioartificial or biosynthetic polymeric materials) that can be used in the biomedical field.[8]

Cellulose is among the biopolymers employed in bioartificial polymeric materials (blends). Cellulose, the most abundant biopolymer, is an interesting polymer due to its renewable nature, affordable cost, high availability, low density, nontoxicity, and strong mechanical characteristics.[9,10] As the main component of plant cell walls, cellulose is made up of β-(1,4)-linked D-glucose-repeating anhydroglucose units. The cellulosic chains contain two ends: the first at C4 is considered the non-reducing end, and the second at C1 is the reducing end. Each anhydroglucose unit contained three free hydroxyls at C2, C3, and C6. Hydrogen bonds between the free hydroxyl

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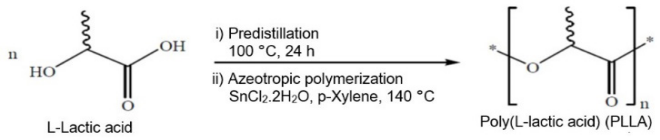

Figure 1: Reaction scheme of the azeotropic polymerization of L-lactic acid

groups connect, creating sheets. The sheets coming together create the microfibrils. The aggregates of microfibrils formed layers with different orientations in the cell walls. Due to its composition, is almost insoluble in water but has a strong affinity for molecules.[10]

Numerous studies published in the literature have studied the use of cellulose and its derivatives in combination with other polymers for various pharmaceutical purposes. For instance, Barakh Ali *et al*. found that core tablets with hydrophilic or hydrophobic drugs can be coated with a cellulose/enteric polymer blend for dual enteric release and delayed release properties.[11] Manna *et al.* developed matrix-type transdermal patches containing glibenclamide using a blend of Eudragit RS 100 and hydroxypropyl cellulose (HPMC). They concluded that these formulations would be preferable to orally administered glibenclamide.[12] In another study, Orasugh *et al*. prepared a cellulose/poloxamer 407 blend. The researchers studied how cellulose nanocrystals affect the gelation of poloxamer 407 and the release of pilocarpine hydrochloride from nanocomposite formulations. The properties, strength of the gel, and release of pilocarpine hydrochloride from the formulations were influenced by the cellulose nanocrystals.[13]

The primary goals of this research are: (i) preparing a ternary mixture of PLLA, cellulose, and IBF using a physical mixture; (ii) examining the impact of PLLA/cellulose blend ratio, percentage of the blend and time of contact on the percentage of IBF released using Box-Behnken design; (iii) identifying the best formulation (lowest percentage of IBF released) using Minitab 17 software; and (iv) conducting *in-vitro* drug release tests on pure IBF and the optimized formulation.

MATERIALS AND METHODS

Materials

PLLA was synthesized by our research team using azeotropic condensation of L-lactic acid in the presence of p-xylene as the solvent and stannous dichloride dihydrate ($SnCl_2.2H_2O$) as the catalyst (Figure 1). Cellulose was obtained from Biochem Chemopharma, and ibuprofen (IBF, 99.9%) was obtained from Hubei Granules-Biocause Pharmaceutical. Other chemical reagents, including sodium hydroxide (NaOH), hydrochloric acid (HCl), and potassium hydrogen phosphate (KH_2PO_4) were used as received.

Preparation of Ternary Mixtures using Box-Behnken Experimental Design

A PLLA/cellulose/IBF ternary mixture containing 100 mg of IBF was prepared by simple physical mixing. The first step consists of introducing the two polymers at different mass ratios (X_1, the first parameter) into a mortar. The mixture was ground with a pestle for 10 minutes. The process was followed by preparing a physical mixture of 100 mg of IBF with a given percentage of the PLLA/cellulose blend (X_2, the second parameter). The ternary mixture PLLA/cellulose/IBF was prepared during a time "time of contact" (X_3, the third parameter).

The ternary mixtures, obtained as homogeneous white powders, were compressed using a laboratory press under a force of 07 KN. Tablets 12 mm in diameter were obtained and kept in plastic bags until further use.

Optimization of the Independent Factors and Statistical Analysis

The effect of three factors, PLLA/cellulose blend ratio, percentage of the blend, and time of contact on the observed responses (the quantity of IBF released as a function of time) was investigated using Box-Behnken experimental design. Minitab 17 software (Minitab Inc., PA, USA) was used to optimize the selected factors and for the statistical analysis. The low (-1), high (+1), and central (0) levels of the three factors are given in Table 1. The low and high levels of the three factors were determined based on the preliminary experiments. According to the Box-Behnken experimental design, fifteen samples were prepared. The central experiment was conducted three times.

The percentages of IBF released at 30, 60, 120, and 180 minutes (Y_1, Y_2, Y_3, and Y_4, respectively) were determined for each sample.

Physicochemical Characterization

The following equation was used to find out the viscosity-average molecular weight (M_v) of the PLLA homopolymer: $[\eta] = 1.29 \times 10^{-4} M_v^{0.82}$.[14]

Solutions of PLLA in chloroform with different concentrations were prepared. For each solution, intrinsic viscosity ([η]) was determined using an Ubbelohde viscometer at 30°C.

The microstructure of the polymers and drug was confirmed by infrared spectroscopy (FTIR) analysis. FTIR spectra of the products were recorded between 400 to 4000 cm^{-1} using an Agilent Cary 630 FTIR spectrometer (USA).

Drug Release Tests

IBF release was carried out in a phosphate buffer of pH 6.8. A Tablet containing 100 mg of IBF was suspended in 90 mL of a buffer solution maintained at 37 ± 1°C and stirred at 50 rpm. At predetermined times (30, 60, 120, and 180 minutes), 5 mL of the dissolution medium was taken out. To maintain the initial volume of the dissolution medium, an equivalent volume of fresh medium replaced each sampling. The concentration of the released IBF was determined using a UV-visible spectrophotometer at 264 nm (Thermo Evolution 600 UV-Vis, UK).

To compare the two release profiles for a pair of drug

Table 1: Variable descriptions and variable levels studied in Box-Behnken experimental design

Parameters	*Coded units*	*Limits*		
		Low	*Central*	*High*
		-1	*0*	*+1*
PLLA/cellulose blend mass ratio	X_1	1	5.5	10
Percentage of the blend (%)	X_2	5	27.5	50
Time of contact (minutes)	X_3	2	16	30

products, an f_2 similarity factor was determined. Equation (1) was used to calculate the f_2 value:

$$f_2 = 50\ x \log\left\{\left[1 + \frac{1}{n}\sum_{i=0}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} x\ 10^2\right\} \quad (1)$$

n: number of samples taken at different times
R_t: amount of drug released at time point t for the reference
T_t: amount of drug released at time point t for the test
If $50 \leq f_2 \leq 100$, the release profiles are considered similar.[15]

RESULTS AND DISCUSSION

Effect of the Independent Variables on the Percentage of Drug Released

Table 2 presents the percentages of IBF released (Y_1, Y_2, Y_3, and Y_4) for each experiment. Figure 2 shows the mean effects of the three parameters on the responses considered. As can be seen, the main effect is present because different levels of the factors affect the responses differently. The percentage of IBF released significantly decreased with increasing PLLA/cellulose blend ratio (X_1) and percentage of blend (X_2). The influence of these two factors on the responses was significant ($p < 0.05$). The percentage of IBF released decreased in proportion to the time of contact (X_3). The effect of contact time on Y_1 was significant ($p = 0.0054$), but on Y_2, Y_3, and Y_4, it was not significant ($p = 0.3001$), ($p = 0.1499$), and ($p = 0.1673$), respectively.

The evaluation of the two-factor interactions was shown using interaction plots. The interaction plots of the PLLA/cellulose blend ratio, concentration of the blend, and time of contact on the percentage of IBF released at 30, 60, 120, and 180 minutes are illustrated in Figure 3.

As shown in Figure 3, there were no significant interactions among the three factors ($p > 0.05$). However, a significant interaction between the PLLA/cellulose blend ratio and percentage of the blend was observed ($p = 0.0323 < 0.05$) in the interaction plots of Y_4.

Box-Behnken Experimental Design Results

The algebraic representations of the regression line that describes the correlation between the resulting responses (Y_1, Y_2, Y_3, Y_4) and the three selected factors (X_1, X_2, X_3) were determined using Minitab 17 software with general optimization techniques. Four polynomial models (Equations (2), (3), (4), and (5)) were found and are given below:

$$Y_1 = 11.11 - 6.857X_1 - 10.313X_2 - 4.060X_3 + 7.15X_1^2 \quad (2)$$

$$Y_2 = 18.49 - 10.36X_1 - 16.14X_2 \quad (3)$$

$$Y_3 = 31.45 - 11.22X_1 - 28.31X_2 \quad (4)$$

$$Y_4 = 42.93 - 12.93X_1 - 28.77X_2 - 14.98X_1X_2 \quad (5)$$

The significance of the refined mathematical models was demonstrated using an ANOVA test at a 5% significance level. If the *p-value* (Prob > F) is below 0.05, a model is deemed

Table 2: Observed responses for each experiment

Trial no.	X_1	X_2 (%)	X_3 (min)	Y_1 (%)	Y_2 (%)	Y_3 (%)	Y_4 (%)
1	1.0	5.0	16	36.69	51.90	76.06	89.93
2	10.0	5.0	16	25.10	39.87	71.36	88.10
3	1.0	50.0	16	20.13	44.74	46.98	71.14
3	10.0	50.0	16	00.00	00.45	06.71	09.40
4	1.0	27.5	2	27.07	40.85	64.47	74.81
5	10.0	27.5	2	18.21	30.02	41.83	59.06
6	1.0	27.5	30	21.66	31.99	49.22	59.55
7	10.0	27.5	30	07.38	16.24	27.07	35.44
8	5.5	5.0	2	28.55	52.66	85.15	87.11
9	5.5	50.0	2	06.89	05.41	14.76	20.67
10	5.5	5.0	30	19.19	41.34	73.33	83.18
11	5.5	50.0	30	00.00	06.01	10.94	16.95
12	5.5	27.5	16	08.71	15.11	26.92	46.12
13	5.5	27.5	16	14.76	30.51	43.80	50.20
14	5.5	27.5	16	09.84	9.84	23.62	32.48
15	1.0	5.0	16	36.69	51.90	76.06	89.93

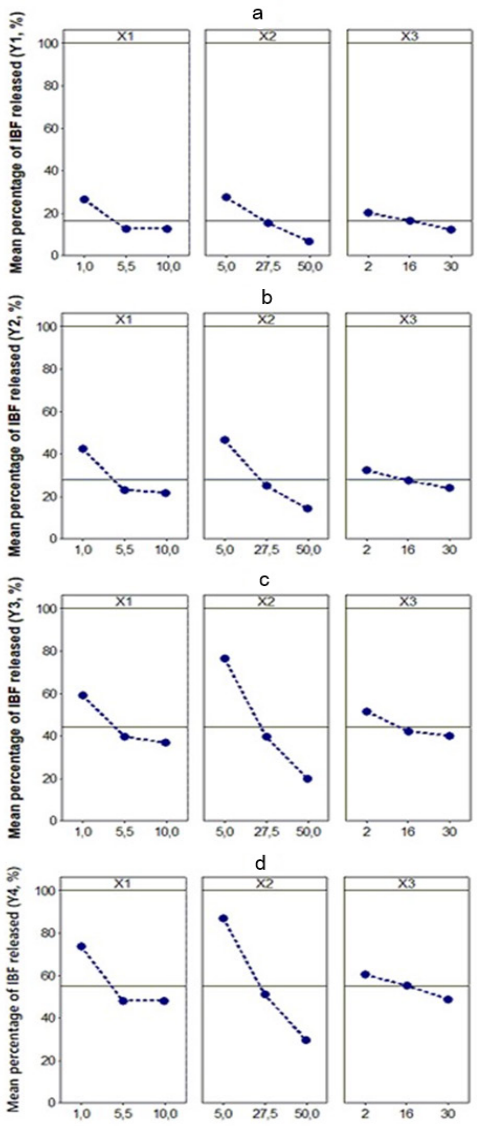

Figure 2: Mean effects of the three factors (X_1, X_2, and X_3) on the percentage of IBF released (a) at 30 minutes, (b) at 60 minutes, (c) at 120 minutes, and (d) at 180 minutes

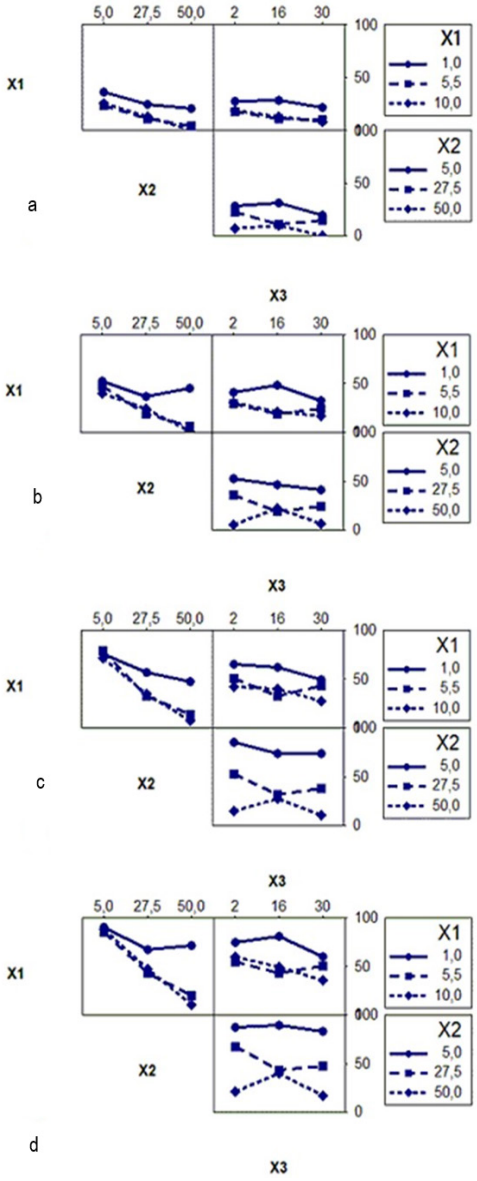

Figure 3: Interaction plots of the percentage of IBF released (a) at 30 minutes, (b) at 60 minutes, (c) at 120 minutes, and (d) at 180 minutes

significant. Table 3 displays the obtained ANOVA results. The most important statistics in the ANOVA table (*p-value*, SS, R^2, adjusted R^2 values) indicate whether the levels are significantly different from each other and how well the models fit the data. As shown in Table 3, there is a *p-value* for each model. The *p-values* of the models Y_1, Y_3, and Y_4 were lower than the chosen α level of 0.05. Consequently, the mathematical model is significant. Response Y_2 had a slightly higher *p-value* than 0.05, indicating that the model was not significant.

The predicted versus actual plots of the four refined models are shown in Figure 4. This Figure exhibits that all points are within the fitted line and have narrow confidence bands. However, a few points distant from the line (Figur 4B) represent possible outliers. These results were evident from the correlation coefficient (R^2) values. The R^2 values of the four responses are shown in Figure 4. High R^2 values were obtained for Y_1, Y_3, and Y_4 (98, 95, and 95%, respectively). Based on these findings, refined mathematical models Y_1, Y_3, and Y_4 can explain more than 95% of the variability in the experimental data. However, model Y_2 explains only 88% of the total variation. Therefore, the investigated total variations can be explained better by the mathematical model equations Y_1, Y_3, and Y_4. Kincl et al. have reported similar results in the literature.[16] These authors investigated the effects of three factors (rotation speed of the basket, pH, and ionic strength of the dissolution medium) on the release of diclofenac sodium (non-steroidal anti-inflammatory drug (AINS) from tablets. According to this study, with R^2 values greater than 95%, the modal polynomial function explains adequately the total variations. However, with an R^2 value of 86.2%, the model function explains inadequately the results.

Table 3: Obtained ANOVA results of the refined models

Response	*Source*	*DF*	*SS*	*MS*	*F-value*	*p-value Prob > F*
Y_1	Model	9	1585.59	176.176	29.34	0.001
	Error	5	30.02	6.005		
	Total	14	1615.61			
Y_2	Model	9	3835.06	426.12	4.09	0.068
	Error	5	521.20	104.24		
	Total	14	4356.26			
Y_3	Model	9	8671.10	963.46	10.69	0.009
	Error	5	450.74	90.15		
	Total	14	9121.83			
Y_4	Model	9	10009.9	1112.21	10.72	0.009
	Error	5	519.0	103.80		
	Total	14	10528.9			

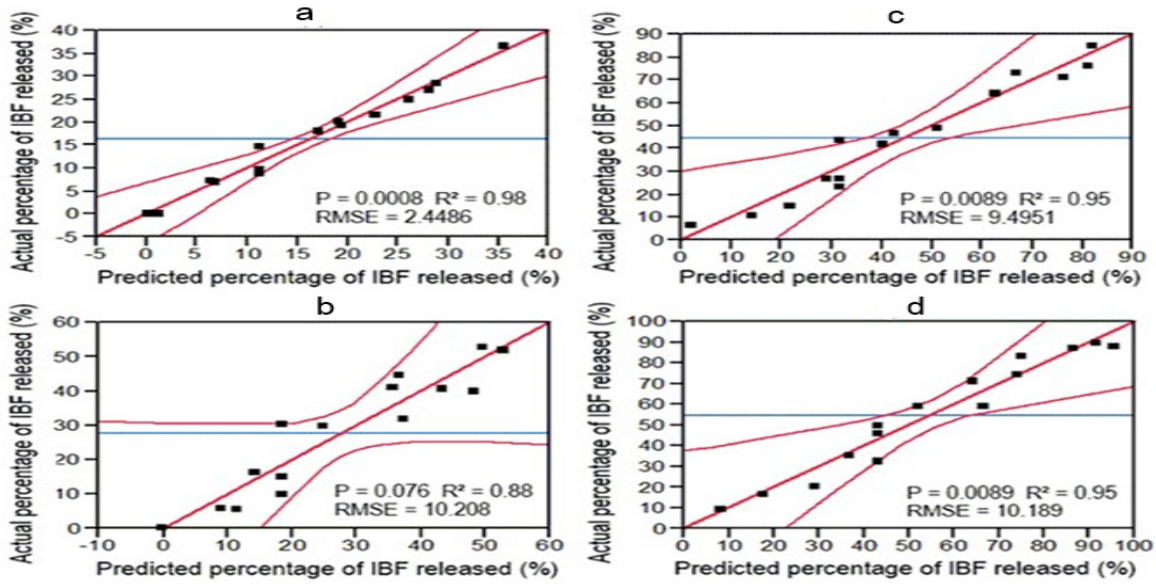

Figure 4: Predicted *vs*. actual values of the percentage of IBF released at 30 minutes (a), at 60 minutes (b), at 120 minutes (c), and at 180 minutes (d)

Optimization of the Experimental Parameters

The optimization of the experimental parameters is a crucial step in a study. Literature shows that a response surface methodology-based computer optimization technique has been proven to select pharmaceutical formulations.[17-21] In the present study, the statistical procedure was conducted using Minitab 17 software (Minitab Inc., PA, USA), and the results are shown in Figure 5. According to this Figure, the optimum parameters obtained with a composite desirability of 0.9730 are X_1 = 7.0, X_2 = 50.0%, and X_3 = 18.5 minutes.

Physicochemical Characterization

The obtained PLLA was first characterized by determining its viscosity-average molecular weight (MV) using an Ubbelohde viscometer. As a result, a PLLA homopolymer with a low molecular weight was obtained (MV = 9170 g.mo^{-1}). It was reported that PLA-based polymers with low molecular weights are widely used in drug delivery systems.[22]

The FTIR spectra of pure IBF, PLLA/cellulose blend and PLLA/cellulose/IBF (optimal formulation) are depicted in Figure 6. The FTIR spectrum of pure IBF shows C-H stretching vibrations at 2955.27 cm^{-1}, C=O acid group stretching vibrations at 1719.74 cm^{-1}, C-C cyclic stretching vibrations at 1507.60 cm^{-1}, and C-C-OH stretching vibrations at 1419.49 cm^{-1}.[23,24] The FTIR spectrum of the PLLA/cellulose blend contained peaks typical of both PLLA and cellulose homopolymers. The absorption band at 1751.06 cm^{-1} is ascribed to C=O stretching vibrations; the absorption band at 2997.3 cm^{-1} is ascribed to C-H stretching vibrations; the absorption bands located between 1300 to 1050 cm^{-1} are ascribed to C-O stretching vibrations; and the absorption band at 3659.05 cm^{-1} is attributed to O-H stretching

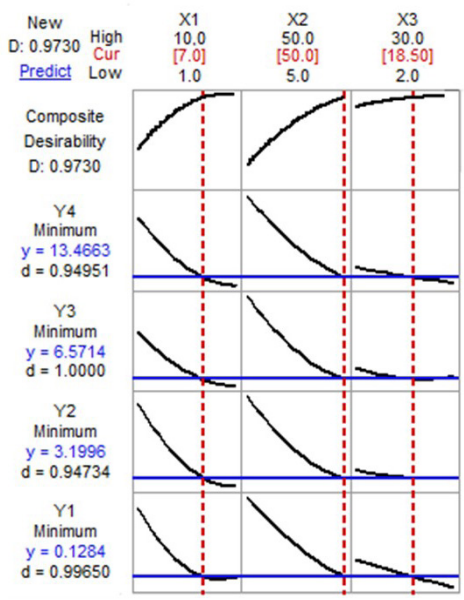

Figure 5: Graphical representation of the optimum parameters

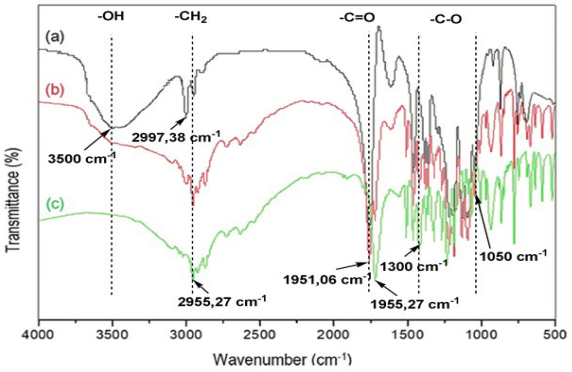

Figure 6: FTIR spectra of (a) blend PLLA/Cellulose, (b) PLLA/Cellulose/IBF, and (c) pure IBF

vibrations of PLLA.[25] The FTIR spectrum of cellulose shows C-H stretching vibrations at 2901.09 cm^{-1}, O-H stretching vibrations between 3000 to 3600 cm^{-1}, antisymmetric stretching vibrations of glycosidic bonds (C-O-C) at 1164.31 cm^{-1}, and C-O stretching vibrations of carbons C_2, C_3, and C_6 of cellulose between 900 to 1200 cm^{-1}.[13,26] The ternary mixture's FTIR spectrum combines peaks that are typical of PLLA, cellulose, and pure IBF. In fact, there was no change in the emergence or disappearance of peaks or peak intensity in the FTIR spectrum of the ternary mixture when compared to the spectra of the PLLA, cellulose, and IBF. According to the literature, this result indicates the absence of significant interactions between polymers and drugs.[27,28]

In-vitro Drug Release Study

Figure 7 shows the release curves of pure IBF, optimal predicted formulation, and optimal experimental formulation. The latter was obtained under optimal conditions and used to confirm the predicted optimal formulation. To compare the dissolution curve of IBF formulated with that of free IBF, the f_2 value was

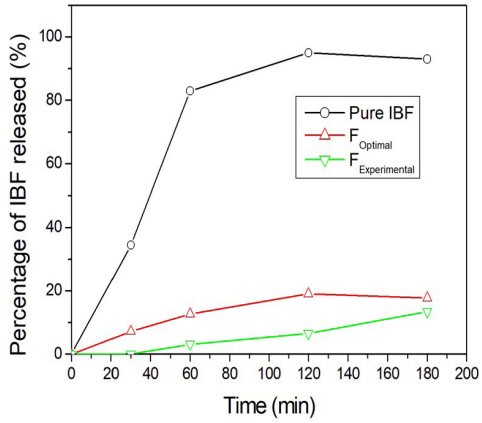

Figure 7: IBF release curves obtained at pH 6.8 following Box-Behnken experimental design: pure IBF, optimal formulation ($F_{Optimal}$), and optimal experiment ($F_{Experment}$)

Table 4: f_2 values of IBF dissolution profiles

Comparison	*f_2 value*
Free IBF *vs.* Optimal formulation	54.79
Free IBF *vs.* Optimal experiment	11.64
Optimal formulation *vs.* Optimal experiment	9.06

determined, and the results are given in Table 4. According to Figure 7, the release curve of the formulated IBF is different and slower than that of free IBF. For the IBF-loaded tablet, the percentage of the IBF released at 180 minutes was less than 20%. Whereas for the untreated IBF tablet, the total released percentage at the same period was more than 90%. This result is confirmed by the f_2 value, which is less than 50 (Table 4). In addition, the comparison between the predicted release curve and experimental release indicates that the two curves are similar ($f_2 > 50$). It can be concluded that there is a good adequacy between the predicted release profile and the observed one.

CONCLUSION

Poly(L-lactic acid), synthesized in our laboratory by an azeotropic condensation route, was used with cellulose as a carrier in tablets containing IBF as a model drug. The ternary mixture was prepared using a physical method. The effect of three selected independent factors (PLLA/cellulose blend mass ratio (X_1), percentage of the blend (X_2), and time of contact (X_3)) on the amount of IBF released at 30, 60, 120, and 180 minutes was investigated using a Box-Behnken experimental design. The mean effect plots revealed that the percentage of IBF released significantly decreased with increasing X_1 and X_2. However, there were no significant interactions between the three factors except between the PLLA/cellulose blend ratio and percentage of the blend, where the interaction was significant only for Y_4 (180 minutes). According to the ANOVA test, the refined mathematical model equations for Y_1, Y_3, and Y_4 are more adequate than Y_2 to explain the investigated total variations. The predicted release profile of the IBF-form tablets is similar to the observed one, indicating good adequacy between them.

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