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ORIGINAL ARTICLE

Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology

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Abstract

Background: This research work was done to design oral sustained release matrix tablets of water-insoluble drug, flurbiprofen, using natural gums as the matrix polymers and to evaluate the drug release characteristics using response surface methodology. The central composite design for two factors at five levels each was employed to systematically optimize drug release profile. *Method*: Matrix tablets were prepared by direct compression technique. Xanthan and acacia gums were taken as the independent variables. Fourier transform infrared spectroscopy studies were also performed to find out the stability of drug during the direct compression and to check the interactions between polymers and drug. Percent drug release in 2 hours and percent drug release in 8 hours were taken as response variables (*Y*1 and *Y*2, respectively). *Results*: Both the polymers were found to have significant effect on the drug release. Polynomial mathematical models, generated for the response variables using multiple linear regression analysis, were found to be statistically significant ($P < 0.05$). Contour plots were drawn to depict the relationship between response variables and independent variables. *Conclusion*: The formulated matrix tablets followed zero-order kinetics with negligible drug release in 0.1 N HCl at pH 1.2, which was the objective of this study to produce a formulation avoiding the gastric effects of flurbiprofen.

Key words: *Central composite design; contour plot; direct compression; response surface methodology; sustained release*

Introduction

For the success of sustained release tablet dosage form, it is crucial to devise an optimized formulation possessing an apt dissolution rate. Numerous statistical designs have been acknowledged as useful practices to optimize the process variables. Response surface methodology (RSM) is one of the rapid techniques used to empirically develop a handy affiliation between an investigational response and a set of contributing variables.

RSM is a collection of mathematical and statistical techniques useful for the modeling and analysis of problems in which a response of interest is influenced by several variables and the objective is to optimize this response[1]. It reduces the number of experimental runs necessary to establish a mathematical trend in the experimental design allowing for the determination of the optimum level of experimental factors required for a given response. Reducing the number of experiments by optimizing a formulation during development of a drug delivery device may also lead to significant reductions in production costs. It is necessary to have a clear understanding of how preparation conditions and inherent characteristics of excipients employed in

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pharmaceutical formulations are influenced by potential interactions between various factors to optimize a formulation[2].

The convenience and easiness to manufacture, resulting in low price of the dosage form, has contributed much to the popularity of hydrophilic matrix systems as a sustained release drug delivery system. The release of drugs from hydrophilic matrix systems is controlled by one or more mechanisms that may be transport of solvent into the device, swelling of the matrix, diffusion of the solute through the swollen matrix, erosion of the swollen matrix, and so on[3].

Xanthan gum as a matrix former has been evaluated for the preparation of sustained release tablets[3–8]. Xanthan gum is very effective in prolonging the release of soluble and sparingly soluble drugs. The release of soluble drugs was mainly via diffusion, whereas sparingly soluble or insoluble drugs were released principally via erosion[9].

Gum acacia is used in the preparation of pastilles and lozenges and as a binder in the tablets[10]. Its use as a sustained release carrier has also been investigated[11–14]. Matrix tablets formulated by gum acacia show fast drug release that is because of the short chains of gum acacia that are rapidly hydrated[11], but at higher concentrations of gum acacia in a matrix formulation, it shows improved drug retarding capability because of its gelling property[12].

Flurbiprofen is a potent anti-inflammatory, analgesic, and antipyretic agent belonging to the family of propionates but has not been used as extensively as many of the newer ones, possibly because it requires round-the-clock administration due to its shorter half-life (2–6 hours) and has harmful gastric side effects[15]. Thus, a sustained release preparation of flurbiprofen, maintaining plasma concentrations adequately over a 24-hour period and evading its gastric adverse effects, will heighten its area of application.

Hence, the aim of this work was to develop and evaluate the release rate characteristics of a sustained release tablet formulation of flurbiprofen with least gastric contact of drug using natural gums: xanthan gum and gum acacia for the first time in combination as matrix polymers and using RSM for optimizing release profiles of the formulations.

Materials and methods

Materials

Flurbiprofen was a free gift from Shrooq Pharmaceuticals (Pvt.) Ltd. (Lahore, Pakistan). Gum acacia was purchased from Fluka Chemie AG (Buchs, Switzerland). Xanthan gum was also a free gift from Hamaz Pharmaceuticals (Pvt.) Ltd. (Multan, Pakistan). All other chemicals, that is, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, magnesium stearate, microcrystalline cellulose (Avicel PH 101), and so on were of analytical grade and were purchased from E. Merck Co. (Darmstadt, Germany).

Preparation of sustained release matrix tablets

Tablets were formulated according to Table 1. Direct compression method was employed for formulations. All the components except lubricant (1% magnesium stearate) were added in plastic bags and shaken for 15 minutes followed by the addition of lubricants and further mixed for 5 minutes. The blend was then compressed using triple punch tablet machine (Type: EK 0; ERWEKA, APPARATEBAU GmbH, Heusenstamm, Germany) to a weight of 60 mg.

Experimental design

A central composite design (CCD) with $\alpha = 2$ was employed as per the standard protocol[16]. The amount of xanthan gum and gum acacia was selected as the factors, studied at five levels each. The central point (0,0) was studied in quintuplicate. All other formulation and process variables were kept invariant throughout the study. Table 2 summarizes the 13 experimental runs studied and their factor combinations. Table 2 also states the translation of the coded levels to the experimental units employed during the study. Percent of drug released in 2 hours and percent of drug released in 8 hours were taken as response variables Y_1 and Y_2, respectively.

Evaluation of tablets

Physical evaluations of tablets

Tablets were evaluated for weight variation ($n = 20$), thickness ($n = 10$), hardness ($n = 10$), and friability ($n = 10$).

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of flurbiprofen and the matrix tablets were obtained using FTIR Spectrophotometer [Model: 8400 S; Shimadzu Scientific Instruments (SSI), Kyoto, Japan] to investigate any interaction between the polymers and the drug in the formulated matrix tablets. The pellets for FTIR spectrophotometry were prepared by triturating

Table 1. Composition of sustained release matrix tablets of flurbiprofen.

Ingredients	Amount (mg)
Flurbiprofen	6
Xanthan gum	3–15
Gum acacia	3–15
Magnesium stearate	0.6
Avicel	qs to 60

Table 2. Factor combinations as per chosen experimental design and translation of coded levels in actual units.

	Coded factor levels	
Trial no.	X_1	X_2
I	–2	0
II	–1	–1
III	–1	1
IV	0	–2
V	0	0
VI	0	2
VII	1	–1
VIII	1	1
IX	2	0
X	0	0
XI	0	0
XII	0	0
XIII	0	0

Coded level	–2	–1	0	1	2
X_1: xanthan gum (mg)	3	6	9	12	15
X_2: gum acacia (mg)	3	6	9	12	15

2 mg of sample with 200 mg of IR grade KBr and then compressing the mixture at a suitable pressure to make the fine disks for spectroscopic studies. The spectra were scanned over the wave number range from 4000 to 400 cm^{-1}.

Drug release study

Drug release from six tablets of each formulation, in triplicate, was determined using the USP apparatus II (paddle method), where 500 mL of 0.1 N HCl and phosphate buffer (pH 6.8) were used as dissolution media maintained at 37°C (±5°C) at 100 rpm. The release rates from the tablets were conducted in a dissolution media of 0.1 N HCl for 2 hours and thereafter in phosphate buffer of pH 6.8 for 6 hours[16]. Aliquots of 5 mL were withdrawn at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours with replacement of 5 mL of the fresh media. All the samples were analyzed directly at 247 nm using an UV-vis 2020 spectrophotometer (Model: U2020; IRMECO, GmbH, Geesthacht, Germany). Drug release profiles were drawn using MS-Excel software.

Drug release kinetics

Drug release kinetics is assumed to reflect different release mechanisms of controlled release matrix systems. Therefore, five kinetic models were applied to analyze the drug release data to find the best fitting equation[17]. These models are zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas given from Equations 1 to 5.

$$Q_t = k_0\, t \tag{1}$$

$$\log Q_t = \log Q_0 - k_1\, t \tag{2}$$

$$Q_t = k_{\mathrm{H}}\, t^{1/2} \tag{3}$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{\mathrm{HC}}\, t \tag{4}$$

$$\frac{M_t}{M_0} = k_{\mathrm{KP}}\, t^n, \tag{5}$$

where Q_t is the amount of drug released at time t; Q_0 is the initial amount of the drug in the formulation, k_0, k_1, k_{H}, k_{HC}, and k_{KP} are the release rate constants for zero-order, first-order, Higuchi model, Hixson–Crowell model, and Korsmeyer–Peppas models, respectively. In Equation 5, M_t and M_∞ are the amount of drug released at time t and ∞ while n is the diffusional coefficient.

Optimization data analysis

Various RSM computations for the current optimization study were performed using Design Expert® software (Design Expert trial version 7.0.1; State-Ease Inc., Minneapolis, MN, USA). Polynomial models including the interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented in the Equation 6.

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2, \tag{6}$$

where β_0 is the intercept representing the arithmetic average of all the quantitative outcomes of 13 runs. β_1, β_2, β_{12}, β_{11}, and β_{22} are the coefficients computed from the observed experimental response values of Y and X_1 and X_2 are the coded levels of the independent variables. The term X_1X_2 represents the interaction term and X_1^2 and X_2^2 are the quadratic terms.

Statistical validity of the polynomials was established on the basis of analysis of variance provision in the Design Expert software. Two-dimensional contour plots were constructed based on the model polynomial functions using Design Expert software. These plots are very useful to see interaction effects of the factors on responses[16].

Results and discussion

Physical evaluation of tablets

The results for physical evaluation of tablets showed that all batches of tablets were within the limits of USP. The average tablet weight varied between 59.50 and 60.90 mg. Hardness varied from 53.50 to 71.85 N.

Thickness varied from 2.28 to 2.58 mm. Friability varied between 0.45% and 0.84%.

FTIR spectroscopy

The FTIR spectra (Figure 1) showed no significant differences between pure flurbiprofen and the sustained release tablets of the flurbiprofen. The main peak remained unchanged and only some peak ratios differed slightly. FTIR spectra of flurbiprofen and sustained release tablets of flurbiprofen showed characteristic broad peak of flurbiprofen in the range of 3500 to 2500 cm^{-1} because of hydrogen bonding. The characteristic peaks of flurbiprofen at 1698 and 2920 cm^{-1} were because of carbonyl and hydroxyl stretching, respectively. FTIR studies are in good agreement with the literature[18], suggesting the drug stability during the direct compression technique.

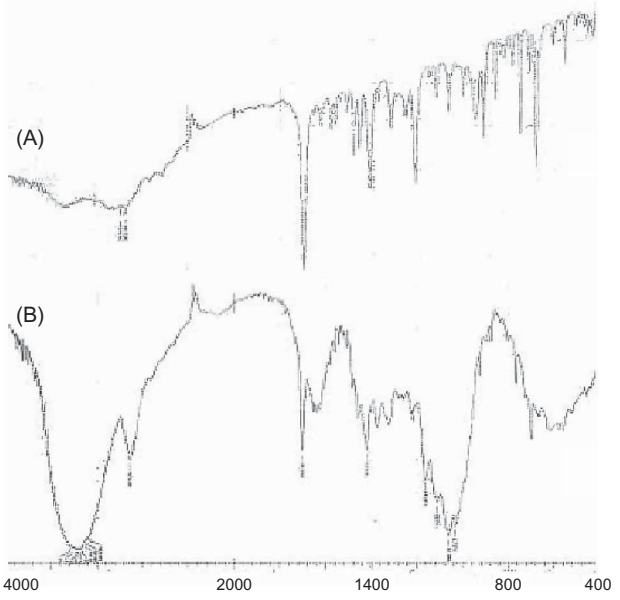

Figure 1. FTIR spectra of flurbiprofen (A) and sustained release matrix tablet of flurbiprofen (B).

Drug release studies

In Figure 2, drug release profiles of formulations prepared according to the experimental design are showed. It is clear from Figure 2 that all the formulations showed almost negligible release at pH 1.2 in first 2 hours varying from 2.87% to 6.47%, and as the medium of dissolution was changed to phosphate-buffered solution of pH 6.8, the drug release was increased considerably and showed a steady release pattern. The negligible drug release in first 2 hours may be attributed to the low solubility of drug at gastric pH. The low solubility of drug hinders the penetrating dissolution media to seep the drug out from the tablet matrices, resulting in the release displayed in Figure 2. This result was desired for the flurbiprofen matrices to avoid its gastric adverse effects that result usually because of its contact with gastric mucosa in case of conventional oral drug delivery.

The maximum drug release till 8 hours of dissolution varied from 72.13% to 93.12%, revealing the sustained release profile of drug in phosphate-buffered solution of

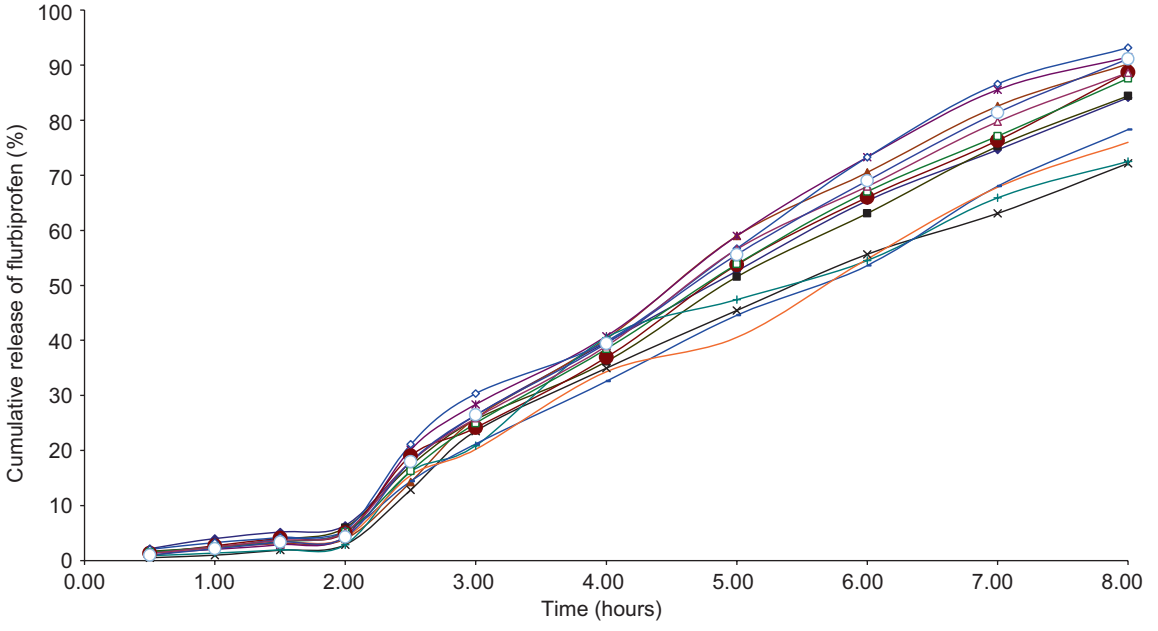

Figure 2. Release profiles of different formulations of sustained release matrix tablets of flurbiprofen (—●—, I; —■—, II; —▲—, III; —✱—, IV; —✱—, V; —●—, VI; —+—, VII; _ _, VIII; ____, IX; —◇—, X; —□—, XI; —△—, XII; and —○—, XIII) prepared as per the experimental design.

pH 6.8. Increasing the concentration of xanthan gum decreased the release rate, but the effect of gum acacia was observed to be opposite; this may be because of high solubility of gum acacia causing drug to be released at increased rate[11].

Figures 3 and 4 present the effect of both xanthan gum and acacia on in vitro release of drug. Figure 3 shows that increasing the percentage of xanthan gum from 5% to 15% and fixing the percentage of gum acacia (formulations I, V, and IX) give an effective prolonged release of drug. The increased drug release or negligible effect on drug release when the concentration of xanthan gum is increased to 15% cannot be attributed to the property of the xanthan gum as the presence of gum

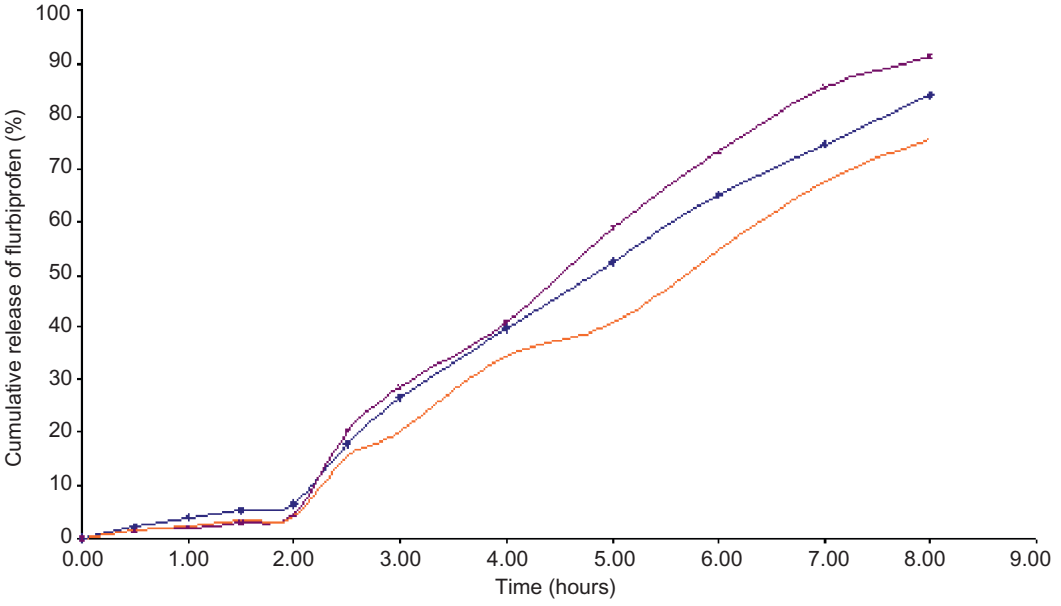

Figure 3. Release profiles of three formulations of sustained release matrix tablets of flurbiprofen (—●—, I; —*—, V; and —— IX) using fixed percentage of gum acacia and various percentages of xanthan gum.

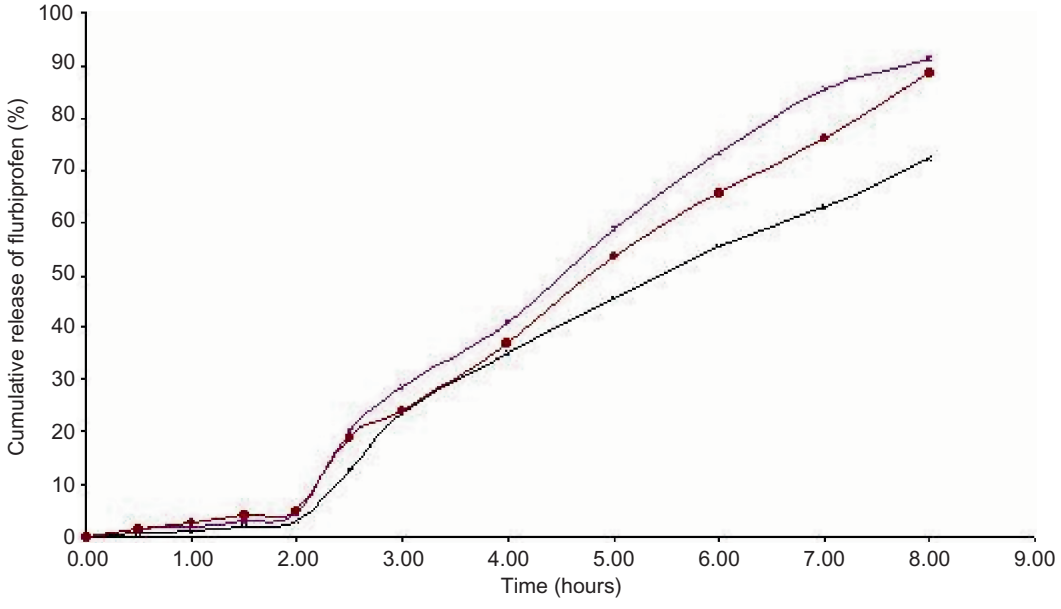

Figure 4. Release profiles of three formulations of sustained release matrix tablets of flurbiprofen (—×—, IV; —*—, V; and —●—, VI) using fixed percentage of xanthan gum and various percentages of gum acacia.

acacia is not easy to be neglected. This phenomenon has never been shown before. So, it is hypothesized that the presence of gum acacia is a hindrance to the release retarding capability of xanthan gum, unless the concentration of xanthan gum exceeds that of gum acacia in the formulation. Xanthan gum retards the release of drug by swelling that is achieved by hydration of its chains. The concentration of gum acacia is greater (formulation I) or equal (formulation V) to the concentration of xanthan gum and prevents the suitable hydration of the xanthan gum that is necessary to decrease the release of drug. But, in formulation IX, xanthan gum is greater than the gum acacia and is reasonably hydrated to sustain the release of drug, and these results are in good agreement with previous findings[3–8]. It can therefore be deducted from Figure 3 that when the concentration of xanthan gum exceeds 15% in the formulation, an effective sustained release formulation is formed.

Figure 4 shows the formulations (IV, V, and VI) in which the percentage of the xanthan gum is constant but the concentration of gum acacia varies. The drug release from formulations IV and V increase as the concentration of the gum acacia is increased while maintaining the same level of xanthan gum. This behavior of gum acacia has been previously reported[11,13,14]. But, it has also been reported[12] that at greater concentration, gum acacia decreases the release of drug from the matrices and the same phenomenon is exhibited by the formulation VI as shown in Figure 4.

The release kinetics of the matrices is shown in Table 3. The best fit model representing the mechanism of drug release from the matrices was of zero order. This is further confirmed by Korsmeyer–Peppas model, the value of n is greater than 1 showing case II drug release or anomalous drug release, indicating that two or more mechanisms for drug release are involved, that is, diffusion, erosion, and chain relaxation. These results comply with the previous findings[3–8].

From literature[19], it is evident that the initial drug release from matrices containing xanthan gum is because of erosion, but after sometime, the matrices begin to swell causing water uptake leading to formation of fronts and decreased erosion that leads to decreased release rate. But, in this study, use of gum acacia helped in maintaining a balance between matrix swelling and erosion as gum acacia is highly soluble and is greatly susceptible to disintegration as demonstrated by Siahi et al.[11] This helped in maintaining the zero order release throughout the experiment showing time-independent release profile, which can be clearly depicted from Figure 2. Intelligent combination of both gums can lead to control of drug release producing greater therapeutic effects with minimum side effects. This also provides a tool for tailoring the drug release for the desired purposes and given conditions.

RSM optimization results

A two-factor CCD with couple of responses and value of $\alpha = 2$ involves 13 experimental runs. The independent factors along with their responses for 13 experimental runs are shown in Table 4, where X_1 (xanthan gum) and X_2 (gum acacia) are the independent variables and Y_1 (cumulative release of flurbiprofen in 2 hours) and Y_2 (cumulative release of flurbiprofen in 8 hours) are the response variables.

Mathematical modeling

Mathematical relationships in the form of polynomial equations are generated using MLRA for the studied response variables as expressed in Equations 7 and 8. The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the

Table 3. Release kinetics of flurbiprofen from sustained release matrix tablets.

	Zero-order kinetics	First-order kinetics	Higuchi kinetics	Hixson–Crowell kinetics	Korsmeyer–Peppas kinetics
Formulations	R^2	R^2	R^2	R^2	n
I	0.9796	0.8728	0.8496	0.9	1.17
II	0.9789	0.8781	0.8402	0.9129	1.09
III	0.9687	0.8727	0.8259	0.9217	1.25
IV	0.9706	0.8419	0.8356	0.909	1.20
V	0.9719	0.8636	0.8355	0.9092	1.17
VI	0.9773	0.8748	0.8356	0.916	1.14
VII	0.966	0.8485	0.8382	0.8984	1.14
VIII	0.9777	0.8913	0.8304	0.9221	1.15
IX	0.9653	0.8837	0.8188	0.9141	1.14
X	0.975	0.8682	0.8392	0.9041	1.13
XI	0.9755	0.8818	0.8339	0.9182	1.21
XII	0.9756	0.874	0.8372	0.9146	1.18
XIII	0.9729	0.8664	0.8334	0.9159	1.17

Table 4. Drug release parameters of various trial formulations prepared as per the experimental design.

Trial no.	X_1 (mg)	X_2 (mg)	Y_1 (%)	Y_2 (%)
I	3	9	6.40	84.08
II	6	6	5.98	84.43
III	6	12	3.95	90.21
IV	9	3	2.87	72.13
V	9	9	4.44	91.47
VI	9	15	5.06	88.68
VII	12	6	2.91	72.47
VIII	12	12	5.32	78.30
IX	15	9	4.18	75.96
X	9	9	5.48	93.12
XI	9	9	5.21	87.57
XII	9	9	5.17	88.64
XIII	9	9	4.29	91.13

main effects show the relative influence of each factor on the response.

$$y_1 = 4.85 - 0.51X_1 + 0.40X_2 + 1.11X_1X_2 + 0.091X_1^2 - 0.24X_2^2 \quad (7)$$

$$y_2 = 89.3 - 3.34X_1 + 3.73X_2 + 0.013X_1X_2 - 2.66X_1^2 - 2.56X_2^2. \quad (8)$$

Statistical validation of the polynomial equations generated by Design Expert and estimation of significance of the models was established on the basis of analysis of variance provision of the software as shown in Tables 5 and 6 for Y_1 and Y_2, respectively. Using 5% significance level, a model is considered significant if the *P*-value (significance probability value) is less than 0.05[16]. In Table 5, *P*-values for response Y_1 represent that the linear contributions (X_1 and X_2) and the cross-product contribution (X_1X_2) are significant. But the quadratic contributions (X_1^2 and X_2^2) are nonsignificant, represented in Table 5 by NS. The values obtained for main effects of both the independent variables from

Table 5. Analysis of variance for response Y_1.

Source	Sum of Squares	df	Mean Square	*F*-value	*P*-value	Significance
Model	11.910	5	2.382	8.950	0.006	S
X_1	3.140	1	3.142	11.810	0.011	S
X_2	1.890	1	1.888	7.100	0.032	S
X_1X_2	4.930	1	4.928	18.520	0.004	S
X_1^2	0.190	1	0.190	0.710	0.426	NS
X_2^2	1.320	1	1.322	4.970	0.061	NS
Residual	1.860	7	0.266	—	—	—
Lack of fit	0.740	3	0.245	0.870	0.527	NS
Pure error	1.130	4	0.282	—	—	—

Table 6. Analysis of variance for response Y_2.

Source	Sum of squares	df	Mean square	*F*-value	*P*-value	Significance
Model	544.2032	5	108.8406	7.0179	0.0118	S
X_1	134.0677	1	134.0677	8.6445	0.0217	S
X_2	166.5820	1	166.5820	10.7410	0.0135	S
X_1X_2	0.0006	1	0.0006	0.00004	0.9951	NS
X_1^2	162.0722	1	162.0722	10.4502	0.0144	S
X_2^2	150.5535	1	150.5535	9.7075	0.0169	S
Residual	108.5633	7	15.5090	—	—	—
Lack of fit	88.3816	3	29.4605	5.8391	0.0606	NS
Pure error	20.1817	4	5.0454	—	—	—

Equation 7 indicate that xanthan gum has greater but negative effect on the response Y_1, confirming the release rate retarding ability of xanthan gum. On the other hand, the gum acacia has a comparatively weaker but positive influence on the response Y_1, showing the rapidly dissolving feature of the gum acacia facilitating the drug release through the tablet matrices.

In Table 6, *P*-values for response Y_2 represent that the linear contributions (X_1 and X_2) and the quadratic contributions (X_1^2 and X_2^2) are significant, represented in Table 6 as S. But the cross-product contributions (X_1X_2) are nonsignificant, represented in Table 6 by NS. According to Equation 8 as the dissolution process proceeds, the erosion phenomenon is increased due to the gum acacia so compensating the swelling behavior that leads to decreased release, thus maintaining the zero-order release rate throughout the dissolution process.

Response surface analysis

Two-dimensional contour plots for the responses Y_1 and Y_2 are shown in Figures 5 and 6, respectively. Figure 5 reflects that the response Y_1 varies in a nonlinear way, showing greater impact of xanthan gum on the release of flurbiprofen in 2 hours. In case of Y_2, the contour plot (Figure 6) shows that increase in gum acacia increases the release of flurbiprofen in 8 hours as compared to xanthan gum's retarding ability, but as the concentration of xanthan gum increases from 9 mg to onwards, there is an effective sustained release of flurbiprofen. These findings are in good agreement with the reported studies[3–8] in which increase in xanthan gum leads to decreased release of drugs to a greater extent. But, gum acacia in the matrix tablet maintains a balance between swelling and erosion in such a way that a prolonged and sustained drug release pattern is achieved.

Conclusion

Natural gum-based matrix tablets of flurbiprofen were prepared and their release profiles were optimized

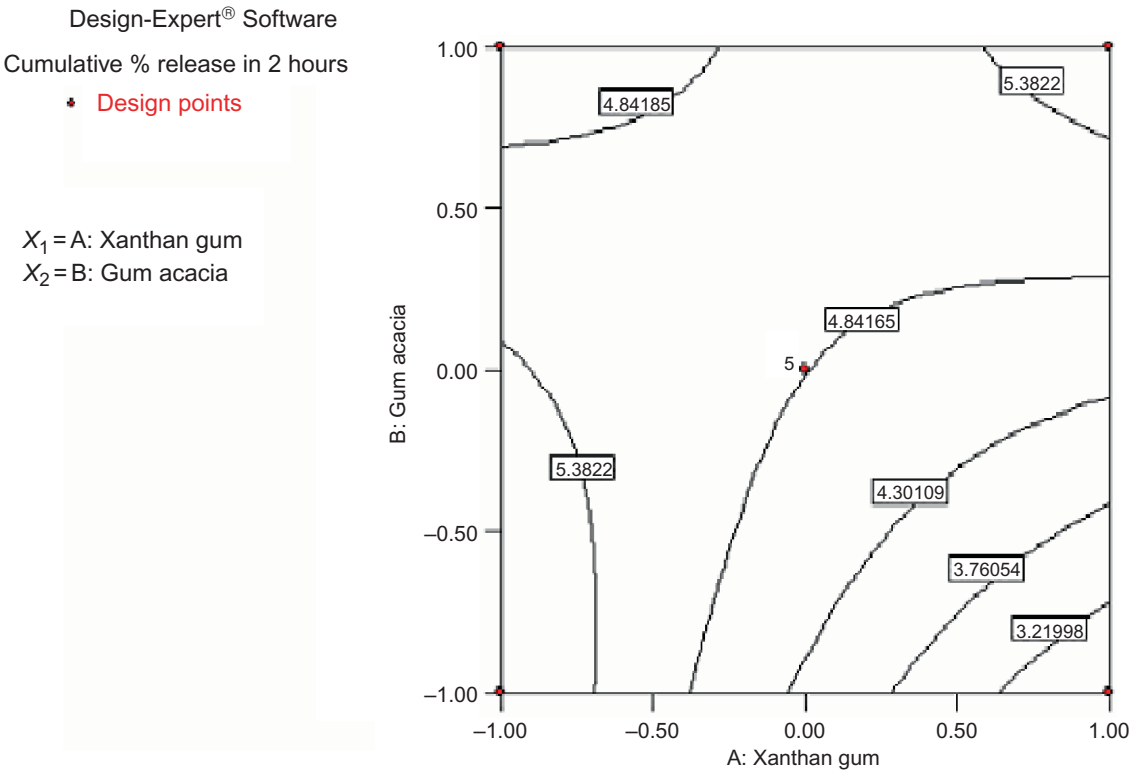

Figure 5. Contour plot showing the relationship between various levels of xanthan gum and gum acacia on cumulative % release of flurbiprofen in 2 hours.

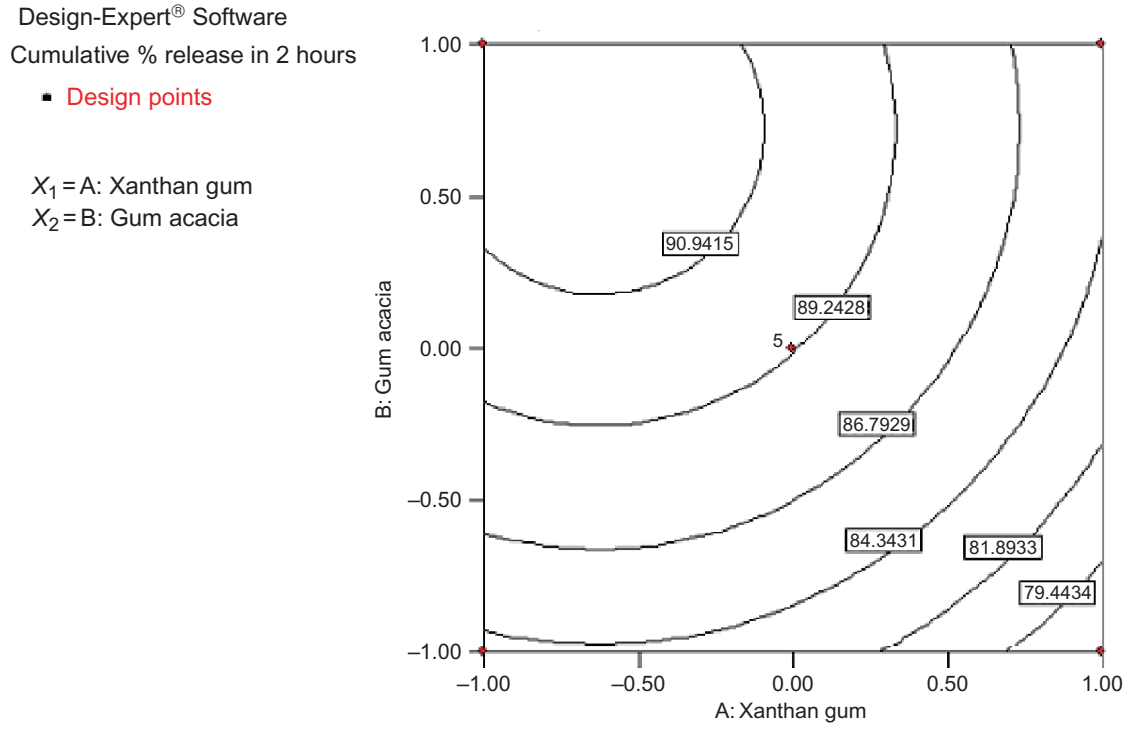

Figure 6. Contour plot showing the relationship between various levels of xanthan gum and gum acacia on cumulative % release of flurbiprofen in 8 hours.

using a CCD. The quantitative effect of variable factors at different levels on the release rate could be predicted by using polynomial equations. The quadratic RSM studied for the release rate helped in understanding the interaction effects between the combination and the ratio of the natural gums. Thus, RSM is quite efficient in optimizing drug delivery systems that exhibit nonlinearity in responses. Both the gums were found to significantly affect the drug release from the matrix tablets. However, appropriate balancing between various levels of both the gums may contribute better results. Sustained drug release following zero-order kinetics attained in this work indicates that matrix tablets of flurbiprofen can be successfully used as sustained release oral drug delivery system, with a benefit of avoiding the harmful gastric effects of flurbiprofen. FTIR studies suggest the absence of any significant interaction between the polymers and the drug in the formulation.

Declaration of interest: The authors report no conflicts of interest.

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