Original Article

Matrix Tablet Containing Quaternary Inclusion Complex of Domperidone for Treatment of Diabetic Gastroparesis

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ABSTRACT

Objective: The present investigation is aimed at development and optimization of a pH independent controlled release matrix tablet containing mannitol based quaternary inclusion complex (QIC) of domperidone (DOM) for the treatment of diabetic gastroparesis. **Methods:** The tablets were prepared by direct compression and central composite design was used to optimize the amount of sodium alginate (SA) and hydroxypropylmethylcellulose (HPMC) to obtain a final formulation with desired release characteristics. The drug release from the optimized formulation was compared with the tablets containing pure DOM, binary and ternary inclusion complexes. **Results and Discussion:** The formulations showed a zero order release profile. The design models suggested greater influence of SA on the drug release. The optimized formulation showed minimum burst effect and released 88.65 ± 3.19% DOM at the end of 12 h. The comparative study revealed that the optimized formulation exhibited nearly complete release of DOM. **Conclusion:** It was concluded that the optimized formulation containing QIC may reduce the dose frequency and improve the bioavailability of DOM.

Key words: Quaternary inclusion complex, pH independent controlled release, Domperidone, Central composite design, Diabetic gastroparesis.

INTRODUCTION

Diabetic gastroparesis is the common complication of diabetes which is associated with delayed gastric emptying. The symptoms of gastroparesis include abdominal pain, anorexia, bloating and vomiting which may create problems with the glycemic control.[1] There are very few effective treatments for this syndrome. Metoclopramide is a prokinetic agent which has been approved for the treatment of this disorder. However, it has been found to develop significant neurologic side-effects due to its ability to cross the blood-brain barrier.[2,3] Domperidone (DOM) is another prokinetic agent which is used in the treatment of nausea and vomiting for decades.[4,5] It has also been used for the treatment of migraine,[6,7] gastroparesis[8] and functional dyspepsia.[9] As it poorly penetrates the blood-brain barrier, it shows few neurological side-effects.[9,10] this makes DOM a better alternative to the metoclopramide in the treatment of diabetic gastroparesis. DOM is administered orally in the dose range of 10-40 mg daily and has an elimination half-life of 5-7 hrs.[11] Due to the short half life, frequent administration of DOM becomes necessary. Also, the previous study indicates that DOM showed promising results in diabetic gastroparesis when administered 20 mg QID. However, the frequent administration of conventional solid dosage forms often reduces the patient compliance. The oral extended release dosage forms prove to be more beneficial than conventional dosage forms as they improve patient compliance and therapeutic efficacy by reducing the dosing frequency, prolonging therapeutic effect and enhancing

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the bioavailability.[12] However, the problem arises when a weakly basic drug is to be formulated as an extended release dosage form. The weakly basic drugs show high aqueous solubility at low pH values, but at higher pH, they precipitate within the formulation and are no longer released.[13] DOM, being a weakly basic drug, may exhibit limited solubility leading into precipitation at intestinal pH if formulated as an extended release dosage form. Due to this reason, Prajapati ST *et al*., (2008) have developed a gastric floating matrix tablet of DOM to obtain its sustained release.[14] In last few years, some works have been reported where sustained release tablets of DOM have been prepared without considering the aforementioned problem associated with DOM.[15,16] β-cyclodextrin (βCD) and its derivatives have been used by many authors to improve the solubility of DOM.[17,18,19] However, βCD itself exhibits low solubility (18 mg/ml) and may cause toxic effects when used in large quantity. On other hand, the highly soluble derivatives of βCD are costlier. The drawback of βCD related to the low solubility can be overcome by incorporating a third component such as hydroxy acid or hydrophilic polymer during the complexation process.[20,21] such ternary inclusion complexes (TICs) reduce the amount of βCD required for complexation, consequently reducing the formulation cost. Furthermore, the preparation of a quaternary inclusion complex (QIC) by adding a fourth component such as hydrophilic polymer in the TIC has been found to enhance the solubilizing efficiency of βCD to a greater extent.[22] We have studied the effect of hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP)[23] and mannitol[24] as a fourth component in the QIC of DOM. Although PVP, in presence of citric acid, showed marked enhancement in the solubilizing efficiency of βCD, it was required in large amount. Mannitol, on other side, was required in small quantity to show a similar effect. Thus, the QIC of DOM prepared using βCD, citric acid and mannitol was found to be more suitable for the formulation of a sustained release tablet as it may help to reduce the tablet weight and size.

HPMC is one of the most commonly used polymers in the preparation of sustained release matrix tablets. Ribeiro *et al*. (2005) have reported the use of HPMC in achieving the pH independent controlled release of the multicomponent inclusion complex of vinpocetine.[25] However, at lower pH, a rapid release of vinpocetine was observed due to increase in the porosity of the tablet due to βCD and high solubility of drug (weak base) at this pH. In order to control the release of drug at low pH, a suitable polymer must be used in combination with HPMC. Sodium alginate (SA) is a natural polysaccharide obtained from the marine brown algae. It is sodium salt of alginic acid and is widely used in food industry due to its stabilizing, thickening and dispersing properties. Some previous studies reveal the formation of a thick gel of SA at lower pH which may be helpful in retarding the release of the weakly basic drugs under acidic conditions.[26,27] As SA is cheap, the matrix tablet composed of SA and HPMC would be a better and cost effective system for the controlled release of QIC of DOM.

Response surface methodology (RSM) is used for optimization of drug delivery systems which involves the use of various types of experimental designs, generation of polynomial relationships and mapping of the response over the experimental domain to select the optimum formulation.[28,29,30] Amongst various experimental designs, the central composite design has been commonly used for designing and optimization of different pharmaceutical formulations and processes.[31,32] This technique is more flexible, effective and provides large extent of information on experimental variable effects. In addition, it requires minimum number of experimental runs and time.

In present work, we have made an attempt to develop a controlled release matrix tablet of SA and HPMC containing QIC comprised of DOM, βCD, citric acid and mannitol. The objective of this study was to achieve pH independent controlled release of DOM for 12 hrs. Central composite design was employed to study the effect of independent variables (amount of HPMC and SA) on the swelling and drug release as well as to optimize the formulation.

MATERIALS AND METHODS

Materials

Domperidone (DOM) was obtained as a gift sample from Vasudha Pharma Chem Ltd. (Hyderabad, Andra Pradesh, India), β-cyclodextrin (βCD), hydroxypropyl methylcellulose (HPMC K4M), sodium alginate (medium viscosity), mannitol, citric acid, magnesium stearate and lactose monohydrate were purchased from Loba Chemie (Mumbai, Maharashtra, India).

Preparation of extended release matrix tablet containing QIC of DOM

The QIC containing equimolar amount of DOM, βCD, citric acid and mannitol was prepared by kneading method as described in our previous report.[24] The extended release matrix tablets containing kneaded complexes equivalent to 30 mg of DOM were prepared by direct compression method depending upon the preformula-

tion studies. The QIC, HPMC K4M, SA, lactose and magnesium stearate (1%) were blended thoroughly with a mortar and a pestle. Formulation mixtures were compressed into tablets using 10 mm flat faced punches to a constant pressure of 3 tons in a single punch tablet compression machine (Microteknik, Ambala, India). The tablet weight was kept constant to 300 mg by adjusting the amount of lactose used in each formula.

Physical characterization of tablets

The weight variation test of 20 tablets was performed according to guidelines mentioned in I.P. 1996 using an electronic balance. Friability of 10 tablets was evaluated by Roche type friabilator for 4 min at the rate of 25 rpm. The tablets were evaluated for hardness (n=10) using Monsanto hardness tester. The diameter and thickness of the tablets (n=10) were determined using vernier caliper and micrometer screw gauge respectively.

Assay of extended release matrix tablet

Twenty tablets were randomly selected and crushed into a fine powder with the mortar and pestle. The powder equivalent to 30 mg DOM was weighed and transferred to a 100 ml volumetric flask containing 25 ml of 0.1N HCl (methanolic). After sonication for 15 min, the solution was filtered through 0.45 µm filter paper. The total amount of drug for each tablet was analyzed spectrophotometrically at 284 nm after suitable dilutions.

Swelling studies

Swelling study was conducted by immersing pre-weighed tablets into beakers containing 900ml of 0.1N HCl (pH 1.2) for 2 hrs and phosphate buffer (pH 6.8) for 10hrs at 37±0.5°C. At specific time intervals, the tablets were removed, wiped gently with a tissue paper to remove the excess water and weighed on the analytical balance. Swelling index was calculated by using the following formula:

$$SI(\%) = \left\{ \frac{M_t - M_0}{M_0} \right\} \times 100 \quad (1)$$

Where M_0 is the initial weight of the tablet and M_t denotes the weight of the tablet at time t. The measurements were run in triplicate and the mean values and standard deviation were calculated.

In vitro dissolution studies

The dissolution study of the formulated tablets was performed using USP Type II dissolution apparatus (TDT-06L, Electrolab, India), in 900ml of 0.1N HCl (pH 1.2) for first 2hs and phosphate buffer (pH 6.8) for next 10hs. The temperature of the dissolution medium was maintained at 37 ± 1°C and the stirring speed was set at 50 rpm. Five ml aliquot samples were withdrawn at 1 h interval with replacement of fresh media. The samples were subjected to spectrophotometric analysis at 284 nm. The studies were conducted in triplicate.

Drug release kinetics

In order to propose a possible release mechanism, release data was fitted to the following equations:

Korsmeyer-Peppas equation:[33] $M_t/M_\infty = k_{KP}t^n$ (2)

Where, M_t/M_∞ = fraction of drug released at time't', k_{KP} = release rate constant, and n = the release exponent.

Zero-order equation:[34] $Q_t = Q_0 + k_0 t$ (3)

First-order equation:[35] $\log Q_t = \log Q_0 - k_1 t$ (4)

Higuchi's equation:[36]uniform matrix which acts as the diffusional medium and (b $Q_t = k_H t^{1/2}$ (5)

Where, Q_t = amount of drug released at time 't', Q_0 = concentration of the drug in the solution at t = 0, k_0 = zero-order release constant, k_1 = first-order release constant, k_H = Higuchi release constant.

Experimental design

Central composite design (face centered of alpha 1.414) was adopted for optimization of extended release tablets containing QIC of DOM according to standard protocol.[37] The model consisted of four full factorial design points, four axial points and five center points. Higher and lower levels of each factor were coded as +1 and −1 respectively, and the mean value was coded as 0. The selected factor levels are summarized in Table 1. The two independent formulation variables evaluated include:

X_1 = amount of SA

X_2 = amount of HPMC

The response variables tested include:

Y_1 = percent drug release after 2h (R_{2h}) (%)

Y_2 = percent drug release after 12 h (R_{12h}) (%)

Optimization data analysis and validation of optimization model

The effect of formulation variables on the response variables were statistically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design-Expert® version 7.00 (Stat-Ease, Inc.). The design was evaluated using quadratic model, which can be expressed as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2 \quad (6)$$

Table 1: Design Summary.		
Normalized levels	**Independent variables (factors)**	
	SA (mg) (X_2)	**HPMC (mg) (X_1)**
-1.414	21.71	35.85
-1	30	40
0	50	50
1	70	60
1.414	78.28	64.14

SA- Sodium alginate; HPMC- Hydroxypropyl methylcellulose

Where, Y is the response variable and b_0 is the constant. b_1, b_2, b_3, b_4 and b_5 are the regression coefficients. X_1 and X_2 stand for the main effects; X_1X_2 are the interaction terms, which show how response changes when two factors are changed simultaneously. X_1^2, X_2^2 are the higher order polynomial terms of the independent variables which are used to evaluate the nonlinearity. Based on the model polynomial functions, response surface plots and contour plots were constructed using Design Expert software. These plots are very useful to study the effects of interaction between the factors on the responses. Desirability approach was used to generate optimized formulation with desired responses.

Compatibility studies

Compatibility in between the QIC and formulation excipients were studied by Attenuated total reflectance – Fourier transform infrared (ATR-FTIR) spectroscopy and differential scanning calorimetry (DSC). The IR spectra of pure DOM, QIC and optimized formulation were recorded using ATR-FTIR (MIRacle 10, Shimadzu, Japan). The samples were scanned in the range of 600 to 4000 cm^{-1}at an average of 25 scans and resolution of 4cm^{-1}. The thermograms of pure DOM, QIC and optimized formulation were recorded using SDT Q600 V20.9 Build 20 instrument (Artesian Technology Group, Champaign, IL, US). Sample were sealed in aluminum pans and heated at the rate 10°C/min from 25°C-500°C under nitrogen atmosphere of flow rate 10 ml/min.

Comparative study of drug release

The DOM release from the optimized tablet formulation was compared with the matrix tablets containing pure DOM and equivalent amount of binary (DOM/βCD – 1:1 molar) and ternary (DOM/βCD/citric acid – 1:1:1 molar) complexes. The complexes were prepared by kneading method. The amount of HPMC and SA in the tablets used for comparison was same as that of the optimized formulation. Lactose was used to adjust the weight of the tablets to 300 mg.

RESULTS AND DISCUSSION

Physical characterization and assay of tablets

According to I.P. 1996, the limit of percentage deviation for the tablets weighing more than 250 mg is ±5%. The tablet weights varied in the range of 297.84 mg to 302.19 mg. The average percentage deviation obtained for the formulated tablets was found within control. The drug content and physical parameters of the formulated tablets, such as hardness, diameter, thickness and friability are shown in Table 2. The drug content was found to be uniform in all the formulations. The values of the physical parameters were found within the acceptable limits.

Swelling studies

Table 2: Physical characteristics of tablets.					
Formulations	**Thickness (mm)**	**Diameter (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Drug content (%)**
F1	2.93 ± 0.02	10.12 ± 0.03	5.66 ± 0.25	0.673±0.04	91.12±1.16
F2	2.90 ± 0.06	10.17 ±0.04	5.58 ± 0.37	0.341±0.03	97.27±0.69
F3	2.90 ± 0.04	10.16 ± 0.07	5.50 ± 0.44	0.338±0.17	94.96±1.38
F4	2.95 ± 0.03	10.18 ± 0.04	5.58 ± 0.37	0.673±0.03	93.04±2.08
F5	2.90 ± 0.03	10.16 ± 0.05	5.50 ± 0.44	0.342±0.02	95.16±1.07
F6	2.93 ± 0.05	10.19 ± 0.03	5.50 ± 0.44	0.671±0.07	90.54±2.84
F7	2.97 ± 0.03	10.16 ± 0.04	5.50 ± 0.54	0.677±0.07	91.12±1.26
F8	2.93 ± 0.08	10.17 ± 0.11	5.58 ± 0.37	0.668±0.05	96.50±1.26
F9	2.92 ± 0.06	10.21 ± 0.05	5.50 ± 0.44	0.342±0.05	94.96±2.54
F10	2.91 ± 0.05	10.16 ± 0.05	5.50 ± 0.44	0.677±0.11	94.00±1.76
F11	2.93 ± 0.07	10.20 ± 0.08	5.83 ± 0.51	0.337±0.02	93.81±1.52
F12	2.91 ± 0.02	10.18 ± 0.04	5.58 ± 0.49	0.336±0.02	94.58±2.21
F13	2.92 ± 0.04	10.16 ± 0.03	5.66 ± 0.40	0.680±0.07	92.27±1.06

Figure 1 shows the swelling behavior of the matrix tablets in 0.1N HCl and phosphate buffer (pH 6.8). The rate of swelling was found to be dependent on the pH of the medium. In first two hs, the swelling was found to be less which can be attributed to the presence of SA within the tablets. SA gets converted in to alginic acid at low pH.[26,38] this leads to the formation of firm gel which exhibits poor swelling. Also, the citric acid within the QIC may interact with the SA leading to the formation of tough gel.[27] The minimum swelling exhibited by formulation F1 in 0.1N HCl may be due to the minimum polymer concentration (SA and HPMC). The swellability of the formulations was found to be increased with increase in the total polymer concentration. It was observed that formulations which carried low polymer concentration (<100mg) (see Figure 1a), exhibited increase in the swelling index up to 4 h followed by erosion. Formulations F2, F6, F10, F11 and F13 (centre points) showed an increase in the swelling up to 5 h (see Figure 1c). These formulations exhibited a similar swelling behavior to some extent which may be due to the same polymer concentration. The remaining formulations which carried high polymer concentration (>100 mg) showed increase in the swelling up to 6 h except F12 which showed increase in swelling till 5 h (see Figure 1b). This indicates that along with the total polymer concentration, the SA: HPMC ratio also affected the swell ability of the formulations to some extent. It is usually observed that SA shows poor swelling property as compared to HPMC.[39] Due to this reason, the formulations containing low SA: HPMC ratio exhibited good swelling. Although formulation F12 carried high polymer concentration, the ratio of SA: HPMC was very high as compared to the other formulations. This may be the possible reason that formulation F12 showed increase in swelling till 5h followed by erosion.

In vitro drug release and kinetics

The drug release profile of all the formulations is illustrated in Figure 2. The release rate of DOM from the formulations was found to be dependent upon their swellability and hence indirectly upon the total polymer concentration and SA: HPMC ratio. The formulations with low swelling index (F3, F4, F5 and F7) showed a maximum release of DOM in the range of 88.52±3.90% to 99.2±3.12% in 12 h (see Figure 2a). As the swelling index of the formulations increased, a marked retardation in the drug release was observed. This may be related to an increase in the diffusion pathlength of the drug with increase in the swell ability of the tablets. The formulation F1 which exhibited a maximum swelling index released 54.15±2.19% DOM at the end of 12 h (see Figure 2b). Figure 2c shows that the release profile of the centre point formulations overlapped with each other indicating minimum errors due to the experimental procedure. This is necessary in order to generate a meaningful fitting for dependent variables.

The release behavior of the tablets was found to be different under acidic (pH 1.2) and nearly neutral (pH 6.8) conditions. It was found that the tablets containing high SA: HPMC ratio profoundly retarded the release of DOM in the acidic medium in spite of high solubility of DOM in this medium. This can be ascribed to the formation of the firm gel of alginic acid which may obstruct the release of DOM. Formulation F9 (SA: HPMC ratio = 1.56) exhibited a maximum retardation in acidic medium by releasing only 17.89±2.48% DOM in 2h. It was noticed that despite of highest SA: HPMC ratio i.e. 1.75, formulation F12 released more amount of DOM (21.14±1.68%). This may be due to the fact that the total polymer concentration in formulation F12 was less as compared to the formulation F9.

In phosphate buffer (pH 6.8), the drug release rate was found to be almost linear in case of all the formulations. At high pH, it is usually observed that the matrix tablets of poorly soluble weak bases containing citric acid show a rapid initial release of the drug due to the acidic microenvironment created by citric acid.[25] However, as the time progresses, the acidity within the matrix depletes which leads to reduction in the release rate of the drug. The presence of acidic microenvironment was confirmed by conducting the dissolution of formulation F6 in 900 ml of 0.1N HCl for 2 h followed by phosphate buffer (pH 6.8) containing 1.25% methyl red indicator. It was observed that the swollen matrix turned pink within few min in the buffer (see Figure 3). The color was found to be intense initially which may be due to the acidic environment within the tablet created by residual HCl and citric acid. The depletion of the acidic environment was noticed as the color of the tablet began to fade after 2 h in buffer; however it did not disappear completely at the end of 12 h. This indicates that the acidic microenvironment created by citric acid within the tablet persisted throughout the dissolution process. It was also found that the depletion in the acidic environment did not affect the release rate of DOM and the linearity was maintained. This may be due to two reasons. Firstly, at high pH, alginic acid gets converted into its soluble salt form. This may cause softening of its firm gel structure followed by erosion and increase in the drug release.[38] It was evident that the formulations containing high SA: HPMC ratio did not exhibit rapid erosion. This may be attributed to the mild acidity created by citric acid till the end of 12 h. The second

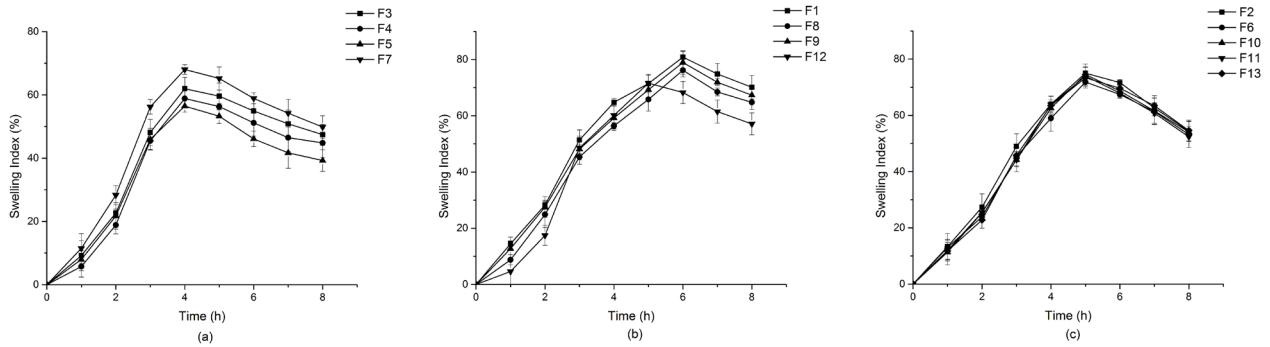

Figure1: Swelling behavior of formulations with polymer concentration (a) less than 100 mg, (b) greater than 100 mg and (c) equal to 100 mg.

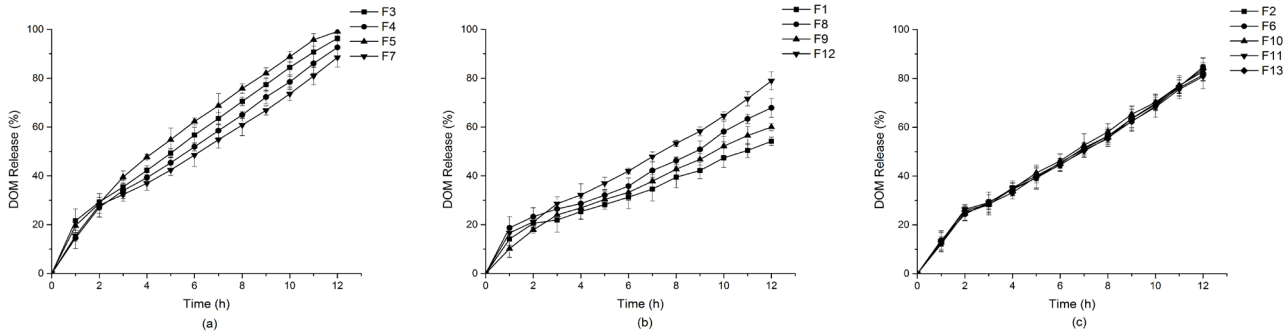

Figure 2: DOM release profiles for formulations with polymer concentration (a) less than 100 mg, (b) greater than 100 mg and (c) equal to 100 mg.

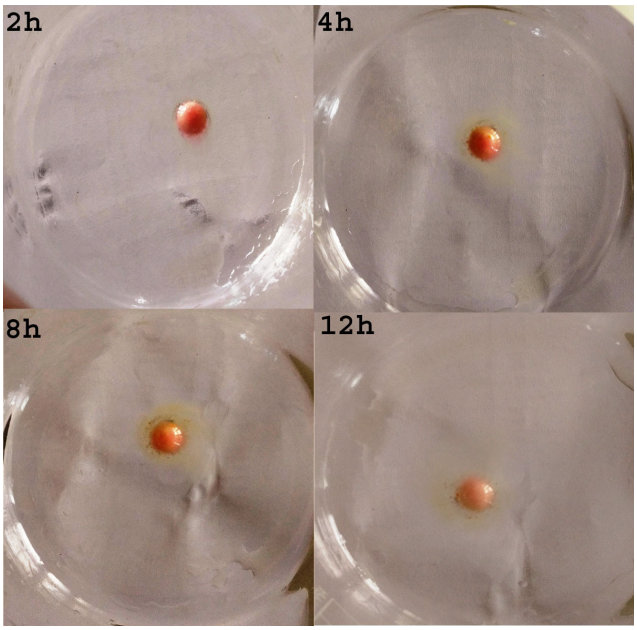

Figure 3: Methyl red test for confirmation of acidic microenvironment in formulation F6.

reason behind the linearity in the release pattern may be the presence of mannitol in QIC which can create channels within the matrix. The formation of channels may enhance the uptake of water within the matrix and promote faster release of DOM.[40] Apart from the channel formation, mannitol can also improve the solubility of non-complexed DOM due to its hydrotropic nature.[41,42]

The zero order, first order, Higuchi and Korsmeyer-Peppas models were used to evaluate the release data. The regression coefficient values of the kinetic models obtained after fitting the release data into the models are summarized in Table 3. The *in vitro* release profile of all the formulations was best expressed by zero order model possibly due to the presence of SA and mannitol. The release mechanism from the cylindrical solid dosage forms can be well explained from the release exponent (n) values obtained using the Korsmeyer-Peppas model. When $n \leq 0.45$, it indicates quasi-Fickian or Fickian diffusion mechanism. For $0.45 < n < 0.89$, it indicates

anomalous transport (non-Fickian), also known as first order release. If $n \geq 0.89$, it indicates case II transport or zero order release. The values of n for our formulations ranged in between 0.57 to 0.71 indicating that the DOM release from the matrix tablets was based on diffusion and erosion mechanisms.

RSM optimization results

Central composite design was selected for the optimization of the matrix tablets containing QIC of DOM. Design-Expert (V.7.0, Stat-Ease Inc, USA) software suggested 13 experimental runs for two independent variables: amount of SA (X_1) and HPMC (X_2). The effect of these independent variables on R_{2h} (Y_1) and R_{12h} (Y_2) was investigated. Table 4 represents the independent variables along with their responses for the 13 runs.

Mathematical modeling

The Design-Expert software generated the mathematical relationships in the form of polynomial equations (models) for the measured responses. Based on maximum Adjusted R^2 and low PRESS value, linear and quadratic models were selected as suitable statistical models for the optimization of R_{2h} and R_{12h} respectively (see Table 5). The models were statistically validated using one way ANOVA as shown in Table 6. The model p values of less than 0.05 for both the measured responses indicated that the models were significant ($p<0.05$). The polynomial equations relating the responses with the independent variables are given below:

$$Y_1 (R_{2h}) = 24.78 - 3.90 X_1 - 0.85 X_2 \quad (7)$$

$$Y_2 (R_{12h}) = 82.67 - 13.25 X_1 - 8.81 X_2 - 3.53 X_1 X_2 - 2.01 X_1^2 \quad (8)$$

It should be noted that only the significant terms are included in the models. The sign and the magnitude of the main effects indicate the influence of each independent variable (factors) on the response. In case of R_{2h} (Y_1), the factors X_1 and X_2 showed significant effect (see Table 6). Equation (7) reveals that both the factors showed negative effect on R_{2h}. For R_{12h} (Y_2), factor X_1, X_2, their interaction and higher order effect of X_1 were found to be significant. All the terms in equation 8 exhibited negative effect on R_{12h}. The high regression coefficient value associated with factor X_1 in both the equations reveals its dominant effect on R_{2h} and R_{12h}. This may be mainly due to the acidic environment created within the tablet matrix by HCl (up to 2 h) and citric acid (till 12 h) which converts SA into the alginic acid and retards the release of DOM as discussed previously.

Response surface analysis

Figure 4a and 4b represents the contour plot and 3D response surface analysis indicating the effect of the independent variables on R_{2h}. A marked linear decrease in R_{2h} was observed with increase in the amount of SA. On other hand, an increase in the amount of HPMC showed a slight reduction in R_{2h}. A maximum retardation of DOM release was observed at high levels of X_1 and X_2. The contour plot and 3D response surface analysis clearly indicate that amount of SA had a great influence on the R_{2h}.

The effect of the amount of SA and HPMC on R_{12h} is demonstrated in Figure 5a and 5b. A non-linear relationship was observed in between the independent variables and R_{12h}. A high amount of drug was released when the X_1 and X_2 were kept at lower level and vice versa. The interaction in between X_1 and X_2 can be explained from the response surface plots (see Figure 5b). When X_2 was kept at low level and X_1 was increased from low level to high level, the R_{12h} decreased from 98.24% to 78.79%. On other side, when X_1 was increased from low level to high level by keeping X_2 at high level, the R_{12h} decreased from 87.68% to 54.11%. A marked decrease in R_{12h} observed at high level of X_2 can be explained on the basis of the amount and viscosities of SA and HPMC in the matrix tablet. An increase in the polymer concentration or viscosity may increase the solution viscosity of the gel layer within the matrix tablet and offer resistance to the diffusion of drug.[43] The total polymer concentration within the tablet at low levels of X_2 was very low (70 mg) due to which a maximum release was achieved. As the X_1 was increased from low level to high level, a gradual decrease in R_{12h} was observed which is mainly attributable to the lower viscosity of SA (~2000 cP). However, when X_2 was kept at high level and X_1 was increased from low level to high level, a considerable decrease in R_{12h} was noticed due to the combined effect of total polymer concentration as well as high viscosity of HPMC (~4000 cP).

Optimization of the matrix tablet

The matrix tablets containing QIC of DOM were optimized for both the responses, Y_1 (R_{12h}) and Y_2 (R_{12h}). The constraints were set for the response values as $17.89\% \leq Y_1 \leq 29.31\%$ and $80\% \leq Y_1 \leq 90\%$. A numerical analysis using Design Expert software was performed in order to get the optimal values for the responses, based on the desirability criterion. The optimized formulation was comprised of 50 mg SA and 40 mg HPMC with a desirability of 0.942. The reliability of the response surface model was tested by preparing the optimized formulation according to the predicted model and evaluating it for the responses. Table 7 shows the exper-

Table 3: Curve fitting analysis data.

Formulations	Correlation coefficient (R^2)				Release exponent (n)
	Zero order	First order	Higuchi	Korsmeyer- Peppas	
F1	**0.992**	0.991	0.960	0.952	0.57
F2	**0.997**	0.983	0.974	0.979	0.68
F3	**0.999**	0.971	0.987	0.991	0.68
F4	**0.999**	0.980	0.978	0.987	0.69
F5	**0.998**	0.957	0.993	0.997	0.71
F6	**0.994**	0.988	0.965	0.979	0.69
F7	**0.995**	0.991	0.965	0.971	0.66
F8	**0.995**	0.994	0.964	0.966	0.61
F9	**0.995**	0.975	0.973	0.983	0.66
F10	**0.998**	0.979	0.979	0.984	0.70
F11	**0.994**	0.991	0.964	0.967	0.65
F12	**0.994**	0.977	0.970	0.985	0.71
F13	**0.992**	0.992	0.959	0.964	0.69

Table 4: Observed responses for various trial formulations as per central composite design.

Run	Independent Variables			Observed responses	
	X_1 (mg)	X_2 (mg)		Y_1 (%)	Y_2 (%)
F1	70	60		20.55	54.15
F2	50	50		25.05	81.4
F3	21.71	50		29.31	96.33
F4	50	35.85		27.09	92.65
F5	30	40		28.77	99.2
F6	50	50		24.31	84.67
F7	30	60		27.94	88.52
F8	50	64.14		23.26	67.89
F9	78.28	50		17.89	59.98
F10	50	50		24.75	82.81
F11	50	50		26.34	80.76
F12	70	40		21.14	78.95
F13	50	50		25.76	83.7

X_1- SA; X_2- HPMC; Y_1- Percent drug release after 2h (R_{2h});
Y_2- Percent drug release after 12h (R_{12h})

Table 5: Model summary statistics for measured responses in central composite design.

	Y_1 (%)					Y_2 (%)			
	R^2	Adjusted R^2	Predicted R^2	PRESS		R^2	Adjusted R^2	Predicted R^2	PRESS
Linear	0.9334	0.9201	0.8808	16.25		0.9553	0.9463	0.9144	181.63
2FI	0.9335	0.9113	0.8511	20.31		0.9788	0.9717	0.9626	79.40
Quadratic	0.9643	0.9388	0.8528	20.07		0.9936	0.9890	0.9814	39.54
Cubic	0.9801	0.9523	0.9276	9.88		0.9942	0.9861	0.9329	142.25

PRESS- Predicted residual sum of squares; 2FI- two factor interaction; Y_1- Percent drug release after 2h (R_{2h}); Y_2- Percent drug release after 12h (R_{12h})

Table 6: Summary of ANOVA for responses.						
Source	**Sum of squares**	**d.f.**	**Mean square**	**F value**	**p-value Prob>F**	**Significance**
R_{2h} (%) (Linear Model)						
Model	127.29	2	63.65	70.05	<0.0001	S
X_1	121.45	1	121.45	133.67	<0.0001	S
X_2	5.84	1	5.84	6.43	0.0296	S
Lack of fit	6.46	6	1.08	1.64	0.3281	NS
R_{12h} (%) (Quadratic Model)						
Model	2107.68	5	421.54	216.5	<0.0001	S
X_1	1405.21	1	1405.21	721.72	<0.0001	S
X_2	621.21	1	621.21	319.06	<0.0001	S
X_1^2	28.06	1	28.06	14.41	0.0067	S
X_2^2	6.2898	1	6.2898	3.2305	0.1153	NS
X_1X_2	49.84	1	49.84	25.60	0.0015	S
Lack of fit	3.29	3	1.10	0.42	0.7467	NS

R_{2h}-Percent drug release after 2h; R_{12h}-Percent drug release after 12h; S- significant; NS- non-significant

Table 7: Comparison between predicted and experimentally observed response values of the optimized formulation.										
Code	**Factors**		**Responses**							
			Y_1 (R_{2h})				Y_2 (R_{12h})			
	X_1 - SA (mg)	**X_2 - HPMC (mg)**	**Predicted (%)**	**Observed* (%)**	**Error (%)**		**Predicted (%)**	**Observed* (%)**	**Error (%)**	
OF	50	40	25.63	24.27±2.69	0.68		90.52	88.65±1.92	0.94	

SA- sodium alginate; HPMC- Hydroxypropylmethyl cellulose; R_{2h}- Percent drug release after 2h; R_{12h}- Percent drug release after 12h; OF: Optimized formulation; * mean±standard deviation.

imentally observed and model predicted responses for the optimized formulation. The small error values indicate a good relation in between experimental and predicted values of the responses. It also confirmed that the mathematical models obtained using central composite design showed proper fitting.

Compatibility study

The ATR-FTIR spectra of DOM, QIC and the optimized formulation are shown in Figure 6. The spectra of DOM and QIC have been described in detail in our previous work. The characteristic peaks of QIC showed negligible shifts in the spectra of extended release matrix tablet except the peak corresponding to C=O stretching which was found to be shifted from 1670 cm^{-1} to 1685 cm^{-1}. This may be attributed to interaction in between hydroxy group of SA and carbonyl group of citric acid.[27] An occurrence of such interaction may weaken the hydrogen bonding in between DOM, βCD and citric acid further leading to reappearance of C=O stretching peak of DOM at 1685 cm^{-1}. However, the dissolution studies revealed that these interactions did not affect the solubilizing efficiency of βCD to large extent. This may be due to the presence of HPMC K4M which also participates in formation of co-complex and may exhibit synergism with mannitol.[22]

Figure 7 illustrates the DSC thermograms of pure DOM, QIC and optimized formulation. DOM showed two endothermic peaks at 249°C and 397°C corresponding to the melting point and decomposition of DOM. QIC exhibited a small peak at 164°C related to the mannitol.[24] The thermogram of the optimized formulation showed presence of the peak corresponding to the mannitol in QIC; however its intensity was reduced possibly due to low concentration of mannitol in the formulation. Thus no any signs of unusual interactions in between the components of QIC and formulation excipients were observed from the ATR-FTIR and DSC analysis.

Comparative study of drug release

The release of DOM from the optimized formulation (OF) and the formulations containing pure DOM (DF), binary complex (BF) and ternary complex (TF) was compared in order to evaluate the efficacy of the

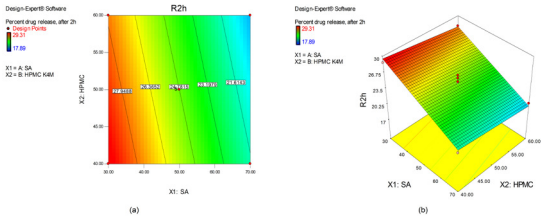

Figure 4: Contour plot (a) and 3D Response surface plot (b) showing the effect of SA and HPMC on R_{2h}.

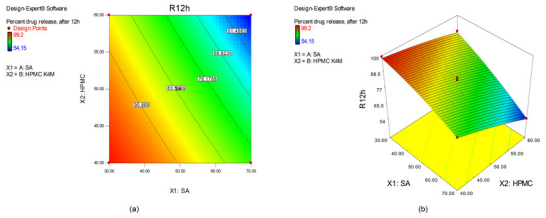

Figure 5: Contour plot (a) and 3D Response surface plot (b) showing the effect of SA and HPMC on R_{12h}.

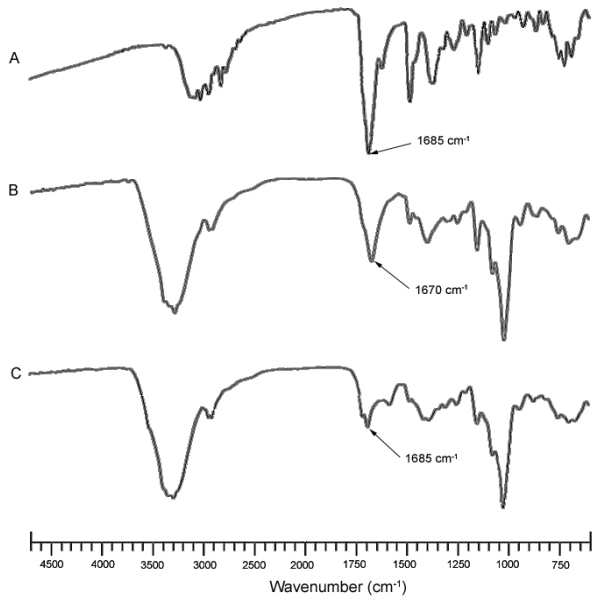

Figure 6: IR spectra of (A) Pure DOM, (B) QIC and (C) Optimized formulation.

optimized formulation. The particulars of the optimized formulation and the formulations used for comparison are given in Table 8. *In vitro* drug release study for these formulations was performed as mentioned earlier. Figure 8 shows the drug release profile of the above mentioned formulations. It was found that the formulation DF released only 19.89±3.72% drug at the end of 5 h which may be due to the poor solubility of DOM at pH 6.8.[24] After 12h, the formulation BF released 57.78±2.57% whereas formulation TF released

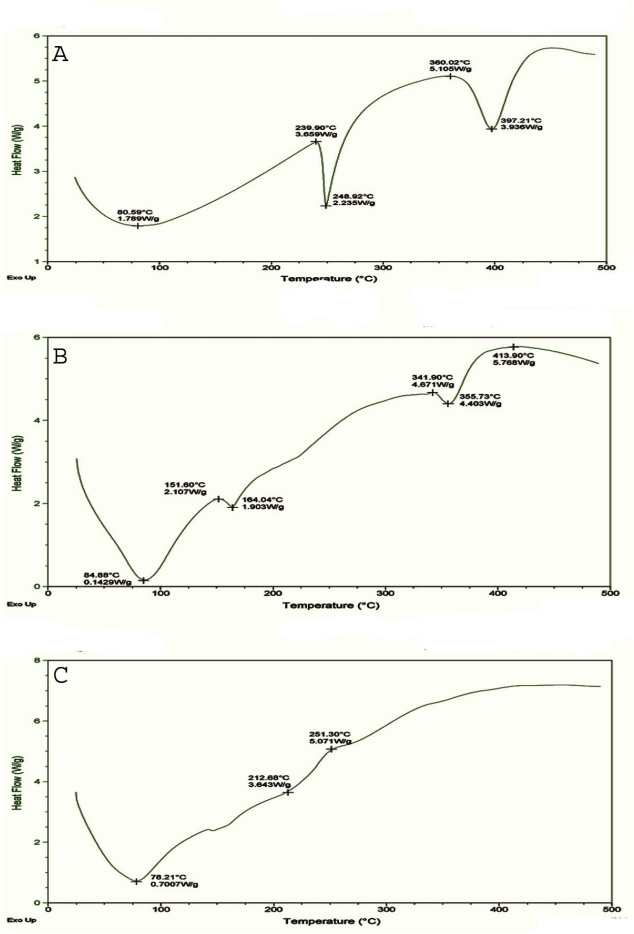

Figure 7: DSC thermograms of (A) Pure DOM, (B) QIC and (C) Optimized formulation.

77.25±1.45% of DOM. The high release rate of formulation TF as compared to BF can be ascribed to the acidic microenvironment created by citric acid of ternary complex within the matrix of the tablet. It was found that the formulation OF released a maximum 88.65±3.19% drug at the end of 12 h. This indicates that along with the acidic environment created by citric acid of QIC, the channel formation and hydrotropic effect of mannitol was responsible for nearly complete release of DOM from the optimized formulation. Thus incorporation of mannitol based QIC of poorly soluble weak bases in the matrix tablets comprised of SA and HPMC may be advantageous over those containing only hydroxyl acid based ternary complex or a binary complex as it may provide a pH independent zero order release of the drug.

CONCLUSION

The physical properties of the matrix tablet formulations containing QIC of DOM were found within the acceptable limits. The release of DOM from the tablets was

Table 8: Optimized formulation and the formulations containing pure DOM, binary complex and ternary complex.

Ingredients	OF	DF	BCF	TCF
DOM (mg)	-	30	-	-
Inclusion complex*	QIC	-	DOM/βCD	DOM/βCD/CA
SA (mg)	50	50	50	50
HPMC K4M (mg)	40	40	40	40
Lactose (mg)	70.73	177	97.07	83.55
Magnesium stearate (%)	1	1	1	1
Total (mg)	300	300	300	300

DOM- Domperidone; βCD- β-cyclodextrin;CA- Citric acid; *- inclusion complex equivalent to 30mg DOM; OF- Optimized formulation; DF- Pure DOM containing formulation; BCF- Binary complex containing formulation; TCF- Ternary complex containing formulation; SA- Sodium alginate; HPMC- Hydroxypropylmethylcellulose; QIC- Quaternary inclusion complex

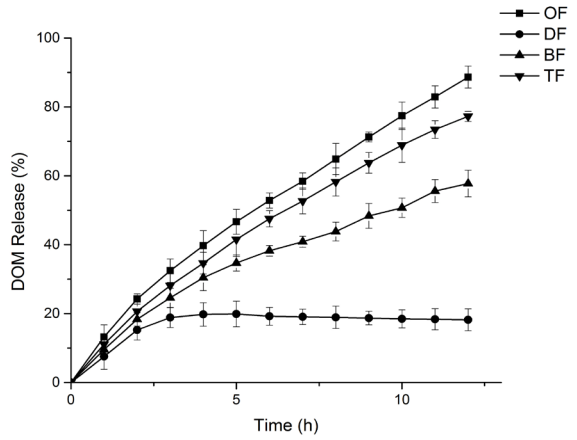

Figure 8: Comparative drug release profiles of DF, BF, TF and OF

found to be dependent upon the SA: HPMC ratio and total polymer concentration. An appreciably high value of SA: HPMC ratio and low value of total polymer concentration was essential for avoiding the burst release of DOM at acidic pH and achieving nearly complete release at the end of 12 h. All the formulations showed zero ordered release as the best fit model mainly due to dual behavior of SA at different pH and channel formation by mannitol within the matrix. A central composite design revealed that the amount of SA had a greater influence on the percent drug release after 2 h and 12 h. An interaction effect was observed in between SA and HPMC amount on the release of DOM in buffer. The optimized formulation (OF) showed a minimum variation in between observed and predicted responses indicating the feasibility of the optimization procedure. The comparative study of drug release in between OF and the formulations containing pure DOM, binary and ternary complexes showed that the OF containing mannitol based QIC of DOM was most suitable for achieving pH independent controlled and complete release of drug. Thus, the OF may be beneficial to reduce the dosage frequency amongst the diabetic patients suffering from gastroparesis and also help to improve its bioavailability, however this could be confirmed only after performing *in vivo* studies.

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CONFLICT OF INTEREST

The authors report no conflict of interest

ABBREVIATIONS USED

ATR-FTIR: Attenuated total reflectance – fourier transform infrared; βCD: β-cyclodextrin; **DSC**: Differential scanning calorimetry; **DOM**: Domperidone; **HPMC**: Hydroxypropyl methylcellulose; **PEG**: Polyethylene glycol; **PVP**: Polyvinyl pyrrolidone; **QIC**: Quaternary inclusion complex; **RSM**: Response surface methodology; **SA**: Sodium alginate; **TIC**: Ternary inclusion complex.

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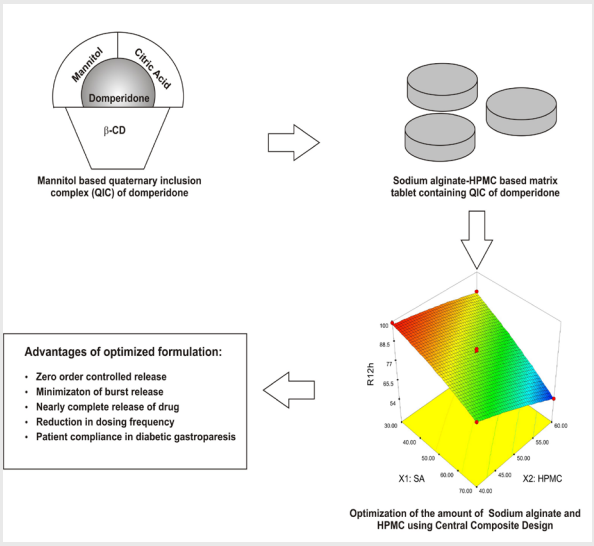
PICTORIAL ABSTRACT



SUMMARY

- pH independent controlled release matrix tablet of sodium alginate (SA) and hydroxypropyl methylcellulose (HPMC) containing quaternary inclusion complex (QIC) comprised of domperidone (DOM), β-cyclodextrin (βCD), citric acid and mannitol were prepared by direct compression for treatment of diabetic gastroparesis.
- Central composite design was used to optimize the amount of SA and HPMC in the formulation.
- The presence of citric acid in the complex helped to maintain acidic microenvironment around the drug molecules at high pH.
- Mannitol assisted in channel formation within the tablet matrix.
- The high value of SA: HPMC ratio and low value total polymer concentration helped to minimize burst release of DOM.
- The formulations exhibited zero ordered drug release.
- SA showed greater influence on the drug release from the matrix.
- The optimized formulation was more better than the formulations containing pure DOM, binary and ternary complexes.

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