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RESEARCH PAPER

Formulation Optimization of Diltiazem Hydrochloride Matrix Tablets Containing Modified Ispaghula Husk Using Factorial Design

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ABSTRACT

The purpose of this study was to develop modified-release tablets of diltiazem hydrochloride using physically modified ispaghula husk as a hydrophilic matrixing agent. Ispaghula husk and water were exposed to heat in a hot air oven or microwave oven. The treated samples were evaluated for swelling and rigid gel formation. Microwave oven treated samples showed rigid gel formation and hence they were systematically studied using 3^2 factorial design using heating time and amount of water as independent variables. Diltiazem tablets were prepared using treated samples and analyzed for in vitro drug release. A polynomial equation was generated using statistically significant terms such as heating time, X_1, amount of water, X_2, and X_1X_2 and X_1^2 for predicting time required for 80% drug dissolution. Heating time was found to have a predominant effect in sustaining the drug release. A contour plot is presented for interpretation of the results. The tablets exhibited more axial swelling than radial swelling. The results of F-statistics revealed that the drug release pattern fit well in the Higuchi model.

INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker and is widely prescribed for the treatment of angina pectoris, arrhythmia, and hypertension. Its high aqueous solubility, short elimination half-life (3–5 hr), and use in chronic diseases makes it a suitable candidate for prolongation of its release from dosage forms (1,2).

In recent years, water-swellable polymers have attracted considerable attention in the field of drug delivery systems. Among the swellable polymers, hydrophilic polymers are quite popular in design of controlled drug delivery dosage forms. Adjuvants such as poly-

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vinylalcohol, hydroxypropyl cellulose, methylcellulose, and hydroxypropyl methylcellulose (HPMC) are commonly used to modify the drug release pattern in the body. These semi-synthetic polymers are relatively expensive. In the formulation of controlled-release tablets based on hydrophilic matrices, HPMC is the most widely used polymer (3).

Natural materials such as guar gum, alginates, etc., are relatively inexpensive, nontoxic, and easily available. They have been used by researchers for the development of modified release dosage forms. Moreover, they can be modified using thermal or chemical treatment for use in sustained-release preparations. Modification by thermal treatment does not involve hazards of crosslinking with chemicals. Ispaghula husk (dried seed coats of *Plantago ovata*) is biocompatible, inexpensive, and easily available. It is official in IP, BP, and USP, and is used in food and pharmaceuticals at a dose level of 5–7 g, twice a day. A list of proprietary names and multiingredient preparations containing ispaghula is given in Martindale (4). The fibers from the husk are not absorbed or digested by the body (5). Ispaghula husk possesses extensive swelling properties (6). The husk forms gel when kept in contact with water but the gel structure disrupts on manual shaking. Physically modified ispaghula husk forms a relatively stiffer gel. The use of ispaghula husk is not fully explored by researchers and hence the present study was undertaken to develop modified release dosage form of diltiazem hydrochloride using physically modified ispaghula husk.

EXPERIMENTAL

Materials

Diltiazem hydrochloride USP was received as a gift sample from Cadila Health Care Pvt. Ltd. Ispaghula husk (Laxmi brand Sat-Ispaghula) was procured from a local pharmacy. All the other chemicals and solvents were of analytical grade. The sample of ispaghula husk met the swelling power and ash content of IP. (7).

Methods

Preparation of Modified Ispaghula Husk

Hot Air Oven Method

Samples of ispaghula (5 g) were kept in contact with 40 ml of water for 10 min to ensure complete soaking in glass petri dishes (6 in.). The wetted ispaghula samples were then kept in hot air ovens at 110°, 120°, and 150°C. After selected time intervals of 6, 8, 10, 12, and 18 hr, the petri dishes were removed from oven. Swelling capacity and rigid gel formation studies were carried out for preliminary screening of the treated samples.

Microwave Oven Method

The procedure was identical to that described above. The results of preliminary trial showed that 5 g ispaghula husk, 12.5 min exposure time, and 70 ml of water yielded a product with satisfactory swelling property. A 3^2 randomized full-factorial design was constructed around this center-point. The time of exposure to microwave irradiation (X_1) and the amount of water (X_2) were selected as independent variables. Power setting on the domestic microwave oven panel was kept constant for all the experiments (i.e., 7 on control panel, Batliboi, India). The amount of water was kept to a maximum level of 20 ml/g of ispaghula because the reported swelling factor is 20 (6). The actual and transformed values of the different batches are shown in Table 1.

Swelling Capacity (8)

The study was carried out in a 100-ml graduated cylinder. The initial bulk volume of 1 g of treated ispaghula husk was noted and water was then added to yield 100 ml of uniform dispersion. The sedimented volume of the swollen ispaghula was noted after 24 hr storage at room temperature. The swelling capacity was calculated by taking the ratio of the swollen volume to the bulk volume. The swelling capacity study was also carried out at pH 1.2. The results are depicted in Table 1.

Rigid Gel Formation Study

For obtaining arbitrary information on stiffness of gel, a simple test was used. Five hundred milligrams of ispaghula husk was mixed with 10 ml water. After 5 min, rigidity of the gel was checked by manually inverting the test tube three times. The results were then recorded as formation of uniform dispersion or intact gel.

Assay

Aqueous solutions of diltiazem hydrochloride in distilled water and simulated gastric fluid (pH 1.2) were prepared and the absorbance was measured at 237 nm using a Hitachi U-2000 UV-VIS spectrophotometer.

Table 1

Full Factorial Experimental Design Layout

Batch No.	Variable Level in Coded Form		Average Response	Swelling Capacity	
	X_1	X_2	t_{80} (hr)	(pH 7)	(pH 1.2)
1	-1	-1	7.724	18	18.46
2	-1	0	9.348	23.6	23
3	-1	1	8.349	21.6	22.2
4	0	-1	7.014	26	25.8
5	0	0	8.806	22.3	22
6	0	1	7.845	25.8	26.2
7	1	-1	5.419	27	27.5
8	1	0	7.351	25.5	26
9	1	1	8.103	21.3	22

Translation of coded levels in actual units

Coded level	-1	0	1
X_1 : Time in min.	10	12.5	15
X_2 : Water in ml	40	70	100

Swelling capacity of untreated ispaghula husk = 19

Linear equations were generated by fitting weighted linear regression model to the data obtained in triplicate (9).

Preparation of Tablets

Conventional Tablet

The tablets of diltiazem hydrochloride (90 mg), lactose (102.5 mg), talc (5 mg), and magnesium stearate (2.5 mg) were prepared using 10% starch paste as a binder. The granules (20/40 #) were compressed using a 12/32-in. die and punch assembly on a single-punch tablet machine.

Modified Ispaghula Husk Tablet

Diltiazem hydrochloride and microwave oven treated ispaghula husk were physically admixed in a weight ratio of 1:1 (i.e., 90 mg each) and then the tablets were prepared by the wet granulation technique described above, omitting lactose.

Dissolution Study

Dissolution studies were carried out to determine the release profiles of diltiazem hydrochloride from various formulations. Tablets containing 90 mg of diltiazem hydrochloride were evaluated for in vitro dissolution study in distilled water (900 ml, 37 ± 0.5°C, $n = 3$) using USP XXII paddle apparatus (50 rpm). Samples (10 ml) were withdrawn at predetermined intervals and assayed spectrophotometrically after they were filtered through a 0.45-μm membrane filter. The data (absorbance values) were converted into percent drug dissolved using the regression equation generated for the standard curve. The same volume (10 ml) of fresh dissolution medium was added to the test medium. The time required for 80% drug to dissolve (t_{80}) for all the batches was calculated by fitting the Higuchi model (10). The results are depicted in Table 1. The tablets of batch 2 were also evaluated at 100 rpm to investigate the effect of agitation rate on the drug release and also in simulated gastric fluid (pH 1.2).

Radial and Axial Swelling Study (11)

The initial diameter and height of the tablets of batch 2 were measured and the tablets were then kept in the dissolution medium (30 ml). The increase in height and diameter was measured at selected time intervals of 0.5–8 hr. To evaluate the relaxation, the equilibrium degree of swelling (Q) was calculated from radial and axial swelling ratio [$Q = V_t/V_0 = (R_t/R_0)^2 \times (I_t/I_0)$]. The V_t and V_0 are volumes, R_t and R_0 are radii, and I_t and I_0 thickness at time t and time zero, respectively. The calculated values are shown in Table 2.

Table 2

Radial and Axial Swelling of Tablets (Batch 2) in Distilled Water

Time (hr)	Diameter (mm)	Thickness (mm)	Normalized Values		
			Diameter	Thickness	Volume (Q)
0	8	3	1	1	1
0.5	9.5	3.5	1.19	1.17	1.65
1	10	5	1.25	1.67	2.60
2	11	6.5	1.38	2.17	4.10
3	12	7	1.50	2.33	5.25
4	12	7	1.50	2.33	5.25
5	12	7.5	1.50	2.50	5.63
6	12.5	7.5	1.56	2.50	6.10
7	12.5	7.5	1.56	2.50	6.10
8	12.5	8	1.56	2.67	6.51

Normalized diameter = diameter at time t/diameter at time zero.
Normalized thickness = thickness at time t/thickness at time zero.

RESULTS AND DISCUSSION

The results of swelling capacity are shown in Table 1. The value of swelling capacity of untreated ispaghula husk was found to be 19, but the gel structure disrupted in rigid gel formation study. The poor gel formation tendency of untreated ispaghula husk may be attributed to incomplete swelling. Moreover, the tablets prepared using untreated ispaghula were found to be soft. The average hardness of the tablets was found to be 2.5 kg/cm^2. It is reported that the untreated husk powder exhibits poor binding power (12). Hence, it was decided to modify ispaghula husk using thermal treatment. The samples of ispaghula that were exposed to hot air treatment exhibited swelling but they did not exhibit rigid gel formation; an essential criterion for obtaining sustained drug release. Hence, it may be concluded that the selected hot air treatment does not yield a product suitable for obtaining sustained drug release. It is reported that on prolonged heating, degradation might take place, and a network of polysaccharide molecules is not obtained (13,14).

All the microwave oven treated samples exhibited superior swelling and rigid gel formation in distilled water and simulated gastric fluid (pH 1.2). The samples showed almost identical swelling in distilled water and simulated gastric fluid (pH 1.2). They were used for making the tablets of diltiazem hydrochloride. The data presented in Table 1 reveal that batches with different swelling capacities exhibited different t_{80}. The probable reason might be the formation of a matrix of different porosities on coalescence of swollen particles of ispaghula husk.

Optimization Study

The attribute selected for the present optimization set was t_{80}. The t_{80} values were calculated using the Higuchi model (10). A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

where Y is the dependent variable (t_{80}), b_0 is the arithmetic average of nine responses, and b_i is the estimated coefficient for the factor X_i. The X_1X_2 and X_i^2 are the interaction and polynomial terms, respectively. The t_{80} values showed a wide variation from a minimum of 5.41 hr to a maximum of 9.34 hr, indicating that the selected variables have some influence on the t_{80} values.

A polynomial equation [full model, Eq.(2)] was generated by carrying out multiple linear regression to quantitatively explain the effect of the independent variables on the selected attribute (i.e., t_{80}).

$$t_{80} = 8.575 + 0.745X_1 - 0.701X_2 + 0.6X_1X_2 - 1.038X_1^2 - 0.118X_2^2 \quad (2)$$

The calculated value of F (8.51) was found to be less than the critical value of F ($F_{5,3} = 9.01$). The ANOVA for full model is significant at $p > 0.05$.

To identify the dominant factors affecting t_{80}, the data were analyzed by applying Student's t-test. The term X_2^2 showing the least absolute t-value was omitted from the regression equation in order to generate the reduced model [Eq. (3)]. The results of t-statistics for the reduced model revealed that the remaining terms are statistically significant.

$$t_{80} = 8.575 + 0.744X_1 - 0.702X_2 + 0.597X_1X_2 - 1.037X_1^2 \quad (3)$$

The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the sign it carries, i.e., positive or negative. The R^2 value for the reduced model was found to be 0.9311, indicating a good fit. The calculated F-value (13.52) was found to be significant at $p < 0.05$. Hence, it can be concluded that Eq. (3) can be used for prediction of t_{80}. The results of multiple linear regression analysis and ANOVA are summarized in Table 3.

The reduced model is depicted in a contour plot in Fig. 1. The figure shows that the relationship is nonlinear, since X_1^2 is found to be statistically significant. The drug release pattern may be changed by appropriate selection of the levels of X_1 and X_2. Different combinations of X_1 and X_2 can yield the same t_{80} value (e.g., 9 hr). The final selection can be made after considering other aspects such as color of the products, energy consumption, time required for modifications, etc.

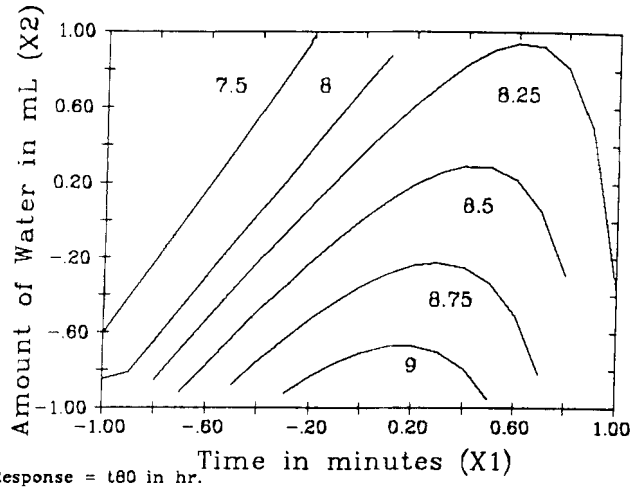

Figure 1. Contour plot for time for 80% drug dissolution (t_{80}).

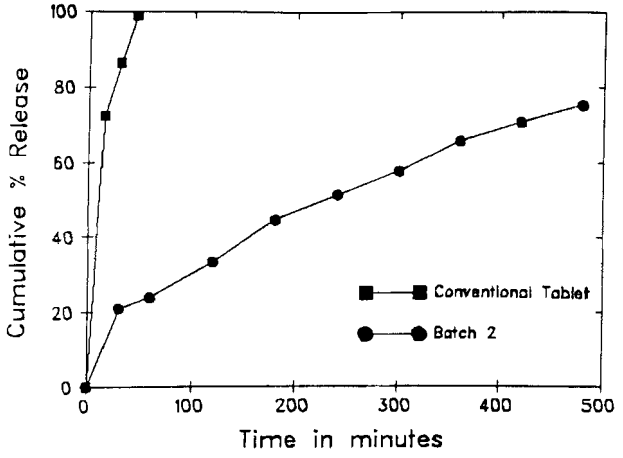

Figure 2. Drug release profiles from Batch 2 and Conventional tablet formulations.

Dissolution Study

Batch 2 (t_{80} = 9.34 hr at 50 rpm) seems to be a promising candidate for achieving the drug release up to 12 hr. Hence, it was selected for further studies. The dissolution data of batch 2 and conventional diltiazem hydrochloride tablets are shown in Fig. 2. The hardness of the tablets (batch 2) was found to be 5.2 kg/cm^2. The

Table 3

Summary of Results of Regression Analysis and ANOVA for Measured Response

Response [t_{80}]		b_0	b_1	b_2	b_{11}	b_{12}	b_{22}
Full model (FM)		8.575	0.745	-0.701	-1.038	-0.6	-0.118
Reduced model (RM)		8.502	0.744	-0.702	-1.037	0.597	-
			DF	SS	MS	F	R^2
Regression	FM		5	9.908	1.981	8.51	0.9341
	RM		4	9.88	2.47	13.52	0.9311
Error	FM		3	0.698	0.232		
	RM		4	0.726	0.181		

DF = degrees of freedom; SS = sum of squares; MS = mean square.

in vitro release profile was not significantly altered by the dissolution medium (t_{80} = 9.48 hr in the acidic medium) or rate of paddle rotation (t_{80} = 9.25 hr at 100 rpm). The probable reasons for imparting sustained-release characteristics are hydration of particles and network formation between long chain polysaccharide molecules (14).

Radial and Axial Swelling

The results of swelling studies are depicted in Table 2. It was observed that the tablets containing ispaghula husk (batch 2) swelled more axially than radially. This is evident from the data of normalized diameter and thickness. After 8 hr, the normalized diameter was found to be 1.56, whereas the normalized thickness was found to be 2.67. The values of normalized volumes were calculated using normalized values of diameter and thickness. Two distinct phases were noted in a plot of time and normalized volume (Q). The value of Q increased steeply up to 3 hr into the test. A good correlation was observed between the data of time (up to 3 hr) and Q (R^2 = 0.9941). After 3 hr into the test, significant increase in Q was not noticed. The probable reason for the slower swelling in terminal phase may be attributed to decreased diffusion of the water in the matrix. It is reported that on hydration, HPMC matrices expand in the axial direction much more than in the radial direction (15,16).

Mechanism of Drug Release

The method of Bamba et al. was adopted for deciding the most appropriate model (17). The dissolution data of batch 2 was fitted to zero-order ($m = b_0t + a_0$), first-order ($\ln m = -bt + a$), Higuchi (10), Hixon–Crowell ($3\sqrt{100} - \sqrt{m} = kt$), Weibull ($m = 1 - \exp[-(t - t_1)^{b/a}]$, and Korsemeyer and Peppas ($M_t/M = kt^n$) models to study the mechanism of drug release. The results of F-statistics were used for the selection of the most appropriate mechanism. The goodness of fit test (F-ratio) indicated insignificant difference between Higuchi, Korsemeyer, and first-order models. However, priority should be given to the model with the lowest F-value. The F-value was found to be lowest with the Higuchi model (4.51) as compared to Korsemeyer (6.38) and first-order models (13.87). Thus, it may be concluded that the drug release from the matrix tablet containing microwave oven treated ispaghula husk is best explained by the Higuchi model (10).

CONCLUSION

This study demonstrates that microwave oven treated ispaghula husk can be used as a hydrophilic matrixing agent. The heating condition was optimized using factorial design by fitting second-order model. The tablets of diltiazem hydrochloride were prepared by wet granulation technique. The tablets swelled considerably and did not erode during in-vitro dissolution testing. The systematic formulation approach enables us to develop sustained-release diltiazem tablets using a relatively inexpensive, naturally biocompatible material.

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