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RESEARCH PAPER

Development of Modified Release Diltiazem HCl Tablets Using Composite Index to Identify Optimal Formulation

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ABSTRACT

This article reports the preparation of tartaric acid treated ispaghula husk powder for the development of modified release tablets of diltiazem HCl by adopting direct compression technique and a 3^2 full factorial design. The modified ispaghula husk powder showed superior swelling and gelling as compared to untreated powder. Addition of compaction augmenting agent such as dicalcium phosphate was found to be essential for obtaining tablets with adequate crushing strength. In order to improve the crushing strength of diltiazem HCl tablets, to modulate drug release pattern, and to obtain similarity of dissolution profiles in distilled water and simulated gastric fluid (pH 1.2), modified guar gum was used along with modified ispaghula husk powder and tartaric acid. A novel composite index, which considers a positive or a negative deviation from an ideal value, was calculated considering percentage drug release in 60, 300, and 540 min as dependent variables for the selection of a most appropriate batch. Polynomial equation and contour plots are presented. The concept of similarity factor (f_2) was used to prove similarity of dissolution in water and simulated gastric fluid (pH 1.2).

Key Words: Modified ispaghula husk powder; Modified guar gum; Tartaric acid; Factorial design; Composite index.

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INTRODUCTION

Oral drug delivery systems continue to dominate the market despite the advancements made in newer drug delivery systems such as transdermal, liposomes, microspheres, etc. Hydrophilic matrix tablets are preferred for obtaining sustained action, as they are relatively simple to formulate, are inexpensive, versatile, and utilize conventional processing equipments.

Natural materials such as alginates, carrageen, ispaghula husk (dried seed coat of *Plantago ovata*) and guar gum are promising matrix carriers for obtaining sustained drug release. Ispaghula husk (*Psyllium husk*) is official in IP, BP, and USP. It is used in food and pharmaceuticals at a dose of 5–7 g twice a day. The husk is available in the Indian market at Rs. 100/kg ($\simeq$ 2$/kg). The husk forms a swollen gel when kept in contact with water, but the gel disrupts on shaking. Ispaghula husk powder has been used by researchers for the development of modified release dosage forms.[1,2] Its characteristics were modified by our team using heat treatment[3] or succinic acid and alcohol treatment.[4] The modified ispaghula husk powder was used as a sustained release matrixing agent.

Guar gum is an interesting adjuvant for preparation of hydrophilic matrix tablets because of its unique properties such as swelling, gel formation, nontoxicity, and biodegradability. Guar gum is found in the seeds of the plant *Cyamopsis tetragonolobus*. Investigators have used guar gum, either alone[5,6] or in combination,[7,8] for fabricating sustained release dosage forms. Its characteristics can be modified by thermal or chemical treatment for successful use in modified release preparations.[9,10] Tablets containing guar gum or modified guar gum showed slow drug release in our earlier studies. An uncontrolled rate of hydration and high intrinsic viscosity limits the use of guar gum as a sustained release agent.

Diltiazem HCl, a calcium channel blocker, is prescribed widely 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 make it a suitable candidate for sustained release dosage forms.[11] Hence, it was selected as a model drug. Tartaric acid was included in the formulations to study its buffering effect on the drug dissolution rate at different pH.[12,13]

The present study was undertaken to modify ispaghula husk powder using tartaric acid–alcohol treatment. The acid-treated ispaghula husk powder was used in combination with acid-treated guar gum for the preparation of modified release tablets of diltiazem HCl using a 3^2 full factorial design.

EXPERIMENTAL

Materials

Diltiazem HCl USP, ispaghula husk powder I.P. (100 #), and guar gum IP were received as generous gifts from Cadila Health Care Pvt. Ltd. Dicalcium phosphate IP (DCP), poly(vinyl pyrollidone) (PVP K30), microcrystalline cellulose (MCC), tartaric acid IP, magnesium stearate IP, and talc IP were used as received. All other solvents and chemicals were of analytical grade and were used without further purification. Deionized double-distilled water was used throughout the study. The process of modification of guar gum is reported in our earlier communication.[14]

Methods

Preparation of Modified Ispaghula Husk Powder

Two grams tartaric acid was dissolved in 15 mL of absolute alcohol. Eight grams ispaghula husk powder was uniformly dispersed in the alcoholic solution. The resultant mixture was stirred for 15 min at room temperature and then dried in a hot air oven at 50°C. The dried mass was pulverized and passed through a No. 100 sieve.

Swelling Capacity

The volume occupied by 1 g of dried matrixing agent was measured in a 10 mL-capacity graduated measuring cylinder. Water was added in sufficient quantity to the cylinder and after 24 hr, the volume of the swollen matrixing agent was measured. Swelling capacity was calculated by taking the ratio of swollen volume to the initial volume.

Gel Formation Study

One gram matrixing agent 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.

Preparation of Diltiazem HCl Tablets

The required quantities of diltiazem HCl, modified ispaghula husk powder (100 #) and/or modified guar gum (100 #), poly(vinyl pyrollidone) (10% w/w), and DCP were physically admixed. Tartaric acid was included in the nine batches of factorial design. The powder blend was then lubricated with 1% w/w talc and 2% w/w magnesium stearate. Lubrication was done in a glass jar for 2 min. Each tablet contained 90 mg of the drug. The tablets were prepared by direct compression on a rotary tablet press (Cadmach, Ahmedabad), fitted with concave punches of 9 mm diameter. The turret was rotated at a fixed speed of 30 rpm. The composition of the preliminary batches (A1 to A8) and the results of their dissolution studies are shown in Table 1. The composition of the nine batches of the factorial design and the results of their dissolution studies are shown in Table 2.

Dissolution Study

The drug release study was carried out using USP XXIII paddle apparatus at $37 \pm 0.5^{\circ}C$ and at 50 rpm using 900 mL distilled water or simulated gastric fluid (pH 1.2) as dissolution medium ($n = 5$). Five milliliters sample solution was withdrawn at predetermined time intervals, filtered through a 0.45-μm membrane filter, diluted suitably, and analyzed spectrophotometrically at 237 nm using a Hitachi U-2000 UV-Vis double beam spectrophotometer. Equal amounts of fresh dissolution medium was replaced immediately after withdrawal of a test sample. The percentage drug dissolved at different time intervals was calculated using regression equation generated from the standard curve.

Friability Tests

Friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, Mumbai) for 4 min at 25 rpm. The tablets then were dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability.

Full Factorial Design

A 3^2 randomized full factorial design was utilized in the present study. In this design, two factors are evaluated, each at three levels, and experimental trials are carried out at all nine possible combinations. The ratio of modified guar gum to modified ispaghula (X_1) and amount of tartaric acid (X_2) were selected as independent variables. The time required for 80% drug dissolution (t_{80}) and percentage drug released in 60 min (Y_{60}), 300 min (Y_{300}), and 540 min (Y_{540}) were selected as dependent variables.

RESULTS AND DISCUSSION

The swelling capacity of untreated ispaghula husk powder was found to be 10. The sample formed a weak gel structure as determined by the gel formation study. The poor gel formation tendency of the untreated ispaghula husk powder may be attributed to incomplete wetting. Moreover, the tablets prepared

Table 1. Formulation of tablets and t_{80} of preliminary batches.

Batch code	Amount of modified guar gum (mg)	Amount of modified ispaghula (mg)	t_{80}[a] in distilled water (min)	t_{80} in simulated gastric fluid (min)
A1	135	0	604	594
A2	108	27	597	587
A3	81	54	584	578
A4	67.5	67.5	560	555
A5	54	81	510	503
A6	27	108	566	561
A7	13.5	121.5	589	575
A8	0	135	636	624

[a]t_{80} = time required for 80% drug dissolution.

Table 2. Formulation and dissolution characteristics of batches in a 3^2 full factorial design.

Batch code	Variable level in coded form		t_{80} (min)	% drug release in distilled water		
	X_1	X_2		Y_{60}	Y_{300}	Y_{540}
D1	−1	−1	699	19.6	50.4	67.1
D2	−1	0	651	19.4	50.9	70.6
D3	−1	1	578	21.2	62.2	86.4
D4	0	−1	658	20.4	49.6	72.3
D5	0	0	614	20.6	52.8	74.5
D6	0	1	587	21.8	55.7	76.7
D7	1	−1	574	23.5	61	73.7
D8	1	0	526	24.5	60.1	81.1
D9	1	1	425	25.4	60.8	97.7

Coded values	Actual values	
	X_1	X_2
−1	0:135	30
0	67.5:67.5	60
1	135:0	90

Note: All the batches contained 90 mg diltiazem HCl and 90 mg dicalcium phosphate.
X_1: Ratio of modified guar gum to modified ispaghula.
X_2: Amount of tartaric acid (mg).

using untreated ispaghula were found to be highly friable (>1%). The average crushing strength of the tablets was found to be $2\,kg/cm^2$ as measured by Monsanto hardness tester. Complete drug release was noted within 2 hr from tablets containing 90 mg ispaghula husk powder and 90 mg diltiazem HCl. The addition of water-insoluble diluents like MCC and DCP did not have significant effect on the drug release. It may be concluded that untreated ispaghula husk powder is unsuitable as a sustained release matrixing agent for diltiazem tablets. Hence, modification of ispaghula husk powder was carried out with the intention of obtaining sustained drug release.

Modification of Ispaghula

Modified ispaghula husk powder exhibited a high swelling capacity (1.5 times as compared to the untreated ispaghula husk powder). The swelling of the matrixing agent results in the alteration of the pore structure of a tablet. Pina et.al. stated that drug dissolution rate can be slowed by increasing the gel layer viscosity, which is dependent on the molecular weight of the polymer.[15] The modified sample also showed improved gelling (rigid gel) as compared to that of untreated ispaghula husk powder (easily redispersible weak gel). The gelling tendency plays a critical role in controlling the drug release by diffusion mechanism.

Confirmation of the Modification by IR Analysis

Ispaghula has some free hydroxyl groups, which can be easily esterified with aliphatic carboxylic acids. As tartaric acid has two free carboxyl groups, there is a possibility that only one carboxyl group will take part in ester formation and the other will remain as a free acid. Presence of sharp peak at 1710 and $1740\,cm^{-1}$ in IR spectra strongly suggests the presence of two carbonyl groups in different forms. One is in the form of carboxyl ($1710\,cm^{-1}$) and the other is in the form of ester group ($1740\,cm^{-1}$). The treated sample was thoroughly washed with alcohol to remove the untreated tartaric acid and the presence of free carboxyl group was confirmed by chemical test ($NaHCO_3$).

The tablets of diltiazem HCl, prepared using modified ispaghula husk powder (90 mg) and diltiazem HCl (90 mg), exhibited a decrease in the crushing strength (3 to $1\,kg/cm^2$) on storage for 24 hr, probably because of stress relaxation. Thus, DCP was included

in the formulation to augment compaction. The crushing strength of the tablets did not decrease after incorporation of DCP. Hence, 90 mg DCP was included in the further trials. In order to investigate the effect of amount of modified ispaghula husk powder on drug release, three batches, 11, 12, and 13, were prepared using 100, 130, and 150 mg modified ispaghula husk powder and 90 mg of DCP. The tablets were subjected to dissolution studies. The time required for 80% drug dissolution (t_{80}) was found to be 417, 680, and 962 min, respectively, for batches 11, 12, and 13. The results of dissolution studies revealed that modulation of drug release could be achieved by varying the quantity of modified ispaghula husk powder.

Modified ispaghula husk powder possessed poor compressional characteristics (crushing strength 3 kg/cm^2). To improve compressional characteristics, modified guar gum was used in combination with modified ispaghula husk powder. The blend yielded tablets with crushing strength >5 kg/cm^2. Modified ispaghula husk powder gives a relatively slower drug release as compared to modified guar gum (see Table 1, batches A1 and A8, and Table 2, batches D1 and D7). Thus, by using a combination of both the matrixing agents, one could achieve a desired release pattern.

Batches A1 to A8 were prepared using different combinations of modified ispaghula husk powder and modified guar gum. The formulation of the batches and t_{80} results are shown in Table 1. An ideal modified release dosage form should release loading dose (20–25, i.e., average 22.5%) in the first hour and later (up to 12 hr), the remaining drug should be released at a constant rate (about 7%/hr). An ideal release pattern was calculated as per these set criteria. Thus, ideal t_{80} is 540 min for a formulation that exhibits drug release up to 12 hr. As per US FDA guidelines for f_2 calculations, two dissolution profiles are considered as identical if calculated f_2 value is greater than or equal to 50. This value is calculated considering 10% deviation between a reference and a test formulation. Thus, $\pm$10% range from ideal profile has been used for arbitrary selection of the optimal batch. Thus, for t_{80} a range of 480 to 590 min was selected. The dissolution study of batches A1 to A8 was carried out in distilled water and simulated gastric fluid. The t_{80} of the batches was found to be different in both dissolution media. Batch A4 showed least deviation in t_{80} in both dissolution media. Inspection of the dissolution profile of batch A4 in distilled water and simulated gastric fluid revealed that the dissolution profile did not overlap each other (Fig. 1). The difference and

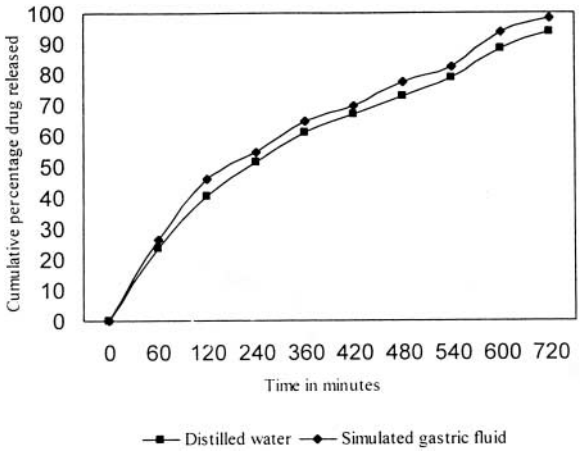

Figure 1. Comparative dissolution profiles of batch A4.

similarity equations are given in the US FDA (1997) guidelines for industry for dissolution testing of immediate release products. The value of the similarity factor (f_2) is equal to 100 when the two dissolution profiles are identical. The method was used here to observe the difference in dissolution. The time points used for calculation of f_2 metrics were 60, 120, 180, up to 540 min (i.e., every hour up to 9 hr). The f_2 value for the drug release profile of batch A4 in distilled water and simulated gastric fluid was found to be 48.58, which indicates that the difference is significant at an average difference of no more than 10% at any sampling time point. [A value of $\geq$50 is necessary for similarity in dissolution profiles at 10% difference.[16]] Thus, tartaric acid was included in the formulations to achieve the same rate of drug dissolution for both media.

Factorial Design

A 3^2 full factorial design was constructed to study the effect of ratio of modified guar gum to modified ispaghula husk powder (X_1) and amount of tartaric acid (X_2) on the drug release of diltiazem HCl tablets. The dependent variables chosen were, t_{80}, Y_{60}, Y_{300}, and Y_{540}, i.e., percentage drug release in 60, 300, and 540 min.

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, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The t_{80} value for the nine batches (D1 to D9) showed a wide variation (425 to 699 min). The data clearly indicate that the t_{80} values are strongly dependent on the selected variables. The fitted equation relating the response t_{80} to the transformed factor is shown in Eq. (2).

$$t_{80} = 626.64 - 67.26X_1 - 56.94X_2 - 7.16X_1X_2 - 43.65X_1^2 - 10.15X_2^2 \quad (r^2 = 0.9660,\ \mathrm{DF} = 8,\ F = 17.06) \qquad (2)$$

The value of correlation coefficient was found to be 0.9660, indicating a good fit. Equation (2) may be used to obtain reasonable estimate of the response since small error of variance was noticed in the replicates. Batches D3, D6, D7, and D8 met the set criteria of t_{80}, i.e., $490 < t_{80} < 590$. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e., positive or negative.

Figure 2 shows the plot of t_{80} vs. the ratio of modified guar gum to modified ispaghula (X_1) and amount of tartaric acid (X_2). The plot was drawn using Sigma Plot® software. The data demonstrate that both the factors (X_1 and X_2) affect the drug release (t_{80}). It may also be concluded that low level of X_1 (ratio of modified guar gum and modified ispaghula, i.e., low level of guar gum) and low level of X_2 (amount of tartaric acid) favor the preparation of sustained release diltiazem HCl tablets. The low value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 is not significant. One can conclude that the drug release pattern may be changed by appropriate selection of the levels of X_1 and X_2.The final selection can be done after considering the other aspects such as dissolution pattern, tablet characteristics, etc.

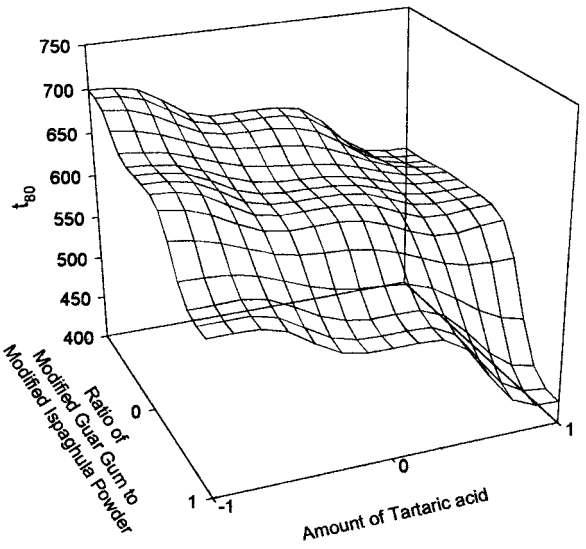

Figure 2. Response surface plot for t_{80}.

The following additional constraints were chosen for the selection of best batch; $12.5\% < Y_{60} < 32.5\%$; $40\% < Y_{300} < 60\%$; $69\% < Y_{540} < 89\%$. The tablets of batch D6 fulfilled the additional selection criteria. It is interesting to note that D7 and D8 are borderline cases. For the selection of a batch from the lot of D6, D7, and D8, another tool was applied to identify the best batch.

Composite Index

A weighted composite index was generated to designate a single score utilizing all the three constraints, i.e., Y_{60}, Y_{300}, and Y_{540}. Many researchers have used the technique of multiple responses for optimization studies. Derringer and Suich illustrated how several response variables can be transformed into a desirability function.[17] The applications of one-sided transformations are also demonstrated by different researchers.[18–20] Ogawa et al. demonstrated the application of generalized distance function to incorporate several objectives into a single function.[21] As the relative contribution of each individual constraint to the ''true'' composite score was unknown, a decision was made to assign an arbitrary value of one-third to each of the three dependent variables.[22] Since a higher or a lower value of Y_{60}, Y_{300}, and Y_{540} may not be desirable, an ideal is most suitable (Table 3). The, empirical composite index was devised to yield a score of 100 for an optimum result for each of the three variables and each test result was transformed to a value between 0 and 33.33. Equations were evolved for the three constraints for higher than ideal and lower than ideal values (Table 3). The respective equations were used for calculating the transformed values. The raw data transformations (refer to Table 3 for sample calculations) and summations are shown in the Table 3. The batch having a highest composite index would be considered as a

Table 3. Composite index.

Batch no.	Y_{60}	Transformed Y_{60}	Y_{300}	Transformed Y_{300}	Y_{540}	Transformed Y_{540}	CI	Rank
D1	19.6	23.66	50.4	32.00	67.1	0	55.66	6
D2	19.4	23.00	50.9	30.33	70.6	5.12	58.45	4
D3	21.2	29.00	62.2	0.00	86.4	8.67	37.66	8
D4	20.4	26.33	49.6	32.12	72.3	10.78	69.23	2
D5	20.6	27.00	52.8	24.00	74.5	18.11	69.10	3
D6	21.8	31.00	55.7	14.33	76.7	25.43	70.76	1
D7	23.5	30.00	61	0.00	73.7	15.44	45.44	7
D8	24.5	31.66	60.1	0.00	81.1	26.33	52.89	5
D9	25.4	33.00	60.8	0.00	97.7	0	23.66	9

CI = Composite index = transformed Y_{60} + transformed Y_{300} + transformed Y_{540}.
Note: Values above and below the specified range are considered as 0.

Variable name	Ideal	Range
Y_{60}	22.5	12.5 to 32.5
Y_{300}	50	40 to 60
Y_{540}	79	69 to 89

Sample calculation for calculating composite index for Y_{60}.

Considering range below ideal

X (Observed Y_{60})	Y (Transformed Y_{60})
12.5	0
22.5	33.33

Performing linear regression.
Transformed $Y_{60} = 3.333 \times X + (-41.6625)$.
Since Y_{60} for batch D1 (19.6) is *below ideal* we use above equation.
Transformed $Y_{60} = (3.333 \times 19.6) - 41.6625$.
Transformed $Y_{60} = 23.66$.

Considering range above ideal

X (Observed Y_{60})	Y (Transformed Y_{60})
22.5	33.33
32.5	0

Performing linear regression.
Transformed $Y_{60} = -3.333 \times X + (108.3225)$.
Since Y_{60} for batch D7 (23.5) is *above ideal* we use.
Transformed $Y_{60} = (-3.333 \times 23.5) + 108.3225$.
Transformed $Y_{60} = 30$.

batch fulfilling all the constraints favorable for a 12-hr sustained release of diltiazem HCl tablets.

The batches are ranked from 1 to 9 as per highest value of composite index and batch D6 with a composite index of 70.76 was ranked as the best batch. Batches D7 and D8 showed poor score in composite index. It indicates higher deviation from ideal than batch D6. The results of this study demonstrate that the composite index is a reasonable approach to the quantification of sustained release of diltiazem HCl tablets. This approach also provides a better characterization of sustained release than an individual test and is based on simple reliable tests.

Table 4. Results of regression analysis for dependent variables.

Dependent variable	b_0	b_1	b_2	b_{12}	b_1^2	b_2^2	log t	r^2
Y_{60}	20.62	2.21	0.82	0.075	1.34	0.47	—	0.9886
Y_{300}	51.36	3.07	2.95	−3.00	4.87	2.02	—	0.9444
Y_{540}	72.11	4.73	7.95	1.18	4.93	3.58	—	0.8403
Y_t	−96.88	2.45	1.91	−0.57	0.57	3.50	61.90	0.9127

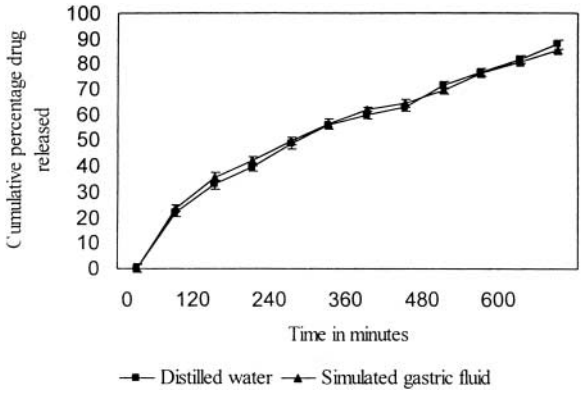

Figure 3. Comparative dissolution profiles of batch D6.

The dissolution data of batch D6 was compared with the ideal release profile using f_2 statistics. An f_2 value of 72.23 indicates that the release profile of batch D6 was comparable with the ideal batch. A value of ≥ 50 is necessary for similarity in dissolution profiles at 10% difference. The results of multiple linear regression for the responses Y_{60}, Y_{300}, and Y_{540} are shown in Table 4. The high value of r^2 indicates a good fit.

The drug release of the best batch D6 was conducted in distilled water and simulated gastric fluid (pH 1.2). Figure 3 depicts the dissolution profiles of batch D6 in both media. The dissolution data of batch D6 in distilled water were compared with the dissolution data in simulated gastric fluid using f_2 statistics. An f_2 of 83.80 indicates that the release profile of batch D6 in distilled water and simulated gastric fluid are comparable.

Kinetics of Drug Release

The method of Bamba and Puisieusx[23] was adopted for deciding the most appropriate model. The dissolution data of best batch D6 were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas, and Weibull models. The results of *F*-statistics were used for the selection of the most appropriate model. The release profile of the best batch D6 fitted best to Korsemeyer and Peppas equation ($F = 2.25$), showing the least residual sum of square as compared to Higuchi ($F = 5.42$) and Hixson-Crowell ($F = 11.95$) model. This superiority is however statistically insignificant among these three models as shown by the goodness of fit test (*F*-ratio test). But the priority should be given to the model with the least *F*-value. Thus, it may be concluded that the drug release from modified release diltiazem HCl tablets is best explained by Korsemeyer and Peppas model. The values of slope and intercept for the Korsemeyer and Peppas model are 0.5717 and −1.6798, respectively.

Prediction of Dissolution Profile

Peck and coworkers[24] used a mathematical relationship for the expression of dissolution profile from matrix tablets. An effort is made in the present investigation to derive a similar relationship. A linear interactive model was evolved using data of percentage drug released at 60, 120, 180, 240, 300, 360, 420, and 540 min from all nine batches. The Korsemeyer and Peppas model fitted well to the data set and hence log time was chosen as an additional independent variable. The multiple linear regression analysis was performed (Microsoft EXCEL®) using the actual values to derive the equation. The derived equation describing the dissolution profile is shown in Table 4 where Y is the percentage drug dissolved at time t. The r^2 was found to be 0.9554 indicating a good fit. The F test was found to be significant at $p < 0.05$. The actual dissolution profile of batch D6 compared quite well with calculated profile as per the derived equation (Fig. 4).

CONCLUSIONS

The study demonstrates that tartaric acid treated ispaghula husk powder can be used as a hydrophilic

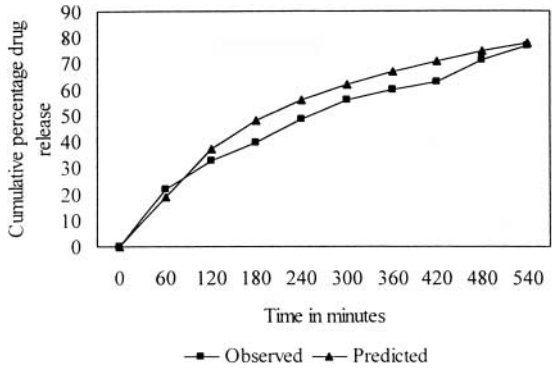

Figure 4. Dissolution profiles of ideal batch D6.

matrixing agent. To improve compressional characteristics, it was used in combination with dicalcium phosphate. Slower drug release was seen from tablets containing ispaghula as compared to guar gum. Different ratios of both matrixing agents showed a significant effect on the t_{80}. Results of factorial design study revealed that low level of X_1 (low level of guar gum) and low level of X_2 (amount of tartaric acid) favor the preparation of modified release diltiazem HCl tablets. Composite index, a mathematical tool, was useful for identifying the best batch. The drug release pattern of the best formulation in distilled water and simulated gastric fluid were comparable. The systematic formulation approach enabled us to develop modified release diltiazem HCl tablets using relatively inexpensive, naturally occurring biocompatible materials.

REFERENCES

1. Jain, N.K.; Kulkarni, K.; Talwar, N. Controlled release tablet formulation of isoniazid. Pharmazie **1992**, *47* (4), 277–278.
2. Gohel, M.C.; Jani, G.K.; Patel, N.K.; Gondaliya, D.P. Optimisation of hydrophilic matrix tablet formulation of diclofenac sodium using a mixture design. Pharm. Pharmacol. Comm. **1998**, *4* (9), 433–438.
3. Gohel, M.C.; Patel, K.V. Formulation optimisation of diltiazem-HCl matrix tablets containing modified ispaghula husk using factorial design. Drug Dev. Ind. Pharm. **1997**, *23* (11), 1055–1061.
4. Gohel, M.C.; Amin, A.F.; Chhabaria, M.T.; Panchal, M.K.; Lalwani, Anita. Modulation of drug release rate of diltiazem-HCl from hydrogel matrices of succinic acid-treated ispaghula husk. Pharm. Dev. Technol. **2000**, *5* (3), 375–381.
5. Khullar, P.; Khar, R.K.; Agrawal, S.P. Evaluation of hydrogel-based controlled-release niacin tablets. Drug Dev. Ind. Pharm. **1998**, *24* (5), 479–483.
6. Kuhrts, E.H.; Friend, D.R.; Parasrampuria, K.Yu.J. Sustained release drug delivery employing a powdered hydrocolloid gum obtainable from higher plants. PCT Int. Appl. WO96 **1996**, *16*, 638.
7. Bhalla, H.L.; Shah, A.A. Controlled release matrices for ketoprofen. Indian Drugs **1991**, *28* (9), 420–422.
8. Jain, N.K.; Kulkarni, K.; Talwar, N. Controlled-release tablet formulation of isoniazid. Pharmazie **1992**, *47* (4), 277–278.
9. Misra, A.N.; Baweja, J.M. Modified guar gum as hydrophilic matrix for controlled release tablets. Indian Drugs **1997**, *34* (4), 216–223.
10. Gohel, M.C.; Amin, A.F.; Panchal, M.K.; Momin, M.; Bajaj, S.; Lalwani, A. Preliminary investigation in matrix based tablet formulation of diclofenac sodium containing succinic acid treated guar gum. Boll. Chim. Farm. **1998**, *137* (6), 198–203.
11. Khan, M.Z.I. Recent trends and progress in sustained or controlled oral delivery of some water-soluble drugs: morphine salts, diltiazem and captopril. Drug Dev. Ind. Pharm. **1995**, *21* (9), 1037–1070.
12. Venkatesh, G.M. Development of controlled release SK & F 82526-J, buffer bead formulations with tartaric acid as a buffer. Pharm. Dev. Technol. **1998**, *3*, 477–485.
13. Gabr, K.E. Effect of organic acids on the release patterns of weakly basic drugs from inert sustained release matrix tablets. Eur. J. Pharm. Biopharm. **1992**, *38*, 199–202.
14. Gohel, M.C.; Patel, M.M. Release rate modulation of diltiazem HCl from hydrophilic matrix of tartaric acid treated guar gum. Int. J. Pharm. Excipients **2001**, *3* (2), 39–45.
15. Salsa, T.; Veiga, F.; Pina, M.E. Drug Dev. Ind. Pharm. **1997**, *23* (9), 929–938.
16. Shah, V.P.; Tsong, Y.; Sathe, P.; Liu, J. In vitro dissolution comparison—statistics and analysis of the similarity factor, f_2. Pharm. Res. **1998**, *15* (6), 889–896.
17. Derringer, G.; Suich, R.; Simultaneous optimization of several response variables. Journal of Quality Technology **1980**, *12* (4), 214–219.
18. Bodea, A.; Leucuta, S.E. Drug Dev. Ind. Pharm. **1998**, *24* (2), 145–155.

19. Robert Lu, D.; Abu-Izza, K.; Chen, W. Pharm. Tech. **1996**, *1* (4), 405–414.
20. Wang, Y. Min.; Sato, H.; Adachi, I.; Horikoshi, I. J. Pharm. Sci. **1996**, *85* (11), 1204–1210.
21. Shigeo, O.; Toshihiko, K.; Yousuke, M.; Masaharn, M.; Hiroshima, S.; Kozo, T.; Nagai, T. J. Pharm. Sci. **1994**, *83* (3), 439–443.
22. Taylor, M.; Ginsburg, J.; Hickey, A.; Gheyas, F. Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development. Pharm. Sci. Tech. **2000**, *1* (3), 18.
23. Bamba, M.; Puisieusx, F. Int. J. Pharm. **1979**, *2*, 307–315.
24. Peck, G.E.; Johnson, A.D.; Aderson, V.L. A statistical approach for the development of an oral controlled-release matrix tablets. Pharm. Res. **1990**, *7*, 1092–1097.