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Application of Simplex Lattice Design to the Preparation of Sustained-Release Diltiazem Hydrochloride Tablets using Modified Guar Gum

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Modified guar gum was used as a matrixing agent to develop sustained-release tablets of diltiazem hydrochloride. Modified guar gum was a combination of guar gum and lactic, citric, or tartaric acid. The lactic acid modified guar gum exhibited improved swelling characteristics at pH 1.2 and 7 as compared to that of the untreated guar gum. Seven formulations were prepared according to the simplex lattice design. The amount of modified guar gum, untreated guar gum, and dicalcium phosphate dihydrate were chosen as independent variables. The time required for 80% drug dissolution (t_{80}) in distilled water was selected as the dependent variable and a response equation with interaction terms was generated. A mathematical model was evolved to describe the dissolution profile using log time as an additional independent variable. The kinetics of drug release is explained by Korsemeyer and Peppas model.

Diltiazem hydrochloride, a calcium channel blocker, is widely prescribed for the treatment of angina pectoris, arrhythmia, and hypertension[1]. Its high aqueous solubility, short elimination half-life (3-5 h), and use in chronic diseases makes it a suitable candidate for prolongation of its release from dosage forms[2,3]. From a practical pharmaceutical viewpoint, matrix tablets containing gums are preferred for oral drug delivery because of ease in controlling the drug release rate and predictable drug release. Guar gum is an inexpensive, biodegradable adjuvant. It is official in IP, USP, and NF.

Swelling and gelling tendencies significantly affects the drug release rate from matrix tablets. Hence, guar gum and other adjuvants were screened for swelling and gelling capabilities. Recently, researchers have demonstrated the application of mixture design for developing solid dosage forms[4-6]. Simplex lattice design provides the advantage of changing the quantity of different ingredients in the formulation in a systematic manner, yet keeping their total amount constant[7]. Therefore, this design was chosen in the present study. Seven batches were prepared one at each vertex, one half way between vertices and one at the center point. A polynomial equation, containing seven terms, may be evolved using the values of dependent and independent variables[7].

$$Y = b_a A + b_b B + b_c C + b_{ab} AB + b_{ac} AC + b_{bc} BC + b_{abc} ABC \quad (1)$$

Where Y is the response variable, A, B and C are transformed components (A + B + C = 1) and b_i are regression coefficients.

In the present study, a blend of untreated guar gum and modified guar gum was used as a matrixing agent to develop sustained-release tablets of diltiazem hydrochloride.

EXPERIMENTAL

Diltiazem hydrochloride USP, hydroxypropylmethyl cellulose (HPMC K4M) (Cadila Health Care Pvt. Ltd., Ahmedabad) and guar gum IP (Indian Gums, Mumbai) were received as gift samples. All the other adjuvants such as starch and hydroxyethyl starch (Anil Starch, Ahmedabad); ethylcellulose (CDH Laboratory Reagents,

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Mumbai); sodium alginate (SD's Laboratory Reagents, Mumbai); pectin, talc, magnesium stearate (JC's Chemicals, Vadodhara); carboxymethyl cellulose sodium, methylcellulose, dicalcium phosphate dihydrate (DCP), polyvinylpyrrolidone (Laser Chemicals, Ahmedabad); tragacanth, lactose (Vikas Pharma, Mumbai) and absolute alcohol (Alembic, Vadodhara) were of either pharmacopoeial or analytical grade.

Modification of Adjuvants:

The adjuvant (4 g) was intimately mixed with a blend of 20 ml alcohol and 1 ml lactic acid. Alcohol was allowed to evaporate at room temperature (30 ± 3°) and the mass was dried in a microwave oven for 1 min (Batliboi, Bombay, power setting = 3). Guar gum was also treated in an identical fashion using either 1 g of citric acid or tartaric acid.

Swelling Capacity and Gel Formation Study:

Swelling capacity and gel formation studies were carried out using the procedure described previously[8]. The swelling study was conducted in water and simulated gastric fluid (pH 1.2). The results of swelling study are depicted in Table 1. The untreated adjuvants were also tested.

Assay method:

Aqueous solutions of diltiazem hydrochloride in distilled water were prepared. The absorbance was measured at 237 nm using a Hitachi U-2000 UV-VIS spectrophotometer[9]. Fitting weighted linear regression model to the data obtained in triplicate, a linear equation was generated.

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 # size) were compressed using a 12/32" die and punch assembly on a single punch tablet machine.

Modified Guar Gum/Untreated Guar Gum Tablet (Preliminary Trials and Simplex Lattice Design):

Diltiazem hydrochloride (90 mg), untreated or modified guar gum (90 mg), and DCP (45 mg) were physically admixed and the tablets were prepared by the wet granulation technique using 3% w/v alcoholic polyvinylpyrrolidone solution as a binder. The granules (20/40 # size) were compressed using a 12/32" die and punch assembly on a single punch tablet machine. Four batches were prepared using untreated guar gum, and guar gum modified by lactic, citric or tartaric acid. Seven more batches were prepared according to simplex lattice design as shown in Table 2. The hardness of the tablets was kept in the range of 5.0 ± 0.5 kg/cm^2.

Dissolution study:

Tablets were evaluated for *in vitro* dissolution study in distilled water (900 ml, 37 ± 0.5°, n = 3) using USP XXIII paddle apparatus with a minor modification in the stirring speed (50 rpm)[9]. 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 data. 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 were calculated by fitting the Korsemeyer and Peppas model[10]. The results are depicted in Table 2.

RESULTS AND DISCUSSION

Screening of Adjuvants:

All the adjuvants were screened for swelling and gel formation capabilities. The swelling and gelling capacities were arbitrarily ranked in between very less (+) to excellent (++++) to evaluate the effect of acid-alcohol treatment. Starch and ethylcellulose did not exhibit swelling and gelling. Sodium alginate, pectin, hydroxyethyl starch, carboxymethyl cellulose sodium, and tragacanth showed no gelling. Significant change in swelling or gelling was not observed between untreated and treated HPMC K4M. The treated HPMC K4M showed very less swelling (+) and good gelling (+++). Guar gum and methylcellulose showed improved swelling and gelling capabilities (+++). Guar gum was selected for the present study because it is a natural biocompatible material and is available at a lower price.

Preliminary Trials:

Preliminary trials were conducted using 4 g guar gum, 20 ml alcohol and 1 or 2 ml lactic acid. A control batch was also prepared in which lactic acid was omitted. The control batch showed identical swelling characteristics as compared to that of untreated guar gum. The mass became too tacky in nature and it was also difficult to dry completely when 2 ml of lactic acid was used. Hence, 1 ml lactic acid was used in further trials.

Additional trials were carried out using citric acid and tartaric acid also for preparing modified guar gum. Improved swelling (Table 1) was observed in the trials carried out using different acids. Almost identical swelling was observed at pH 1.2 and 7. Hence, it may be concluded that the modified guar gum may be used as a pH independent matrixing agent.

Tablets containing guar gum modified by lactic or citric acid showed almost similar dissolution profile, but the tablets containing guar gum modified by tartaric acid showed a relatively faster drug release. Citric acid is more hygroscopic in nature than tartaric and lactic acid. Hence, lactic acid was selected for further studies.

Complete drug release was obtained within one hour from the conventional tablets. The drug was released at a very slow rate from the tablets prepared using untreated guar gum (90 mg drug, 90 mg gum and 45 mg DCP) in the terminal phase of the dissolution test i.e. 6 to 8 h, probably because of increased resistance to drug diffusion. The total amount of drug release was found to be 66% after 8 h. On the other hand, the tablets containing modified guar gum (90 mg drug, 90 mg gum and 45 mg DCP) showed burst effect (39% drug release in 1 h) and about 90% of the drug was released in 8 h. Therefore, it was decided to use a blend of untreated and modified guar gum to obtain controlled release for about 12 h. The results of initial trials revealed that the amount of untreated guar gum, modified guar gum and DCP are the three important formulation parameters that may affect the drug release profile. Hence, a simplex lattice design (Table 2) was constructed using these three variables.

Simplex Lattice Design:

The values of t_{80} for the seven batches showed a wide variation from a minimum of 265 min to a maximum of 477 min, indicating that the selected variables have some influence on the t_{80} values (Table 2). To simplify the computations, the actual concentrations were transformed so that the minimum amount corresponds to zero and the maximum amount corresponds to one[7]. The coefficients were calculated using SPSS software by performing multiple regression through the origin. The calculations yielded the following polynomial equation:

$$t_{80} = 477.5A + 393.7B + 302.5C - 681.2AB - 91.2AC + 204.4BC + 2160.3ABC \quad (2)$$

where A, B, and C are transformed amount of modified guar gum, untreated guar gum, and DCP, respectively. The polynomial equation can be used to draw conclusions. The value of coefficient associated with modified guar gum was found to be highest in magnitude amongst the three main effects. However, interaction terms were also found to be significant in nature. The joint effect of these variables can be best interpreted by the help of a contour plot (Fig. 1). The figure shows that faster drug release is obtained if both the modified and untreated guar gum are used at low levels in the design. (See the contour line of 350 min). The results reveal that the formulations should be prepared using higher level of either modified guar gum or guar gum to obtain a higher t_{80} value. The tablets containing higher level of untreated guar gum showed slow drug release in the terminal phase in the *in vitro* dissolution study. It is concluded that the required dissolution pattern can be obtained by using a suitable blend of modified and untreated guar gum. A drug is generally released at a faster rate from the tablets containing water soluble adjuvant such as lactose whereas if a water insoluble adjuvant such as DCP is used the same drug is released at a relatively slower rate. The dissolution profile may also be modulated using lactose in place of DCP.

Dissolution Studies:

Peck and co-workers[11] derived mathematical relationship for the expression of dissolution profile from matrix tablets. An effort is made in the present investigation to derive similar type of relationship. A linear interactive model was generated using the data of percentage drug dissolved at 60, 180, 300, 360, and 480 min from all the seven batches (Table 2). The Korsemeyer and Peppas[10] model showed an excellent fit to the data of drug dissolution in the seven batches. Therefore, log

Table I - Preliminary Trials of Acid-Alcohol Treatment

Trials	Lactic acid (ml)	Citric acid (g)	Tartaric acid (g)	Swelling Capacity pH 7	pH 1.2
1	-	-	-	4	4.33
2	1	-	-	7.66	7.49
3	2	-	-	*	*
4	-	1	-	6.9	7.11
5	-	2	-	*	*
6	-	-	1	8.44	8.23

*Four grams guar gum was used in all the trials. Twenty millilitres alcohol was used in trials 2 to 6. * Indicates that the mixture was tacky in nature and was difficult to dry.*

Table II - Actual and Transformed Values of Seven Formulations (Design)

Batch No.	Formulation Components Modified guar gum (mg)	Guar gum (mg)	DCP (mg)	Transformed Fraction Modified Guar gum	Guar gum	DCP	t_{80}	Y_{60}	Y_{180}	Y_{300}	Y_{360}	Y_{480}
1	100	0	35	1	0	0	478	28.2	47.0	64.4	70.1	82.4
2	80	20	35	0	1	0	394	37.5	57.6	71.4	80.8	86.2
3	80	0	55	0	0	1	303	45.1	63.5	80.2	87.8	97.2
4	90	10	35	0.5	0.5	0	265	49.6	66.3	83.9	89.5	95.4
5	90	0	45	0.5	0	0.5	367	39.6	63.7	76.1	82.8	88.3
6	80	10	45	0	0.5	0.5	399	32.3	53.1	69.5	78.7	86.6
7	86.66	6.66	41.66	0.33	0.33	0.33	403	31.2	52.6	69.1	76.8	89.2

Note: Each batch contained 90 mg diltiazem hydrochloride. t_{80} is the time (min) required for 80% drug release. Y_{60}, Y_{180}, Y_{300}, Y_{360} and Y_{480} are the percent drug released in 60, 180, 300, 360 and 480 min, respectively.

time was chosen as an additional independent variable for carrying out multiple linear regression analysis using the actual values. Microsoft EXCEL® (Version 5.0) was used to derive the equation. The derived equation describing the dissolution pattern is shown below:

$$Y = -1.27A - 82.6B - 2.03C + 1.06AB + 0.03AC + 2.04BC - 0.02ABC + 57.03 * \log \text{time} \quad (3)$$

where Y is the percent drug dissolved at time ' t '. The R^2 was found to be 0.971, indicating a good fit. The *F* - test was found to be significant at $p < 0.05$.

The derived equation (3) may be used for calculating percent drug release from different batches within the factor space. A good formulation is the one in which about 30% of the drug is released in the first hour as a loading dose and thereafter the remaining drug is released at a fairly constant rate. Accordingly 70% of the drug should be released in between 2 and 12 h at a constant rate of about 6.36%. The following additional constraints were arbitrarily chosen for the selection of batches; $25\% < Y_{60}$

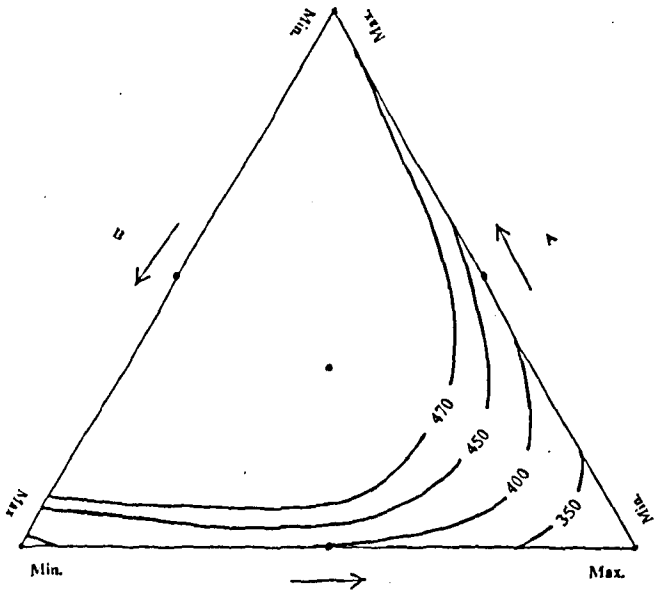

Fig. 1 : Contour Plot Lines for 60% Drug Dissolution A represents Modified Guar Gum, while B represents Guar Gum and C Dicalcium Phosphate

< 35%; 55% < Y_{300} < 70%; 75% < Y_{480} < 90%. The dissolution pattern of batches 1, 6 and 7 met the selection criteria (Table 2). The final selection can be done using other aspects such as cost of ingredients. The batch 6 contained least amount of modified guar gum amongst the batches 1, 6, and 7 and hence it may be ranked as the most suitable formulation for obtaining 12 h *in vitro* release profile. The predicted values of percent drug dissolved at different time are in good agreement with the observed values for the batch 6 (Fig. 2). Recently, Moore and Flannar[12] proposed a simple model independent approach to define similarity factor (f_2) to compare dissolution profile. The value of f_2 was found to be 66.3 indicating that the difference is insignificant at 5% level.

Kinetics of drug release:

The method of Bamba *et al.*[13] was adopted for deciding the most appropriate model. The dissolution data of batch 6 was fitted to zero-order ($m = b_0t + a_0$), first-order ($\ln m = - bt + a$), Higuchi ($m = 100 - Q\sqrt{t}$)[14], Hixon-Crowell ($\sqrt[3]{100} - \sqrt{m} = kt$)[15], Weibull ($m = 1 - \exp[-(t - t_1)^{b/a}]$)[16] and Korsemeyer and Peppas ($M_t/M_\infty = kt^n$)[10] models to study the kinetics of drug release. The results of *F*-statistics were used for the selection of the most appropriate model. The goodness of fit test (*F*-ratio) indicated insignificant difference between Korsemeyer and

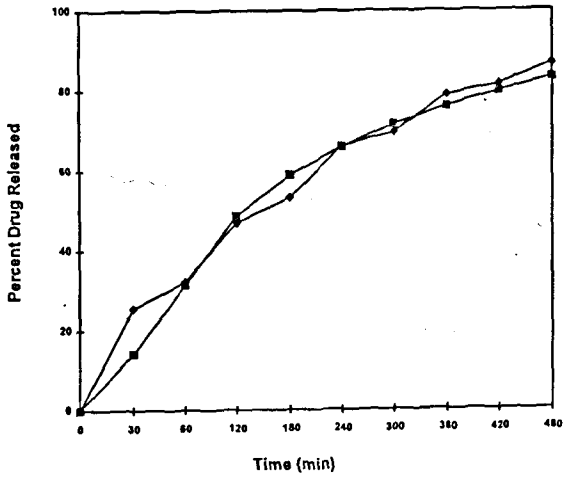

Fig. 2 : *In vitro* drug release from batch 6 (♦——♦) and predicted drug release (□——□)

Peppas, Higuchi and Weibull models. The *F*-value was found to be lowest with the Korsemeyer and Peppas (3.4) as compared to the Higuchi model (4.2) and the Weibull model (11.3). Thus, it may be concluded that the drug release is best explained by the Korsemeyer and Peppas model.

This study demonstrates that a blend of untreated guar gum and modified guar gum can be used as hydrophilic matrixing agent. By the use of simplex lattice design, one can develop sustained release tablets of diltiazem hydrochloride using a relatively inexpensive and biocompatible material.

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Dr. Rao V.S.V. Vadlamudi