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RESEARCH PAPER

Novel Use of Similarity Factors f_2 and S_d for the Development of Diltiazem HCl Modified-Release Tablets Using a 3^2 Factorial Design

M. C. Gohel* and M. K. Panchal

Department of Pharmaceutics and Pharmaceutical Technology, L. M. College of Pharmacy, P. O. Box No. 4011, Navrangpura, Ahmedabad 380 009, India

ABSTRACT

The objective of this study was to develop modified-release tablets of diltiazem HCl using a direct compression technique. A 3^2 factorial design was employed using the amount of alkali-treated guar gum and cetyl alcohol as independent variables. This article proposes the use of a novel approach—f_2 and S_d values as dependent variables—to evaluate the effect of selected independent variables along with other dependent variables (i.e., percentage drug released in x min, Y_x; time required for z% drug release, t_z; and mean dissolution time (MDT)). It is concluded that when a decision is to be made for the selection of a best batch, it is perhaps more realistic to use the f_2 or S_d value which takes into account the dissolution profile as a whole, as opposed to Y_x and t_z values which use just one point from the dissolution plot. The batch showing the f_2 value nearest to 100 or the S_d value nearest to zero is ranked as the best batch (diltiazem HCl 90 mg, alkali-treated guar gum 80 mg and cetyl alcohol 15 mg). The gel strength and matrix erosion of the formulated tablets were dependent on the type and amount of the adjuvants. The drug release rate is well correlated with matrix erosion. The kinetics of drug release fitted best to the Korsmeyer and Peppas model. It is concluded that by using a proper combination of the hydrophilic polymer and cetyl alcohol one can achieve a desirable drug release pattern.

*Corresponding author. Fax: 91-79-6304865; E-mail: mukeshgohel@hotmail.com

INTRODUCTION

The development of modified-release drug delivery systems has long been a major research area in the pharmaceutical industry. The last few years have seen a notable increase in technologically sophisticated products on the marketplace. Of the approaches known for modified drug release, the compressed matrices continue to receive maximum attention, as these devices incur the lowest fabrication cost and there is the possibility of incorporating optimum levels of drug in them.

Hydrophilic polymers are widely used in the formulation of modified-release oral dosage forms. Various synthetic polymers (hydroxypropyl methylcellulose, sodium carboxymethylcellulose, polymethylmethacrylate, etc.) and natural materials (xanthan gum, guar gum, chitosan, etc.) have been tried by various researchers. It has been shown that in case of hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously and both of them contribute to the overall drug release rate (1).

Waxes have a long history of use in semisolid pharmaceuticals and cosmetic preparations. Although not as frequently used as hydrophilic polymers, waxes represent another class of adjuvants. Wax-based modified-release drug delivery systems include granules, tablets, hard gelatin capsules, and microspheres. The probable reason for limited use of wax in tablet dosage form is difficulty in compression at higher levels. In a wax-based matrix system, drug release is preceded by penetration of the dissolution medium into the porous matrix followed by diffusion/leaching of the dissolved drug out of the matrix through the pores, cracks, and intergranular spaces.

Sometimes two or more matrixing agents are used to overcome the disadvantages of a particular matrixing agent or to achieve a desired drug-release pattern (2,3). Very few researchers have tried a combination of a hydrophilic polymer and a wax to achieve the desired drug-release pattern (4). Rashid et al. (5) reported that the release rate of salbutamol sulfate decreases linearly with increase in the concentration of cetyl alcohol (up to 40%) in the hydroxypropyl methylcellulose matrices.

Guar gum, a natural macromolecular galactomannan, is now becoming familiar as a sustained-release agent as it is significantly less expensive than hydroxypropyl methylcellulose and other cellulosic derivatives (6). In our previous study (7), we have reported that modification of guar gum by alkali (sodium hydroxide) treatment improves its swelling capacity and hydration rate. The drug-release profile of the tablets containing untreated guar gum showed a tailing effect in the terminal phase, which was not observed in the tablets containing alkali-treated guar gum. The alkali-treated guar gum also showed good compressional characteristics. The purpose of the present investigation was to check the effect of cetyl alcohol on release of diltiazem HCl with an assumption that replacing a part of alkali-treated guar gum with cetyl alcohol, up to a certain level, would decrease the drug release.

The development of a new pharmaceutical formulation is usually an optimization problem. The frequently applied trial-and-error technique, including a careful control of the variables one at a time in a series of logical steps, usually leads to a satisfactory formulation rather than an optimal one. The optimization techniques, on the basis of a few experiments and statistical analysis of the results, can provide an efficient and economical method for the predication of the optimal composition. In this study, a 3^2 factorial design was employed to optimize modified-release tablets of diltiazem HCl by selecting the amount of alkali-treated guar gum and cetyl alcohol as independent variables.

Drug dissolution is one key property, and dissolution testing is now recognized as an important in-vitro test during development of modified-release formulations. During formulation optimization of modified-release dosage forms using an experimental design, the percentage drug released at a given time (e.g., Y_{60}, Y_{300} or Y_{480}) or the time required for a given percentage of drug to be released (e.g., $t_{50\%}$, $t_{80\%}$, or $t_{90\%}$) are often selected as responses (8–10). Predetermined dissolution constraints for the responses are also applied to distinguish "good" and "bad" batches (2,11,12). Although, these time point approaches (Y_x or t_z) are widely used for the selection of the best batch, it may be inadequate for complete characterization of the dissolution profiles.

Moore and Flanner (13) recently proposed a "similarity factor, f_2" for comparison of dissolution profiles that has been adopted in SUPAC IR guidelines (14). This similarity factor f_2 has been used to compare dissolution profiles of a test and a market formulation (15), to check the effect of hardness on drug release (13), to investigate the effect of position of controlled release tablets in dissolution apparatus on drug release (16), and during design

and development of oral solid dosage form (17). Pillay and Fassihi (16) concluded that the results derived from the application of the similarity factor f_2 are superior to the individual time points (e.g., $t_{x\%}$) and mean dissolution time (MDT) values in differentiating between overall release patterns or the borderline release profile differences. Recently, we have proposed a new versatile model—an independent mathematical approach, using similarity factor S_d, for comparing dissolution profiles (18).

The primary advantages of the similarity factor S_d over f_2 are simplicity and flexibility, because the data can be expressed either as the amount of drug dissolved or as the percentage drug dissolved. Another advantage is that, unlike the similarity factor f_2, linear interpolation can be used to accurately express the results. This article proposes the use of a novel approach using f_2 and S_d values as dependent variables along with other dependent variables (Y_x, t_{80}, and MDT) to evaluate the effect of selected independent variables. The results obtained from Y_x, t_{80}, and MDT were compared with those of f_2 and S_d.

Furthermore, to get a deeper insight into the effect of cetyl alcohol on drug release, gel strength and matrix erosion studies were undertaken.

EXPERIMENTAL

Materials

Diltiazem HCl USP (Cadila Health Care Pvt. Ltd., Ahmedabad, India) and guar gum (H. B. Gum Industries Ltd., Kalol, India) were received as gift samples. Cetyl alcohol IP (Laser Laboratories, Ahmedabad, India), magnesium stearate IP, and talc IP (JC's Reagent, Baroda, India) were used as received. All the other chemicals and solvents were of analytical grade and were used without further purification. Deionized double-distilled water was used throughout the study.

Methods

Tablet Preparation

To the melted cetyl alcohol (heated above its melting point, i.e., 60°C) diltiazem HCl was added and mixed properly. The mixture was allowed to cool slowly with constant stirring, the congealed mass was granulated by forcing it through a 60 mesh sieve. The granules were then mixed with alkali-treated guar gum (7) and the blend was lubricated with 1% w/w talc and 0.5% w/w magnesium stearate. The tablets were prepared on a 16-station rotary tablet press equipped with concave punches of 8-mm diameter. Fifteen die cavities were blocked with stainless steel solid blocks. The compositions of the preliminary trials are shown in Table 1. For each formulation, the batch size was of 500 tablets. The compression force was adjusted so that the corresponding crushing strengths of the tablets were in the range of 50 ± 10 N. The average weight and the drug content of the tablet were 180 and 90 ± 5 mg, respectively. For the 3^2 factorial design, the tablets were prepared by the same method. The design layout is shown in Table 2.

Table 1

Composition and Responses of Preliminary Batches

	Ingredients (mg)		Response Values							
Batch[a]	Alkali-Treated Guar Gum	Cetyl Alcohol	Y_{60}[b]	Y_{360}[b]	Y_{540}[b]	Y_{720}[b]	t_{80}[c]	MDT[d]	f_2[e]	S_d[e]
A1	90	—	26.3	71.2	89.8	99.8	427	245	53	0.0550
A2	75	15	16.3	55.7	77.3	89.4	575	274	65	0.0347
A3	60	30	22.3	66.1	87.6	99.8	466	261	59	0.0425
A4	45	45	38.8	82.4	95.7	100.0	339	188	39	0.1210
A5	—	90	33.5	79.5	95.6	100.0	366	202	41	0.1046

[a]Each tablet of the batch contained 90 mg diltiazem HCl.
[b]Y_{60}, Y_{360}, Y_{540}, Y_{720} are the percent drug released in 60, 360, 540, and 720 min, respectively.
[c]t_{80} is the time (min) required for 80% drug release.
[d]MDT is the mean dissolution time (min).
[e]f_2 and S_d are the similarity factors.

Table 2

Compositions and Responses for a 3^2 Factorial Design

	Variables		Response Values							
Batch	X_1	X_2	Y_{60}	Y_{360}	Y_{540}	Y_{720}	t_{80}	MDT	f_2	S_d
M1	−1	−1	23.3	59.5	81.5	98.7	536	281	75	0.0214
M2	0	−1	18.2	56.2	77.1	90.3	595	278	65	0.0296
M3	1	−1	21.5	57.6	79.2	97.6	560	292	82	0.0143
M4	−1	0	20.4	57.8	80.5	96.5	548	283	78	0.0182
M5	0	0	19.7	56.1	75.1	92.4	610	296	66	0.0367
M6	1	0	23.4	57.1	77.9	98.3	578	304	87	0.0136
M7	−1	1	18.2	54.3	77.2	88.5	615	279	62	0.0382
M8	0	1	13.3	48.9	69.7	89.3	645	315	53	0.0850
M9	1	1	16.5	52.1	73.4	90.5	626	301	59	0.0553

	Levels		
Independent Variables	Low	Medium	High
X_1 = amount of alkali-treated guar gum (mg)	70	75	80
X_2 = amount of cetyl alcohol (mg)	10	15	20
Transformed values	−1	0	1

Dissolution Study

A dissolution study was carried out in accordance with the USP 23 paddle apparatus (Electrolab, model TDT-06 T, Mumbai, India) using 900 ml of deaerated distilled water (37 ± 0.5°C) with paddle rotation speed of 50 rpm. Samples (5 ml) were withdrawn at every hour up to 12 hr, filtered through 0.45-μ membrane filter, diluted suitably and analyzed spectrophotometrically at 237 nm (Hitachi UV-VIS Spectrophotometer, model U-2000, Japan). An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r = 0.9995$). The dissolution test was performed in triplicate for each batch. For the batches prepared according to factorial design, t_{80} was calculated using the Korsmeyer and Peppas equation (19).

Gel Strength

The gel strength of hydrated matrix tablets was determined using the method of Aerde and Remon (20). The gel strength was defined as the amount of water (ml) necessary to perforate the tablet. A beaker was balanced on one plate of a two-armed balance, at the underside of which a cone-shaped pin was fixed. Water was continuously added to the beaker, causing the pin to exert an increasing force on the wet tablet. The gel strength test was performed in triplicate for each batch. The results of gel strength, measured at two time points (after 1 and 8 hr), are shown in Table 3.

Matrix Erosion

The matrix erosion study was carried out by the method of Dhopeshwakar and Joel (21) to check the effect of formulation ingredients on matrix erosion and to establish a correlation between matrix erosion and drug release. In brief, representative samples were subjected to erosion in the USP 23 basket apparatus (50 rpm, 37 ± 0.5°C, 900 ml distilled water, $n = 3$). At a particular time point, the basket containing the remnants of matrix tablets was removed and the tablets were dried in a hot-air oven at 75°C to a constant weight. The results of average weight loss in the tablets at 1 and 8 hr are shown in Table 3.

Table 3

Results of Gel Strength and Matrix Erosion

Batch	After 1 hr			After 8 hr		
	Cumulative Percent Released	Gel Strength (ml) (SD)	Matrix Erosion (%) (SD)	Cumulative Percent Released	Gel Strength (ml) (SD)	Matrix Erosion (%) (SD)
M1	23.3	13.1 (0.32)	14.7 (0.65)	75.3	7.5 (0.40)	40.6 (1.29)
M2	18.2	15.7 (0.78)	10.3 (0.39)	71.3	9.4 (0.50)	37.1 (1.58)
M3	21.5	17.2 (1.03)	11.7 (0.86)	74.9	10.9 (0.80)	37.2 (2.04)
M4	20.4	10.7 (0.72)	12.6 (0.63)	74.7	7.1 (0.47)	39.4 (1.14)
M5	19.7	12.4 (0.50)	11.1 (0.27)	68.8	9.4 (0.47)	35.0 (0.94)
M6	23.4	13.6 (0.82)	12.4 (0.54)	71.7	10.4 (0.12)	35.7 (0.75)
M7	18.2	8.9 (0.90)	9.4 (0.42)	69.5	6.5 (0.35)	34.4 (1.24)
M8	13.3	11.1 (0.90)	7.0 (0.36)	62.7	8.4 (0.21)	30.3 (1.33)
M9	16.5	12.8 (0.55)	8.4 (0.76)	65.7	10.0 (0.50)	31.6 (0.87)

RESULTS AND DISCUSSION

The following equation was used to calculate the MDT from the mean dissolution data:

$$MDT = \frac{\sum_{i=1}^{n} t_{\text{mid}} \times \Delta M}{\sum_{i=1}^{n} \Delta M} \quad (1)$$

where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and $i-1$, and ΔM is the additional amount of drug dissolved between i and $i-1$. The MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate. Linder and Lippold found that application of MDT provides a more accurate drug release rate than the $t_{x\%}$ approach (22).

The similarity factor f_2 was calculated from the mean dissolution data according to the following equation:

$$f_2 = 50 \,\text{Log}\left\{\left[1 + \frac{1}{n}\sum_{n=1}^{n} W_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the number of pull points, w_t is an optional weight factor, R_t is the reference profile at time point t and T_t is the test profile at the same time point. For a dissolution profile to be considered similar, the value of f_2 should be between 50 and 100 (14). An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

The similarity factor S_d is defined as

$$S_d = \frac{\sum_{t=1}^{n-1} \left|\text{Log}((\text{AUC}_{Rt})/(\text{AUC}_{Tt}))\right|}{n-1} \quad (3)$$

where n is the number of data points collected during the in-vitro dissolution test and AUC_{Rt} and AUC_{Tt} are the areas under the dissolution curves of the reference and test formulations, respectively, at time t. The percentage difference between two dissolution profiles was calculated using the following equation:

$$\text{Percentage difference} = (S_d - 0.0022)/0.0038 \quad (4)$$

For the test and reference formulations to be identical, the S_d value should be zero. The percentage difference between dissolution profiles increases with increase in the S_d value.

Preliminary Batches

An ideal modified-release dosage form should release the loading dose (25%) in the first hour and the remaining drug (75%) should be released at a constant rate, i.e., 6.8%/hr. This ideal release pattern was considered as a reference release pattern for the calculation of t_{80}, MDT, and f_2. Accordingly, ideal t_{80} and MDT values are 544 and 300 min, respectively. The following constraints were chosen for the selection of acceptable batches: $15\% < Y_{60} < 25\%$; $55\% < Y_{360} < 65\%$; $75\% < Y_{540} < 85\%$;

$Y_{720} > 85\%$; 490 min $< t_{80} <$ 600 min; and 270 min < MDT < 330 min.

Figure 1 shows drug-release profiles of the preliminary batches. The values of the selected dependent responses are shown in Table 1. When the ratio of drug to alkali-treated guar gum was 1 : 1 (batch A1), fast release of drug was observed. The values of Y_{360} (71.2%), Y_{540} (89.8%), t_{80} (427 min), and MDT (245 min) reveal that 90 mg of alkali-treated guar gum is not able to retard the drug release sufficiently. When a part of alkali-treated guar gum was replaced by cetyl alcohol (batch A2), relatively slower drug release was observed than that of batch A1. Batch A2 met the set criteria of Y_x, t_{80}, and MDT. The slower drug release was observed due to decrease in dissolution of diltiazem HCl because of the presence of cetyl alcohol, a hydrophobic adjuvant. However, with further increase in the amount of cetyl alcohol (batches A3 and A4), the drug release was found to increase. The fast drug release is also evident from the high values of Y_x and low values of t_{80} and MDT.

In Batch A2, sufficient amount of alkali-treated guar gum was present to form a gel structure and the presence of small amount of cetyl alcohol was able to retard the dissolution of diltiazem HCl. On the other hand, as more of the alkali-treated guar gum was replaced by cetyl alcohol (batches A3 and A4), neither the amount of alkali-treated guar gum was able to form a strong gel structure nor the amount of cetyl alcohol was able to retard the drug dissolution. The release profile of Batch A5 indicates that the 1:1 ratio of drug to cetyl alcohol is not enough to achieve the desired modified drug release.

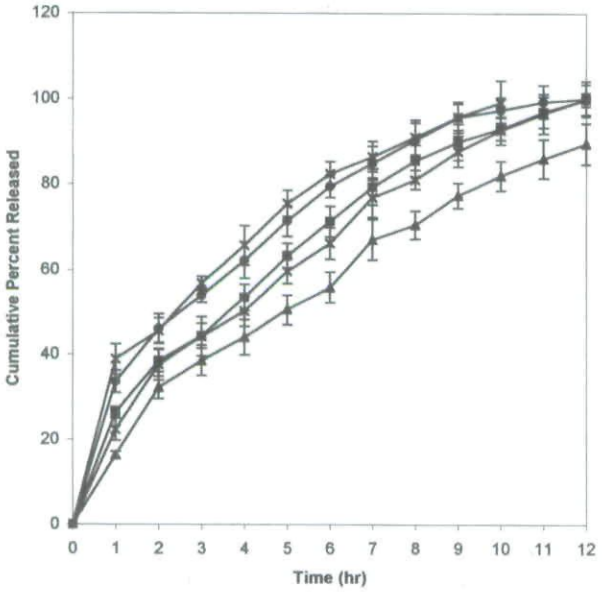

Figure 1. Dissolution profiles of preliminary batches: batch A1 (■), batch A2 (▲), batch A3 (×), batch A4 (*), and batch A5 (●). Values represent mean of three determinations with standard deviation.

The f_2 value was considerably close to the limiting value of 50 in the case of batch A1. The f_2 value of 59 for the batch A3 indicates relatively good similarity in dissolution profile. However, the highest value of f_2 (65) for the batch A2 indicates that batch A2 showed nearest to but not an ideal drug-release profile. For the batches A4 and A5, values of f_2 revealed an overall lack of similarity in dissolution profiles compared with the ideal release pattern.

The percentage difference from the ideal dissolution profile was calculated from the S_d values (Table 1) using Eq. (4). Accordingly, the percentage difference for the batches A1, A2, A3, A4, and A5 were 13.9, 8.6, 10.7, 31.3, and 27.0, respectively. Since the batch A2 showed the least percentage difference, it may be considered as the best batch of the preliminary study. The identification of best batch among preliminary batches was quite obvious by checking a single value—f_2 (65) or S_d (0.0347)—rather than by checking a number of time points (Y_x, t_{80}, and MDT).

The results of preliminary batches revealed that it was necessary to use the amount of cetyl alcohol that would not adversely affect the swelling and gelling properties of alkali-treated guar gum and at the same time would provide enough hydrophobicity to the matrix to reduce the dissolution of diltiazem HCl. Finally, it was concluded that by selection of a proper amount of alkali-treated guar gum and cetyl alcohol, it might be possible to achieve nearly ideal drug release.

Factorial Design

A two-factor, three-levels full factorial design was used for the optimization. The levels for the selected independent variables were determined from the preliminary batches: for alkali-treated guar gum, low (70 mg) and high (80 mg) levels, and for cetyl alcohol, low (10 mg) and high (20 mg) levels, were selected.

The factorial design is a simplified representation in analytical form of a given reality. In this mathematical approach, each experimental response (Y) can be represented by a quadratic equation of the response surface:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_{12} + b_{22}X_{22} + b_{12}X_1X_2 \quad (5)$$

where Y is the measured response and b_i is the estimated coefficient for the factor X_i. The coefficients corresponding linear effects (b_1 and b_2), interaction (b_{12}), and the quadratic effects (b_{11} and b_{22}) were determined from the results of experiments. The models relating the selected responses to the transformed factors are shown in Table 4. From the high correlation coefficient (r), one can conclude that a good fit was found for all the responses. These polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative).

Batch Selection

The ideal values of Y_{60}, Y_{360}, Y_{540}, Y_{720}, t_{80}, and MDT are 25%, 59.1%, 79.5%, 100%, 544 min, and 300 min, respectively. The values of Y_x, t_{80}, and MDT for the nine batches are shown in Table 2. According to the set constraints, batches M1, M2, M3, M4, and M6 met the set criteria of Y_x and t_{80}, whereas all the nine batches met the set constraint for MDT. To select the best batch among these five batches, the observed response values were compared with that of the ideal response values. However, it was difficult to identify the best batch, as one or other batches among M1, M2, M3, M4, or M6 could be ranked as the best considering a particular response. Therefore, it can be concluded that, particularly in this study, the time point approaches (Y_x and t_{80}) proved to be inadequate for the selection of best batch.

The results of similarity factor f_2 are shown in Table 2. The batch showing f_2 value nearest to 100 may be ranked as the best batch. Accordingly, batch M6 can be ranked as the best batch among all the batches ($f_2 = 87$). Shah et al. suggested that the average difference between two dissolution profiles is 2, 5, 10, 15, or 20% for calculated f_2 of 83, 65, 50, 41, or 36, respectively (23). The only batch, that showed less than 2% difference in dissolution profile compared with the ideal dissolution profile is batch M6. The results of multiple linear regression analysis (Table 4) reveal that a good correlation exists between the type and amount of adjuvants and the f_2 value. The alkali-treated guar gum has an additive effect, whereas cetyl alcohol has antagonistic effect on the f_2 value. Also, the negative effect of cetyl alcohol is higher in magnitude than that of the alkali-treated guar gum. It can be concluded that the desired f_2 value (i.e., 100) can be obtained by selecting a suitable amount of cetyl alcohol and alkali-treated guar gum.

Table 2 shows the results of S_d for the nine batches of factorial design. The calculated percentage differences from the ideal batch were 5.1, 7.2, 3.2, 4.2, 9.1, 3.0, 9.5, 21.8, and 14.0 for the nine batches, respectively. Batch M6 showed the lowest percentage difference from the ideal release profile and, therefore, it can be selected as the best batch among the nine batches of the factorial design. The result of multiple linear regression analysis (Table 4) indicates good correlation between the type and amount of ingredients and S_d value. The positive effect of cetyl alcohol ($b_2 = 0.0189$) was higher in

Table 4

Results of Regression Analysis for Dependent Variables

Responses	Intercept	b_1	b_2	b_{11}	b_{22}	b_{12}	r	P value
Y_{60}	18.844	−0.083	−2.500	3.483	−2.667	0.025	0.9446	0.1086
Y_{360}	55.222	−0.800	−3.000	2.667	−2.233	−0.075	0.9787	0.0283
Y_{540}	74.956	−1.450	−2.917	4.317	−1.483	−0.375	0.9909	0.0082
Y_{720}	92.833	0.450	−3.050	4.350	−3.250	0.775	0.9231	0.1680
t_{80}	605.000	10.833	32.500	−39.500	17.500	−3.250	0.9874	0.0131
MDT	298.534	8.868	7.191	−6.559	−3.287	2.700	0.8353	0.4194
f_2	68.556	2.067	−7.967	12.667	−11.033	−2.445	0.9831	0.0203
S_d	0.0386	0.0009	0.0189	−0.0236	0.0178	0.0060	0.9679	0.0510

magnitude than that of alkali-treated guar gum ($b_1 = 0.0009$). It is concluded that one can reduce the percentage difference from the ideal release profile by carefully selecting the settings of X_1 and X_2.

The comparative dissolution profiles of batch M6 with that of an ideal batch (Fig. 2) reveal that batch M6 showed slower drug release than that of the ideal batch. Figures 3 and 4 show the response surface plot for the similarity factors f_2 and S_d, respectively. The plots were drawn using SigmaPlot® software. It is obvious that both the selected independent variables significantly affect the similarity factors f_2 and S_d. From Fig. 3 it can be concluded that the desired f_2 value (i.e., near to 100) can be obtained when high level (+1) of X_1 (amount of alkali-treated guar gum) and medium (0) to low (−1) level of X_2 (amount of cetyl alcohol) were used. The desired S_d value (near to zero) and therefore the minimum percentage difference from the ideal dissolution profile can be obtained by using low levels of X_1 and X_2.

Finally, it was found that batch M6 met all the criteria selected for responses (Y_x, t_{80}, and MDT) and showed the least percentage difference with the ideal batch. Hence it may be ranked as the best batch among the nine batches of the factorial design. It is concluded that when a comparison is to be made between dissolution profiles, it is perhaps more realistic to use the f_2 or S_d value, which takes into account the dissolution profile as a whole, as opposed to Y_x and t_{80} values, which use just one point from the plot.

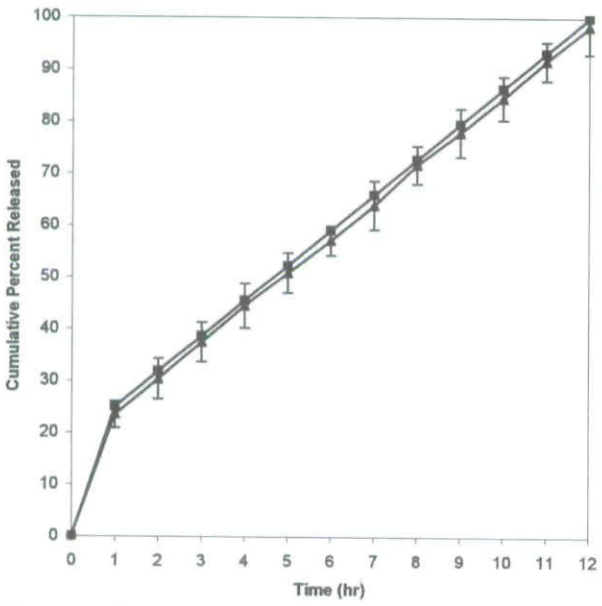

Figure 2. Dissolution profiles of ideal batch (■) and batch M6 (▲). Values for batch M6 represent mean of three determinations with standard deviation.

Gel Strength

In hydrophilic matrix tablets, on exposure to aqueous fluid, the hydrocolloid swells and a gel layer is formed, which helps retard drug dissolution. This follows slow penetration of aqueous fluid into

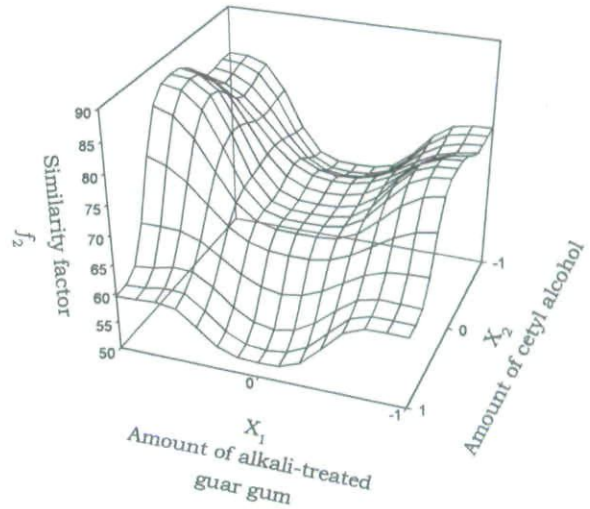

Figure 3. Response surface plot for similarity factor f_2.

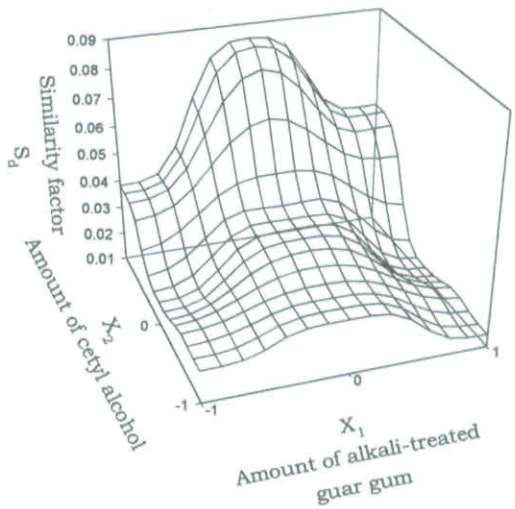

Figure 4. Response surface plot for similarity factor S_d.

the tablets and, simultaneously, erosion/dissolution of the gel layer occurs. The rate of erosion is dependent on the gel strength of the swollen gel. Thus, the formation of a strong and cohesive gel structure is a prerequisite for retarding drug release from hydrophilic matrix tablets.

To check the effect of formulation ingredients, the gel strength of matrix tablets was measured. The full model was evolved and refined by excluding the terms for which the level of significance was greater than 0.05. The resultant refined polynomial equations are given below:

$$G_1 = 12.233 + 1.817X_1 - 2.2X_2 + 0.9X_2^2 \quad (6)$$
$$(r = 0.9932,\ \mathrm{DF} = 8,\ F = 120.43,\ P = 4.41 \times 10^{-5})$$

$$G_8 = 8.844 + 1.7X_1 - 0.483X_2 \quad (7)$$
$$(r = 0.9895,\ \mathrm{DF} = 8,\ F = 140.37,\ P = 9.16 \times 10^{-6})$$

where G_1 and G_8 are the gel strengths of the matrix tablets after 1 and 8 hr, respectively. As indicated by the high value of r, a good correlation was found between the type and amounts of the sustained-release agents used and the gel strength. The amount of alkali-treated guar gum (X_1) has a strong positive effect on the gel strength [Eqs (6) and (7)] and one can consider this as being normal, since alkali-treated guar gum is the gel-forming agent in the present formulation. From Eqs (6) and (7), it can be concluded that the amount of cetyl alcohol (X_2) has a remarkably negative effect on the gel strength at 1 hr. The negative effect of cetyl alcohol is also evident on the gel strength after 8 hr. The results are obvious for those who are skilled in the art of formulation design.

Matrix Erosion

The matrix erosion study measured the weight loss from the matrix tablets as a function of time. The following refined equations were generated to check the effect of formulation ingredients on matrix erosion:

$$\mathrm{ME}_1 = 10.656 - 1.983X_2 + 2.067X_1^2 - 1.783X_2^2$$
$$(r = 0.9323, \mathrm{DF} = 8, F = 11.07,\ P = 0.0120) \quad (8)$$

$$\mathrm{ME}_8 = 35.133 - 1.65X_1 - 3.1X_2 + 2.35X_1^2 - 1.5X_2^2$$
$$(r = 0.9971, \mathrm{DF} = 8, F = 172.19,\ P = 9.96 \times 10^{-5}) \quad (9)$$

where ME_1 and ME_8 represent percentage weight loss after 1 and 8 hr, respectively. High values of r indicate good correlation between the type and amount of formulation ingredients and matrix erosion. As evident from the equations, as the amount of cetyl alcohol is increased, the weight loss increases. The amount of alkali-treated guar gum has no significant effect on matrix erosion at the initial stage of the matrix erosion study (i.e., at 1 hr); however, at the later stage (8 hr), with increase in amount of alkali-treated guar gum, the percentage weight loss increases. This is probably due to decrease in gel strength with time and, hence, increases in erosion rate. The exponential terms are significant, indicating a nonlinear relationship between the independent variables and matrix erosion.

Multiple linear regression was carried out to check the effect of matrix erosion on percentage drug released at 1 and 8 hr. The high values of correlation coefficients ($r = 0.9410$ for 1 hr and $r = 0.9560$ for 8 hr) reveal that good correlation exists between drug release and matrix erosion. It can be concluded that erosion is one of the mechanisms for the drug release from the matrix tablets.

Kinetics of Drug Release

The method of Bamba et al. (24) was adopted to study drug-release kinetics. The dissolution data of nine batches were fitted to zero order ($Q_t = kt$), first order ($Q_t = Q_0\ [1 - e^{-kt}]$), Higuchi ($Q_t = kt^{1/2}$), Hixson–Crowell ($Q_0^{1/3} - Q_t^{1/3} = kt$), Weibull ($M_t/M_\alpha = 1 - e[\{t - t_0/T_d\}^{\beta}]$), and Korsmeyer and Peppas ($M_t/M_\alpha = kt^n$) models. The results of F statistics were used for the selection of the most appropriate model. The goodness of fit test (F ratio) indicated that for all the nine batches the lowest F values were observed for the Korsmeyer and Peppas model. For the selected best batch M6, the lowest F value was found for the Korsmeyer and Peppas model (13.50) as compared with zero-order (18.66) and Higuchi (23.87) models. The values of correlation coefficient, slope, and intercept were found to be 0.9906, 0.5971, and −1.7462, respectively. The value of exponent n was found to be 0.60, which indicates that the drug is released by anomalous diffusion.

CONCLUSION

An attempt was made to sustain the release of diltiazem HCl from matrix tablets containing alkali-treated guar gum and cetyl alcohol. Slower drug release was observed when a part of alkali-treated guar gum (up to a certain level) was replaced by cetyl alcohol in the preliminary batches. The purpose of this study was also to take inventory of the status quo of f_2 and a new similarity factor S_d values as responses during optimization study and to identify their advantages over the other commonly used dependent variables (Y_x, t_{80}, and MDT). The time point approaches (Y_x, t_z, and MDT) proved to be inadequate for the selection of a best batch. The results of a 3^2 factorial design revealed that similarity factors f_2 and S_d are superior responses for the selection of the most appropriate formulation. The advantage of the new similarity factor S_d over f_2 is that the results can be expressed quantitatively. It can be concluded that summation of drug-release data into a single figure enables a ready comparison of formulations. Analyzing matrix tablet properties such as gel strength and matrix erosion allowed us a better understanding of the mechanism of drug release. Gel strength and matrix erosion tests can be used as quality control tools, since the drug release was found to be highly correlated with these factors. A proper combination of hydrophilic polymer and wax yielded prolonged release of a highly water-soluble drug.

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