Research Article

Influence of Formulation Factors on Tablet Formulations with Liquid Permeation Enhancer Using Factorial Design

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Abstract. For a drug with low bioavailability, a matrix tablet with liquid permeation enhancer (Labrasol®) was formulated. Factorial design was used to evaluate the effect of three formulation factors: drug percentage, polymer type (Methocel® K100M or Eudragit® L 100-55), and tablet binder percentage (Plasdone® S-630) on tablet characteristics. Tablets were prepared by direct compression and characterized. Compressibility index values ranged between 15.90% and 29.87% and tablet hardness values from 7.8 to 29.78 Kp. Eudragit®-containing formulations had better compressibility index values with higher tablet hardness. Time for 75% of drug release (T_{75}) was calculated, and formulations containing Eudragit® L 100-55 had faster release rates than tablet formulations with Methocel® K100M. Formulations with Methocel® K100M fit well in the Higuchi model as indicated by their R^2 values (>0.98). Among all the formulation factors studied, polymer type displayed the highest and statistically significant effect on compressibility index, tablet hardness, and dissolution rate. Statistical design helped in better understanding the effect of formulation factors on tablet characteristics important for designing formulations with desired characteristics.

KEY WORDS: Eudragit L 100-55; factorial design; Labrasol; Methocel K100M; tablet.

INTRODUCTION

Most new drug candidates have poor water solubility or low permeability, or both. Unfavorable physicochemical and chemical features of drug molecules can lead to poor permeability. Poor membrane permeation is most commonly due to either poor partitioning into the lipid membrane or low membrane diffusivity (1). Several strategies, such as formulating with permeation enhancers, structural modification of the drug molecule to increase lipophilicity, pro-drug method, ion pairing, and complexation, have been developed and reported in the literature (1–8). Structural modification or pro-drug methods involve extensive chemistry, toxicological, and efficacy studies and also needs additional regulatory approval procedures. But, strategies using formulation with permeation enhancers which are safe and non-toxic provide an easier and faster solution and a faster approval process. In recent years, attention has focused on lipid-based formulations for biopharmaceutics classification system (BCS) class II and III compounds. A majority of the lipid-based excipients that are permeation enhancers are liquids or semisolids at room temperature. Incorporation of a lipid-based liquid excipient into a solid dosage form combines the advantages of a lipid-based drug delivery system with those of a solid dosage form and overcomes some of the limitations of liquid formulations.

In the current study, a matrix tablet containing a lipid-based liquid permeation enhancer was designed for an SRI proprietary drug (SRID). SRID is highly soluble in water but has poor oral bioavailability (less than 5%) because of low intestinal permeability. According to the BCS, SRID can be classified in class III: a high-solubility, low-permeability compound (9). SRID is an approved drug currently available only as a parenteral injection and is indicated for a condition that requires administration for at least 1 to 3 months. Therefore, an oral dosage formulation would offer several advantages such as stability, cost effectiveness, and patient compliance. The overall objective of this funded project is to develop SRID a bioavailability-enhanced formulation for SRID drug. In this paper, we report the effect of formulation factors on the tablet characteristics.

In our preliminary studies, permeability of SRID was studied in Ussing chambers with rat intestinal tissue segments in the presence of several permeation enhancers. Enhanced permeability of the compound was demonstrated in the presence of Labrasol. Labrasol (caprylocaproyl macrogol-8 glyceride), developed by Gattefosse Corp., is a nonionic surfactant. It has been reported to increase the solubility of water-insoluble drugs by emulsification (10) and to facilitate oral bioavailability of water-soluble drugs (11,12). The absorption-enhancing mechanism of Labrasol remains largely unclear, although it has been reported that Labrasol, which increases membrane lipid fluidity, enhances permeability of micellar solubilized gentamicin sulfate through a transcellular route (13).

Incorporation of oils into solid dosage forms often results in a blend suffering from poor flow and compaction properties. To overcome these problems, fine partic-

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ulates such as silicates can be added to adsorb the oil ([14–16]). In the current project, colloidal silicon dioxide (CAB-O-SIL EH-5) was used to adsorb Labrasol. It has an average particle (aggregate) length of 0.2–0.3 μm and a BET surface area of 380 m^2/g with an oil adsorption capacity of ~300–350 g/100 g oil ([17]).

Most of the matrix-based tablets are formulated with hydrophilic or hydrophobic polymers ([18]). Hydroxypropyl methyl cellulose (HPMC) is one of the most commonly used cellulosic polymers in controlled release dosage forms ([19–21]). Methacrylic acid copolymers such as Eudragit L 100-55 and Eudragit L 100 have traditionally been employed for enteric coating, but these polymers have also been suggested for use in sustained release matrix formulations ([18,22]). In the current study, two types of polymers, HPMC (Methocel K100M) and polymethacrylic copolymer (Eudragit L 100-55), were evaluated for the development of matrix tablets.

Several formulation factors such as the percentage of drug-Labrasol blend and binder percentage can influence tablet strength and integrity, and the polymer type can govern the drug release rate from the tablet. Effect of percentage of the tablet binder, Plasdone S-630 on tablet characteristics was included as one of the formulation factors studied. Plasdone S-630 has been demonstrated to improve tablet hardness compared with other binders ([23]). As part of the formulation development, a 2^3 full factorial experimental screening design was employed to study the influence of some key formulation factors and to arrive at a tablet formulation with the desired characteristics. Statistical designs have been documented for the formulation of many pharmaceutical solid dosage forms ([24–27]).

MATERIALS AND METHODS

Materials

Ac-Di-Sol® (croscarmellose sodium) and Avicel® PH-102 (microcrystalline cellulose; FMC Corporation, Newark, DE), CAB-O-SIL® EH-5 (fumed silica; Cabot Corporation, Tuscola, IL), Eudragit® L 100-55 (methacrylic acid copolymer, type C) (Rohm America LLC), Methocel® K100M Premium (hydroxypropyl methyl cellulose) (Dow Chemical Company, Midland, MI), and Plasdone® S-630 (copovidone; ISP, Wayne, NJ) were obtained as gift samples. Labrasol® (caprylocaproyl polyoxylglycerides; Gattefosse, Paramus, NJ), magnesium stearate (Spectrum Quality Products Inc., Gardena,

CA), Starch 1500® (Colorcon, West Point, PA), and talc (Mallinckrodt Baker Inc., Phillipsburg, NJ) were purchased.

Experimental Design

A 2^3 full factorial design was created to optimize and determine the effect of the three formulation factors using four responses. Two continuous factors, drug-liquid permeation enhancer blend percentage (A) and tablet binder (Plasdone S-630) percentage (C), were tested at two levels designated as −1 and +1 with 0 as the center point. A discontinuous factor, polymer type (B), either Eudragit L 100-55 or Methocel K100M, was specified as −1 or +1, respectively, in the design. The following responses were analyzed: compressibility index, tablet hardness, and dissolution profile. Table I lists the factor levels for the ten tablet formulations encompassed by the full factorial design; the remaining percentages of each formulation consisted of Avicel PH-102 (8.0–38.0% w/w), Starch 1500 (0.5% w/w), Ac-Di-Sol (1.0% w/w), and magnesium stearate (0.5% w/w) as the tableting excipients.

Preparation of Tablets

Drug blend was prepared by mixing the drug, Labrasol, and CAB-O-SIL EH-5 at 10:2.5:1 ratio, respectively. Drug and CAB-O-SIL were first mixed followed by addition of Labrasol and mixed thoroughly at low shear to obtain the drug blend with Labrasol adsorbed. The drug blend, along with the remaining tablet formulation ingredients except magnesium stearate, was blended together by mixing for 15 min using a laboratory shaker. Magnesium stearate was added at the end of primary mixing, and the combination was blended for three more minutes. Tablets weighing 300 mg were prepared for each formulation by direct compression on a Carver hydraulic hand press (Carver 3912 Model C, Wabash, IN) using a 3/8 inch standard concave tooling, 1.8 metric tons (4,000 lb) compression pressure, and 5 s dwell time.

In Vitro Characterization

Compressibility Index

Formulation blend (6 g) was poured lightly into a 50-mL graduated cylinder. The powder was tapped until no further

Table I. Factor Levels for the Formulation Combinations Generated by the 2^3 Full Factorial Design

Formulation	Drug blend % (A)		Polymer type at 20% (B)		Binder (Plasdone S-630), in percentage (C)	
	Statistical level	Percentage	Statistical level	Type	Statistical level	Percentage
F1	−1	40	−1	Eudragit L100-55	−1	0
F2	0	50	1	Methocel K100M	0	5
F3	1	60	−1	Eudragit L100-55	1	10
F4	1	60	1	Methocel K100M	1	10
F5	0	50	−1	Eudragit L100-55	0	5
F6	−1	40	−1	Eudragit L100-55	1	10
F7	1	60	−1	Eudragit L100-55	−1	0
F8	1	60	1	Methocel K100M	−1	0
F9	−1	40	1	Methocel K100M	1	10
F10	−1	40	1	Methocel K100M	−1	0

change in volume was observed. The compressibility index was determined by measuring the unsettled apparent volume (V_o) and the final tapped volume (V_f). Percentage compressibility was computed according to Eq. 1.

$$\text{Compressibility Index} = 100 \times [(V_o - V_f)/V_o] \qquad (1)$$

Hardness Tests

For all the tablet formulations, hardness was measured using a Vanderkemp VK200 hardness tester.

In Vitro Dissolution Studies

Testing of drug dissolution and release from the matrix tablet formulations was performed using a USP type II (paddle) apparatus (Vankel 7100) at 50 rpm in 900 mL deionized water as dissolution media at $37 \pm 0.5°C$. Samples (1 mL each) were collected at 0.5, 1, 2, 4, 6, and 8 h, and their volumes were replaced with fresh media. Samples were analyzed by a validated high-performance liquid chromatography (HPLC) method, and the average cumulative percentage of drug dissolved at each sampling time was calculated. HPLC analysis was performed using an Agilent 1100 system with C18 column (250×4 mm, 5 μ) at 25°C using 1.1 mM cupric acetate in 7.6 mM dodecyltriethylammonium phosphate (ion pairing agent) as mobile phase at flow rate 1.0 ml/min with DAD detector at 290 nm. This method was also validated in presence of the excipients used in the formulation. Similarity factors (f_2) were calculated to study the effect of polymer type on dissolution rate using Eq. 2.

$$f_2 = 50 \log\left\{ \left[1 + 1/n^n \Sigma_{t=1}(R_t - T_t)^2\right]^{-0.5} \times 100 \right\} \qquad (2)$$

Where log is equal to logarithm to base 10, n is the number of sampling time points, Σ is the sum over all time points, R_t is dissolution at time point t of the reference product, and T_t is dissolution at time point t of the test product. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar (28). Formulation F1 (see Table I) was selected as the reference, and f_2 values were calculated for dissolution profiles of all

Table II. Tablet Characterization Responses (±standard deviation) for the Ten Formulations of the Full Factorial Design

Formulation	Compressibility index (%; $n=3$)	Hardness (Kp; $n=6$)
F1	15.90±1.85	21.18±0.45
F2	20.51±2.22	10.02±0.46
F3	18.95±3.96	23.36±1.48
F4	20.95±0.82	10.02±0.75
F5	15.96±0.29	23.36±1.48
F6	12.50±0.00	29.78±0.75
F7	18.38±0.64	23.35±1.04
F8	20.83±0.00	7.80±0.49
F9	25.54±0.47	15.32±0.50
F10	29.87±0.42	11.05±0.62

Table III. Regression Equations for the Responses

Regression equations for the responses
$Y1 = 19.939 - 0.5875A + 3.601B - 0.88C - 2.82AB + 1.0525AC - 0.1725BC$
$Y2 = 17.524 + 17.524A - 1.6B - 6.682C + 1.8875AB - 0.5375AC - 1.33BC$
$Y3 = 2.565 - 0.23A + 1.539B - 0.0175C - 0.1AB - 0.1AC - 0.1275BC$

A Drug percent, *B* polymer type, *C* Plasdone percent, *Y1* compressibility index, *Y2* hardness, *Y3* dissolution T_{75}

other formulations for comparison with the dissolution profile of F1.

Statistical Analysis

Data obtained from the experimental formulation testing was analyzed by t test and analysis of variance (ANOVA). StatGraphics[TM] Centurion (StatPoint, Inc., Version XV) was used to generate the study design and to perform the statistical analysis.

RESULTS AND DISCUSSION

Properties of Tablets

Ten formulations were prepared (Table I), as required by the full factorial experimental design for the three factors studied. Table II gives the measured tablet responses. The results obtained from the experiments were statistically analyzed using StatGraphics software. The design was evaluated by multiple linear regression analysis, and the mathematical relationships in the form of regression equations for the measured responses are listed in Table III (27,29).

Compressibility Index

Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these factors can influence the observed compressibility index (30). All the formulations prepared for this study include an adsorbed liquid, which influences the flow properties of the formulation blend. Increase in drug blend percentage also increases the percent of liquid in the formulation, which in turn can influence the compressibility index value. A compressibility index value less than 25% is considered to be acceptable, although a value less than 10% is considered to be excellent (30,31). Compressibility index values for the formulations prepared for this study ranged from 12.50% to 29.87%, as shown in Table II. The standardized Pareto chart and the Main Effects plot in Fig. 1 illustrate that polymer type (B) had the most significant effect on compressibility index.

To better understand the effect of polymers on the compressibility index of tablet formulations, compressibility index was determined for Eudragit L 100-55 and Methocel K100M and were found to be 3.85% and 33.33%, respectively. Thus, the statistically significant difference in the
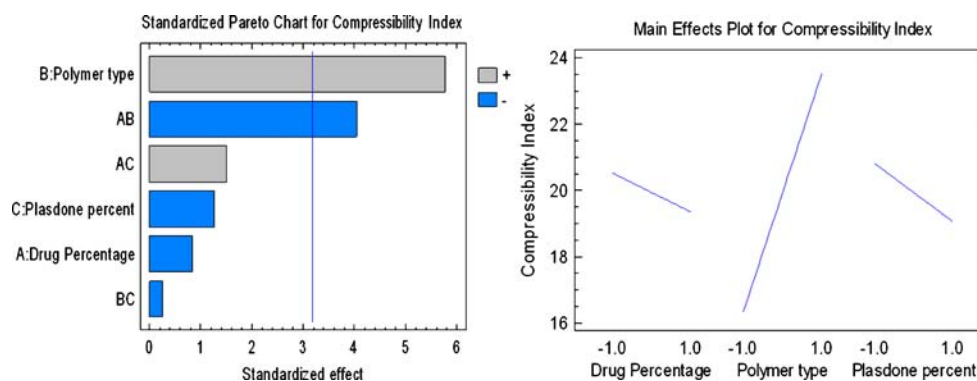
Standardized Pareto Chart for Compressibility Index

Main Effects Plot for Compressibility Index

Fig. 1. Standardized Pareto chart and main effects plot for compressibility index. Polymer type has significant effect on compressibility index. Formulations containing Eudragit L 100-55 scored better on the compressibility index. (Drug percentage (*A*) −1=40%, 0=50%, and 1=60%; polymer type (*B*), −1= Eudragit L100-55 and 1=Methocel K100M Premium; Plasdone percent (*C*), −1=0%, 0=5%, and 1=10%)

compressibility index values of the tablet formulations with Methocel K100M compared with those with Eudragit L 100-55 is probably attributable to the significant differences between the flow properties of the two polymers. Formulations containing Eudragit L 100-55 scored better, with lower compressibility index values.

As predicted, the compressibility index of a formulation did not increase with increasing drug percentage (A), although the relationship was not statistically significant. The decrease in compressibility index could be due to the proportionate increase in silica (CAB-O-SIL) along with the drug present in the drug blend. Silica is known to promote and improve flow properties (17). A statistically significant effect on compressibility index was observed for drug percentage in combination with polymer type (AB).

Tablet Hardness

Tablet hardness values for the ten formulations ranged from 7.8 to 29.78 Kp. Polymer type (B) had the greatest effect on tablet hardness, and this effect was statistically significant; Plasdone S-630 percent (C) had the next largest effect, as shown in the standardized Pareto chart and Main Effects plot for hardness in Fig. 2. Drug percentage (A) did not significantly influence tablet hardness. Tablet hardness values

were greater for tablets containing Eudragit L 100-55 compared with Methocel K100M.

Measures of tensile strength or tablet hardness provide basic information for understanding the compaction properties of compressed powders. In this study, because of the presence of liquid in the formulations, good compaction properties are imperative for an acceptable tablet formulation.

Eudragit L 100-55, a methacrylic acid–ethyl acrylate copolymer, has been used as polymer matrix material for directly compressed tablets. In one comparative study, Eudragit L 100-55 was found to yield tablets with the highest tensile strength among five poly(meth)acrylate copolymers evaluated (18,32).

Based on extensive studies of the deformation behavior of binary systems comprising HPMC and methacrylic acid copolymers (Eudragit L 100-55 and Eudragit L 100), Tatavarti *et al.* reported greater elasticity (elastic recovery) for HPMC compared with Eudragit L 100-55 and Eudragit L 100. The researchers reported that higher elastic recovery indicates greater area under the decompression profiles, which may indicate mechanically weaker compact formation. Net energy expended during compact formation can be defined as the difference between the area under compression and the decompression profiles. The
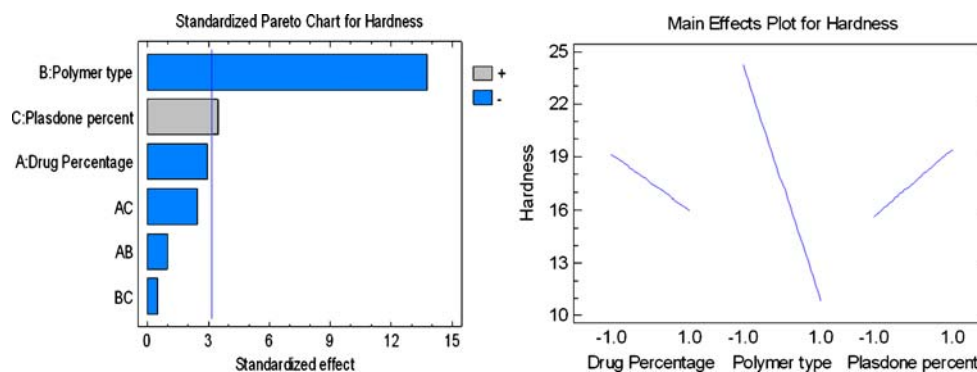
Standardized Pareto Chart for Hardness

Main Effects Plot for Hardness

Fig. 2. Standardized Pareto chart and main effects plot for tablet hardness. Polymer type has significant effect on hardness. Formulations containing Methocel K100M produced tablets with lower hardness. (Drug percentage (*A*), −1=40%, 0=50%, and 1=60%; polymer type (*B*), −1=Eudragit L100-55 and 1=Methocel K100M Premium; Plasdone percent (*C*), −1=0%, 0=5%, and 1=10%)
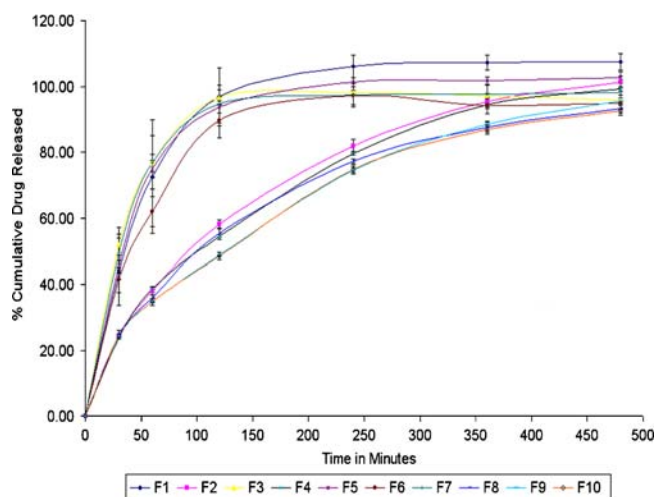
Fig. 3. Dissolution profiles of the ten tablet formulations with percent cumulative drug released (±standard deviation and $n=3$)

net energy expended during compact formation for HPMC was found to be lower than that for Eudragit L 100-55 because of the higher elastic recovery for HPMC (33). This difference could be one of the reasons for the lower tablet hardness values obtained in the current study for HPMC-based tablet formulations compared with the formulations with Eudragit L 100-55.

Dissolution Profile

Figure 3 illustrates the dissolution profiles for the ten tablet formulations prepared for this study. The standardized Pareto chart and Main Effects plot for T_{75} (time for 75% of drug released) shown in Fig. 4 illustrate that polymer type had the greatest effect on the dissolution profile, and the effect was statistically significant. T_{75} values calculated by calibration curves are listed in Table IV. Formulations with Methocel K100M (F2, F4, F8, F9, and F10) exhibited longer release times compared with formulations containing Eudragit L 100-55. This finding is in agreement with previously reported results (18).

Because of the nature of the polymers used in the tablet formulations and the high water solubility of SRID, diffusion

may be the main mechanism of drug release from the formulations (34,35). When the dissolution data were plotted following Higuchi's model, all the formulations fitted well with the model, as indicated by the correlation coefficient values (R^2); this pattern confirms the suggestion that diffusion is the mechanism of drug release (36–38). Table V lists the R^2 values and the corresponding slopes (Kh), which conform to Higuchi's model for matrix tablets with water-soluble drugs.

Formulations with Eudragit L 100-55 (F1, F3, F5, F6, and F7) had faster release rates, as indicated by higher slope values compared with those for formulations with Methocel K100M. This difference might reflect the solubility of Eudragit L 100-55 at intestinal pH, which allows formation of pores in certain matrix systems. Interstitial channels are created in these pores as a result of the dissolution of these polymers, and this process enables enhanced drug release via diffusion through the channels (39). This effect, when combined with the high water solubility of SRID, speeds drug release. Formulations with Methocel K100M (F2, F4, F8, F9, and F10) fit well in the Higuchi model for the entire release for up to 8 h, as indicated by their R^2 values (>0.98).

Similarity factors listed in Table V reinforce the differences in dissolution profiles according to the polymer type used. As mentioned earlier, an f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. For the calculation of similarity factors, formulation F1, which has Eudragit L 100-55, was used as an arbitrary reference formulation. All the formulations containing Eudragit L 100-55 had dissolution profiles similar to those of F1, as measured by the predicted similarity factors. Similarly, all the formulations with Methocel K100M had similarity values of less than 50, implying their difference in dissolution profiles compared to F1. At the same time, all the Methocel K100M formulations had similar dissolution profiles (28).

Once all the responses were separately analyzed, a multiple response optimization feature available in Stat-Graphics software was performed. Multiple response optimization enables the investigator to determine settings of the experimental factors which achieve desired characteristics for more than one response simultaneously. This is done by
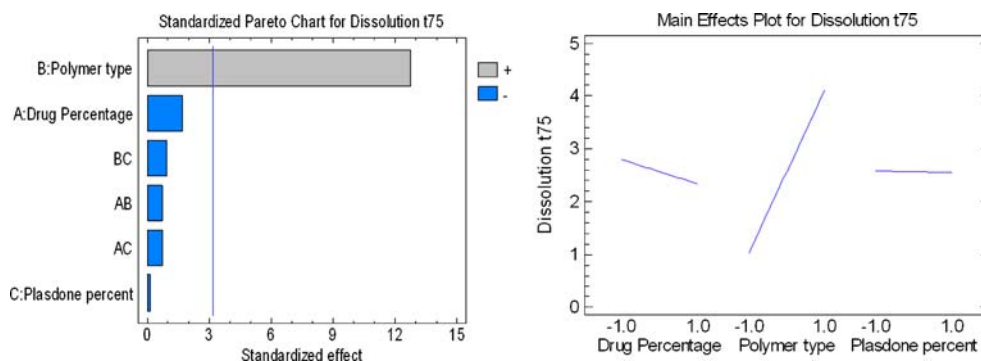

Fig. 4. Standardized Pareto chart and main effects plot for T_{75} (time for 75% cumulative drug release). Polymer type had a highly significant effect on the dissolution rates, which were higher for formulations with Methocel K100M. (Drug percentage (A), −1=40%, 0=50%, and 1=60%; polymer type (B), −1= Eudragit L100-55 and 1=Methocel K100M Premium; Plasdone percent (C), −1=0%, 0=5%, and 1=10%)

Table IV. Time for 75% Drug Released Values Calculated by Calibration Method for the Dissolution Profiles

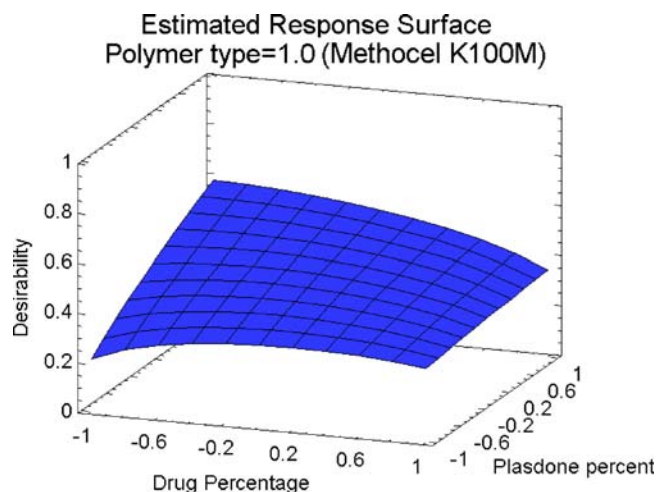| Formulation	T_{75} (min)
F1	56.16
F2	210.90
F3	53.90
F4	221.77
F5	57.14
F6	84.45
F7	56.03
F8	248.30
F9	270.62
F10	278.74

T_{75} 75% drug released

Fig. 5. Estimated response surface plot for the desired tablet characteristic features showing the levels for drug blend percentage (A) and binder (Plasdone S-630) percentage (C) with polymer type (B) as Methocel K100M. (Drug percentage (A), −1=40%, 0=50%, and 1=60%; polymer type (B), −1=Eudragit L100-55 and 1=Methocel K100M Premium; Plasdone percent (C), −1=0%, 0=5%, and 1=10%)

constructing a desirability function based on values of the response variables. In the current study, multiple response optimization was performed to determine the drug percentage, polymer type, and binder percentage to be used in the optimized formulation to give the desired characteristics. The goal was to create a tablet formulation with a hardness value of less than 20 Kp, a dissolution T_{75} of 3 h, and a low compressibility index. Figure 5 shows the estimated response surface plot of the desirability levels for different drug percentages and polymer types, with binder percentage at 10% w/w (indicated as 1.0).

As indicated by the surface plot, the optimized formulation (prepared using the procedures explained earlier and the standard excipients) consisted of 50% w/w drug blend loading, 10% w/w Plasdone S-630, and Methocel K100M as the polymer. The observed values of the responses for the optimized formulation were in close agreement with the predicted values. No statistically significant differences ($p>0.05$) were found, as shown in Fig. 6. These results demonstrate the reliability of the statistical design used to predict the effect of formulation variables on the characteristics of tablet dosage forms with a liquid permeation enhancer.

CONCLUSION

A matrix tablet formulation with a liquid permeation enhancer and with the desired characteristics was successfully prepared with the help of the statistical design. Statistical analyses of the data indicated that the type of polymer used had the most significant effect on the matrix tablet characteristics and that drug blend percentage had the next greatest effect. As expected, drug blend percentage as a single process factor, did not significantly alter the tablet characteristics; however, drug percentage in combination with other factors, such as polymer type, did have a significant effect on compressibility index. Information from this study significantly reduced the development time needed to identify tablet formulations with the desired characteristics.
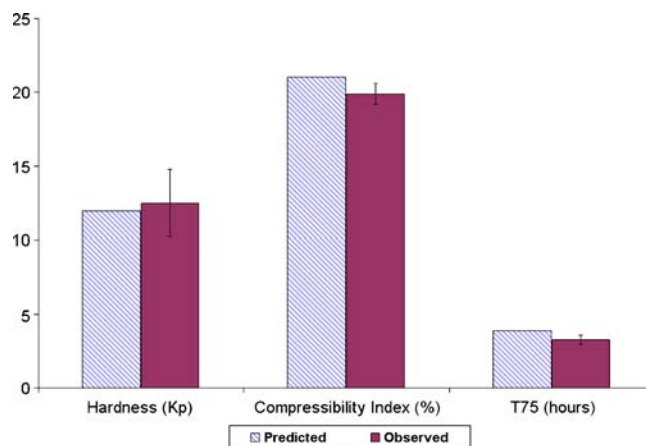
Table V. Higuchi Slope, Linearity Factors, and Similarity Factors Comparing the Dissolution Profiles for all the Formulations

Formulations compared	Correlation coefficient	Slope (Kh)	Similarity factor (f_2 values)
F1[a]	0.9784	9.5471	100.00
F2	0.9803	4.8061	29.83
F3	0.9743	8.0341	54.60
F4	0.9827	4.7302	28.67
F5	0.9514	8.5604	69.30
F6	0.997	8.7394	50.24
F7	0.9513	8.0895	56.77
F8	0.9756	4.3113	27.29
F9	0.9906	4.5373	25.69
F10	0.9847	4.3691	25.41

All formulations containing Eudragit L 100-55 had similar dissolution profiles, with similarity factors greater than 50, and similar rates of dissolution
[a] Formulation F1, which includes Eudragit L 100-55, was used as the reference for the similarity factors calculation

Fig. 6. Predicted and observed response values for tablets. Observed values were practical confirmation of the optimized formulation prepared. A strong correlation was found between the observed and the predicted values. As per t test, p values for hardness ($p=0.700$), compressibility index ($p=0.221$), and T_{75} ($p=0.08$) indicate no statistically significant differences

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REFERENCES

1. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J Pharm Sci. 1993;82(10):979–87.
2. Irwin GM, Kostenbauder HB, Dittert LW, Staples R, Misher A, Swintosky JV. Enhancement of gastrointestinal absorption of a quaternary ammonium compound by trichloroacetate. J Pharm Sci. 1969;58(3):313–5.
3. Caramazza I, D'Atri G, Bossi ML, De Ponti F, D'Angelo L, Crema A. Intraduodenal absorption of the new UF-heparin salt ITF 1057 in the conscious dog. Thromb Res. 1991;62(6):785–9.
4. Levy G, Reuning RH. Effect of complex formation on drug absorption. I. Complexes of salicylic acid with absorbable and nonabsorbable compounds. J Pharm Sci. 1964;53:1471–5.
5. Uekama K, Narisawa S, Hirayama F, Otagiri M. Improvement of dissolution and absorption characteristics of benzodiazepines by cyclodextrin complexation. Int J Pharm. 1983;16(3):327–38.
6. Sharma P, Varma MV, Chawla HP, Panchagnula R. Absorption enhancement, mechanistic and toxicity studies of medium chain fatty acids, cyclodextrins and bile salts as peroral absorption enhancers. Farmaco. 2005;60(11-12):884–93.
7. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. Eur J Pharm Sci. 2000;11(Suppl 2):S93–8.
8. Nazzal S, Nutan M, Palamakula A, Shah R, Zaghloul AA, Khan MA. Optimization of a self-nanoemulsified tablet dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm. 2002;240(1–2):103–14.
9. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–20.
10. Yuksel N, Karatas A, Ozkan Y, Savaser A, Ozkan SA, Baykara T. Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation. Eur J Pharm Biopharm. 2003;56(3):453–9.
11. Rama Prasad YV, Eaimtrakarn S, Ishida M, Kusawake Y, Tawa R, Yoshikawa Y, et al. Evaluation of oral formulations of gentamicin containing Labrasol in beagle dogs. Int J Pharm. 2003;268(1-2):13–21.
12. Djordjevic L, Primorac M, Stupar M, Krajisnik D. Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. Int J Pharm. 2004;271(1–2):11–9.
13. Koga K, Kusawake Y, Ito Y, Sugioka N, Shibata N, Takada K. Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate. Eur J Pharm Biopharm. 2006;64(1):82–91.
14. Ito Y, Arai H, Uchino K, Iwasaki K, Shibata N, Takada K. Effect of adsorbents on the absorption of lansoprazole with surfactant. Int J Pharm. 2005;289(1–2):69–77.
15. Ito Y, Kusawake T, Ishida M, Tawa R, Shibata N, Takada K. Oral solid gentamicin preparation using emulsifier and adsorbent. J Control Release. 2005;105(1–2):23–31.
16. Ito Y, Kusawake T, Prasad YV, Sugioka N, Shibata N, Takada K. Preparation and evaluation of oral solid heparin using emulsifier and adsorbent for in vitro and in vivo studies. Int J Pharm. 2006;317(2):114–9.
17. Cabot-Corporation. Untreated fumed silica: Cab-O-Sil EH5. Cabot Corporation 2006.
18. Takka S, Singh Bharaj S, Sakr A. Influence of methacrylic acid and hydroxypropylmethyl cellulose on the tablet properties and in vitro release of dextromethorphan hydrobromide. Die Pharmazie. 2003;58(12):886–90.
19. Nellore RV, Rekhi GS, Hussain AS, Tillman LG, Augsburger LL. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. J Control Release. 1998;50(1–3):247–56.
20. Solinis MA, de la Cruz Y, Hernandez RM, Gascon AR, Calvo B, Pedraz JL. Release of ketoprofen enantiomers from HPMC K100M matrices—diffusion studies. Int J Pharm. 2002;239(1–2):61–8.
21. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS PharmSciTech. 2007;8(3):E73.
22. Takka S, Rajbhandari S, Sakr A. Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. Eur J Pharm Biopharm. 2001;52(1):75–82.
23. Moroni A. A Novel Copovidone Binder for Dry Granulation and Direct-Compression Tableting. Pharm Technol. 2001;25(9):8–12.
24. Gao JZ, Jain A, Motheram R, Gray DB, Hussain MA. Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation. Int J Pharm. 2002;237(1–2):1–14.
25. Khanvilkar KH, Huang Y, Moore AD. Influence of hydroxypropyl methylcellulose mixture, apparent viscosity, and tablet hardness on drug release using a 2(3) full factorial design. Drug Dev Ind Pharm. 2002;28(5):601–8.
26. Akin-Ajani OD, Itiola OA, Odeku OA. Effects of plantain and corn starches on the mechanical and disintegration properties of paracetamol tablets. AAPS PharmSciTech. 2005;6(3):E458–63.
27. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: stability assessment and optimization of some processing parameters. Int J Pharm. 2006;315(1–2):110–21.
28. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Technol. 1996;20(6):64–75.
29. Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS PharmSciTech. 2006;7(2):E34.
30. Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163–8.
31. USP31-NF26. Chapter 1174 Powder flow. USP31–NF26 ed. Rockville, MD 2009:618.
32. Schulze MD, Williams RO, McGinity JW. Compaction properties of acrylic resin polymers with plastic and brittle drugs. Drug Dev Ind Pharm. 1990;16(5):741–54.
33. Tatavarti AS, Muller FX, Hoag SW. Evaluation of the deformation behavior of binary systems of methacrylic acid copolymers and hydroxypropyl methylcellulose using a compaction simulator. Int J Pharm. 2008;348(1–2):46–53.
34. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123–33.
35. Mehta KA, Kislalioglu MS, Phuapradit W, Malick AW, Shah NH. Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix. Int J Pharm. 2001;213 (1–2):7–12.
36. Higuchi T. Physical chemical analysis of percutaneous absorption process from creams and ointments. J Soc Cosmet Chem. 1960;11:85–97.
37. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci. 1961;50:874–5.
38. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145–9.
39. Oren PL, Seidler WMK, inventors; Sustained release matrix patent 1990, 4,968,508.