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Research Article

Design and Optimization of Sustained-Release Divalproex Sodium Tablets with Response Surface Methodology

Farnaz Monajjemzadeh,[1] Hamed Hamishehkar,[1] Parvin Zakeri-Milani,[2] Afsaneh Farjami,[3,4] and Hadi Valizadeh[5,6]

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Abstract. Response surface methodology is defined as a collection of mathematical and statistical methods that are used to develop, improve, or optimize a product or process. In the present study, a statistical design (Mixture Design) was employed for formulation and optimization of a sustained-release hydrophilic divalproex sodium matrix tablet. Different excipients were used to improve the drug's poor flowability. The hardness of the prepared tablets and also their release pattern were tested. The formulation design was carried out employing mixture design using four excipients in three levels. The Carr's index of formulations and tensile strength were determined and analyzed using Minitab software. The suitable formulations regarding flowability and tablet tensile strength were selected by this software for subsequent drug release studies. The dissolution tests were carried out in acidic and basic phases which were previously proved to be biomimetic. Samples were analyzed using HPLC, and release data were compared to Depakine® (sustained-release divalproex from Sanofi). Release kinetics was also determined for selected formulations. Selected formulations were subjected to dissolution test and showed similar dissolution profiles with Depakine® based on difference and similarity factor calculations. The software selected an optimized formulation which had a slightly different release pattern *in vitro* compared to innovator but of nearly zero-order kinetics. It can be concluded that application of Mixture Design is a shortcut method to design suitable formulations of sustained-release divalproex sodium containing hydrophilic matrix tablets by direct compression method.

KEY WORDS: divalproex sodium; epilepsy; matrix; mixture design; sustained release.

INTRODUCTION

Response surface methodology (RSM) is defined as a collection of mathematical and statistical methods that are used to develop, improve, or optimize a product or process. It comprises statistical experimental designs, regression modeling techniques, and optimization methods. Most applications of RSM involve experimental situations where several independent (or control) variables potentially impact one (or more) response variable. The independent variables are controlled by the experimenter, in a designed experiment, while the response variable is an observed output of the experiment (1).

Recently, pharmaceutical researchers have used this method in preformulation studies (2–4). RSM is the best method for parameters optimization with reduced number of experiments without affecting the accuracy of results, but qualitative variables cannot be optimized (6). Central composite design is defined as a RSM method for designing experiments with two to ten independent variables and is used to determine optimal settings for each factor (5).

Divalproex sodium is a stable compound comprised of sodium valproate which is connected to valproic acid with a coordinate bonding (Fig. 1; 6). Sodium valproate occurs as an essentially white and odorless, crystalline, deliquescent powder, and divalproex sodium exists as a white powder with a characteristic odor (7,8). Divalproex sodium is less hygroscopic than sodium valproate and is therefore more suitable for tableting procedures (9).

Divalproex has been administrated in various conditions such as seizures, bipolar disorder, and migraine headaches (10). Its effects are dependent on dose and serum concentration, and rapid antimanic effects are achieved with loading doses of 20 mg/kg per day (11). It has been reported that desired pharmaceutical responses result from two to three times administration of divalproex per day (12). Divalproex is available as delayed-release (125, 250, and 500 mg) and extended-release dosage form (500 mg) tablets (13). Dutta and Reed, who studied divalproex extended-release systems' bioavailability compared to conventional divalproex tablets, concluded that when converting from conventional tablets to

[1] Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[2] Liver and Gastrointestinal Diseases Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[3] Biotechnology Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[4] Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[5] Research Center for Pharmaceutical Nanotechnology and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[6] To whom correspondence should be addressed. (e-mail: valizadeh@tbzmed.ac.ir)

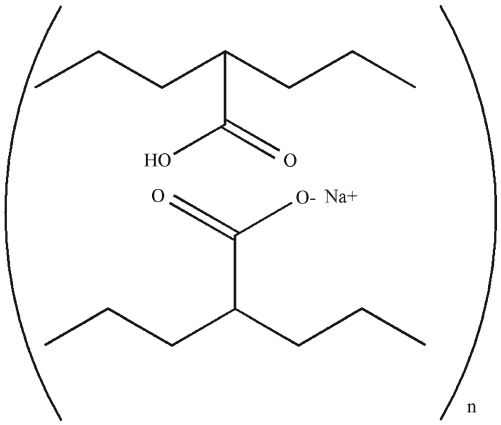

Fig. 1. Divalproex sodium chemical structure (1)

extended-release formulations, an 8–20% increase in total daily dosage is needed. Obviously extended-release dosage forms offer some benefits to the patients such as lower dosing frequency and then consequently better following their treatment plans (10).

Depakine® (sustained-release divalproex from Sanofi), a well-known commercial sustained-release preparation of divalproex sodium, contains 500 mg of the active agent per dosage form (10). This controlled-release formulations provide desired therapeutic plasma concentration over 24 h (12).

Oral sustained-release systems can be simply classified to (a) insoluble, slowly eroding, or swelling matrices, (b) polymer-coated tablets, pellets, or granules, and (c) osmotically driven systems (12).

The most suitable mechanism of drug release from oral sustained-release dosage forms is defined as diffusion through the matrix systems and can be achieved by using appropriate type and concentration of matrix substance, and also manufacturing processes (12). Different excipients were used in this study such as hydroxypropylmethylcellulose (HPMC) as release retardant, lactose as filler, colloidal silicon dioxide (SiO_2) as lubricant, and microcrystalline cellulose (MCC) as binder in direct-compression processes, which can also act as lubricant and/or disintegrant.

HPMC is the major hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. One of its most important characteristics is the high gelation velocity and viscosity, which has a significant effect on the release kinetics of the incorporated drug. It was proven that HPMC at high concentration promoted the drug release approaching to a zero-order release kinetic because of its gelation properties (12). Lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting. The particle size of lactose influences parameters like flow; in general, a decrease in particle size will decrease the flow which is due to the drug/fine particle fraction (14). SiO_2 is a fine and amorphous powder consisting of particle about 7–40 nm in size that has been used in the tablet manufacturing as a glidant (15).

Tablet formulations were performed by statistical design (design of experiment) using Minitab software. The purposes of this research were to design and optimize divalproex sustained-release matrix tablets with response surface methodology, using HPMC as matrix former by direct compression technique, and to compare drug release of the developed tablets to that of a commercial product, Depakine®. The effect of excipients on physical properties and drug release from matrix tablet along with release kinetics was also investigated.

MATERIALS AND METHODS

Divalproex sodium was purchased from Katwijk Chemie B.V. (Katwijk, Netherlands). Colloidal silicon dioxide was provided (Merck, Germany), hydroxypropylmethylcellulose (Methocel K_{100}M PREMIUM EP®; Colorcon, England), microcrystalline cellulose (Avicel® PH 101; Brussels, Belgium), and lactose (Alpavit, Netherlands) were all used as excipients. Sodium lauryl sulphate (SLS), phosphoric acid, acetonitrile, dibasic sodium phosphate, citric acid, monobasic potassium phosphate, sodium hydroxide, and hydrochloric acid were obtained from Merck (Merck, Germany).

Formulation Methods

Formulation Design and Matrix Tablet Preparation

Design of formulations was done using response surface methodology, mixture design (Minitab software version 16). The tablet formulations evaluated consisted of the active ingredient, release-retarding polymer, filler, and lubricants.

Divalproex sodium content of each formulation and the sum of excipients (colloidal silicon dioxide, lactose, microcrystalline cellulose, and hydroxypropylmethylcellulose) in each formulation were kept constant at 500 and 250 mg, respectively. Thus, the final weight of each tablet was 750 g. Matrix tablets were produced by weighting, screening, and mixing the excipients through a 40-mesh sieve, to which the active ingredient was added and mixed thoroughly. Powder flowability evaluation was then performed for blended tablet

Table I. Divalproex Sodium Matrix Tablet Composition Designed by Minitab

	HPMC(mg)	Lactose(mg)	MCC(mg)	Sillicone dioxide (mg)
F1	50.00	100.00	40.00	60.00
F2	65.00	100.00	75.00	10.00
F3	85.25	78.25	63.25	23.25
F4	65.00	100.00	25.00	60.00
F5	77.75	60.75	63.25	48.25
F6	160.25	28.25	38.25	23.25
F7	85.25	78.25	38.25	48.25
F8	135.25	28.25	63.25	23.25
F9	50.00	100.00	75.00	25.00
F10	115.00	100.00	25.00	10.00
F11	165.00	0.00	25.00	60.00
F12	115.00	0.00	75.00	60.00
F13	215.00	0.00	25.00	10.00
F14	105.50	56.50	51.50	36.50
F15	50.00	65.00	75.00	60.00
F16	165.00	0.00	75.00	10.00
F17	110.25	28.25	63.25	48.25
F18	135.25	28.25	38.25	48.25
F19	77.75	78.25	63.25	30.75
F20	110.25	78.25	38.25	23.25
F21	77.75	78.25	45.75	48.25

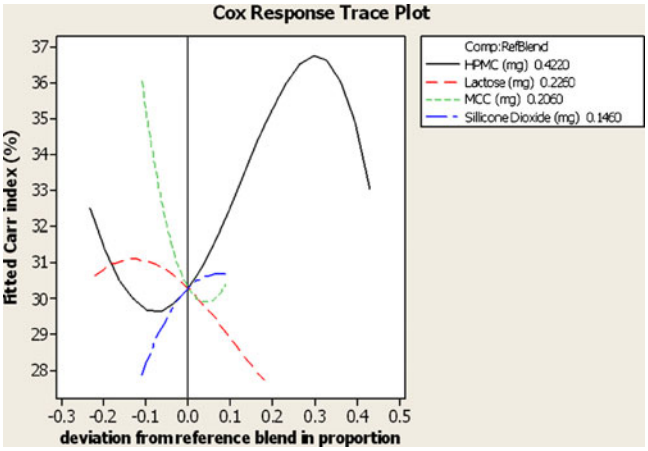

Fig. 2. Response trace plot for Carr's Index

components. Tablets were directly compressed using a hydraulic press machine using an oblong punch (0.86×1.9 cm) under 160 N pressures. The prepared matrix tablets were subjected to hardness and drug release tests.

Evaluation of Blended Tablet Powder Flowability

Constant volume (25 ml) of the blended components of each formulation in the powder form was transferred into a 25-ml volumetric cylinder; the powders were tapped about 200 times in the cylinder, and the volumes of tapped powders were measured accordingly. The compressibility was calculated using the Carr's index indicating the flowability (16):

$$C = 100(V_B - V_T)/V_B$$

Where V_B is the freely settled volume of a given mass of powder, and V_T is the tapped volume of the same mass of powder.

Evaluation of Matrix Tablets Physical Properties

Thickness and Hardness

Three matrix tablets of each formulation were individually tested using a hardness tester (Erweka, Germany), and then, their dimensions were recorded by a micrometer.

Friability

According to USP32 guidelines for tablets with a unit mass more than 650 mg, a sample of ten whole tablets was recommended for testing. The tablets were carefully dedusted prior to testing. Maximum mean weight loss was calculated after 4 min rotation at 25± 1 rpm.

Dissolution Studies

Biomimetic *in vitro* dissolution testing method used in this study was previously developed by Qiu *et al.* (6). Briefly, USP apparatus II, operating at 100 rpm, was used as a dissolution tester, and the test was performed in 500 ml of 0.1 N **HCl** for 45 min as the acid stage, followed by 900 ml of 0.05 M phosphate buffer pH 5.5, containing 0.5% SLS as the buffer phase. Temperature was maintained at 37±0.5°C (17). Samples was withdrawn at predetermined time intervals (15 and 45 min initially and 1, 2, 4, 6, 12, and 24 h thereafter). The medium was replenished with fresh buffer at each sampling time. Samples were filtered through a 0.45-μm filter. The samples were assayed by high-performance liquid chromatography (HPLC) method. The dissolution data obtained were plotted as percent cumulative drug release *versus* time.

Table II. Physical Properties of the Prepared Tablets

	Thickness (mean ± SD) (cm)	Friability (%)	Tensile strength (MPa)	Hardness (mean ± SD)	Carr's Index (mean ± SD)
F9	0.578±0.0076	0.48	0.483	83.32±2.65	28.00±1.74
F8	0.596±0.0058	0.49	0.289	51.32±8.89	26.00±1.20
F7	0.590±0.0100	0.47	0.329	57.84±5.62	32.00±1.39
F6	0.593±0.0058	0.27	0.283	50.13±2.46	35.71±1.89
F5	0.576±0.0058	0.43	0.331	56.93±2.46	30.00±1.74
F4	0.580±0.0050	0.28	0.313	54.13±2.14	32.14±1.89
F3	0.575±0.0050	0.41	0.336	57.63±5.26	32.14±2.14
F21	0.593±0.0076	0.49	0.434	76.74±6.51	22.00±1.83
F20	0.600±0.0000	0.52	0.309	55.32±8.08	32.00±0.80
F2	0.586±0.0058	0.41	0.287	50.13±7.29	24.00±0.69
F19	0.593±0.0058	0.48	0.359	63.44±7.74	28.00±1.44
F18	0.600±0.0000	0.37	0.287	51.32±8.05	28.00±2.12
F17	0.596±0.0058	0.43	0.303	53.92±1.21	34.00±1.44
F16	0.596±0.0058	0.45	0.321	57.14±5.96	36.36±1.82
F15	0.573±0.0058	0.42	0.344	58.82±3.90	36.00±1.06
F14	0.590±0.0100	0.44	0.264	46.42±4.77	32.00±1.39
F13	0.610±0.0100	0.45	0.352	64.14±8.87	18.00±0.69
F12	0.596±0.0058	0.39	0.262	46.63±8.92	30.00±1.44
F11	0.600±0.0000	0.35	0.220	39.42±3.59	21.43±1.24
F10	0.580±0.0100	0.59	0.306	52.94±14.69	33.33±3.00
F1	0.593±0.0058	0.46	0.493	87.24±12.24	32.00±1.05

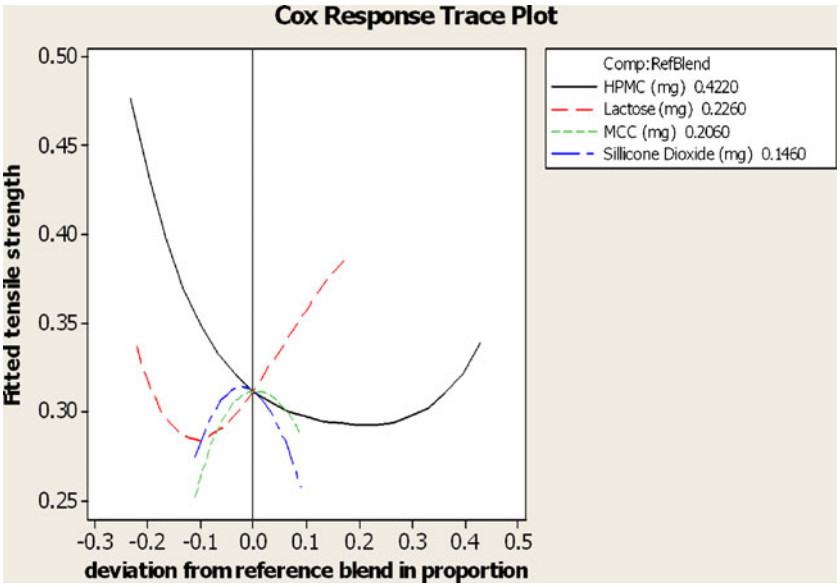

Fig. 3. Response trace plot for tensile strength

Evaluation of Similarity Factor and Difference Factor of Release Profiles

Dissolution studies of divalproex sustained-release tablets were compared to that of the Depakine®. The similarity and difference of release profiles of the developed formulation were compared to that of the commercial formulation Depakine ® in terms of difference factor (f_1) and similarity factor (f_2) using the following equations;

$$f_1 = \left[\{\sum_{t=1} R_t - T_t\}/\{\sum_{t=1}^{n} R_t\}\right] \times 100$$

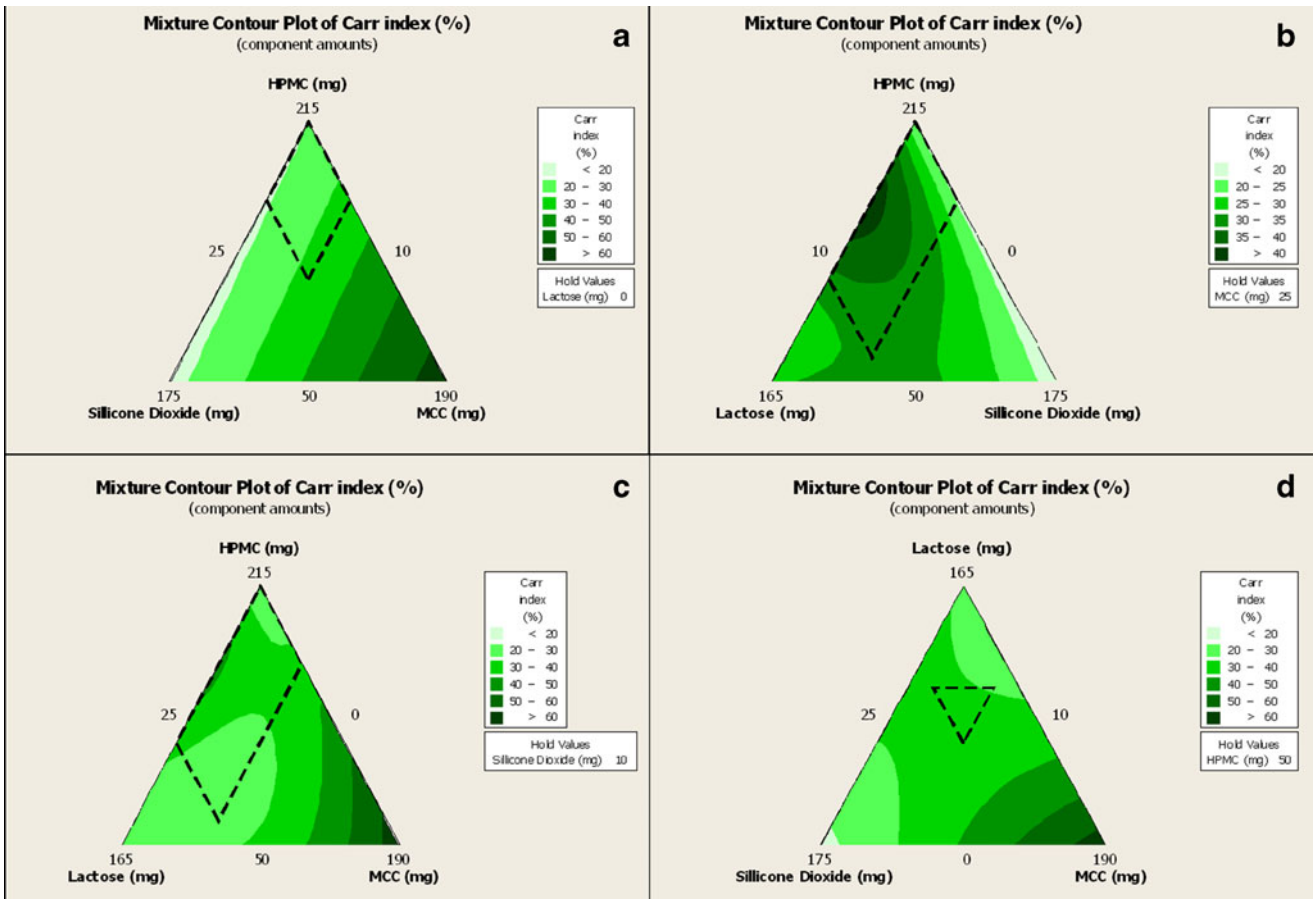

Fig. 4. Mixture counter plots for Carr's index

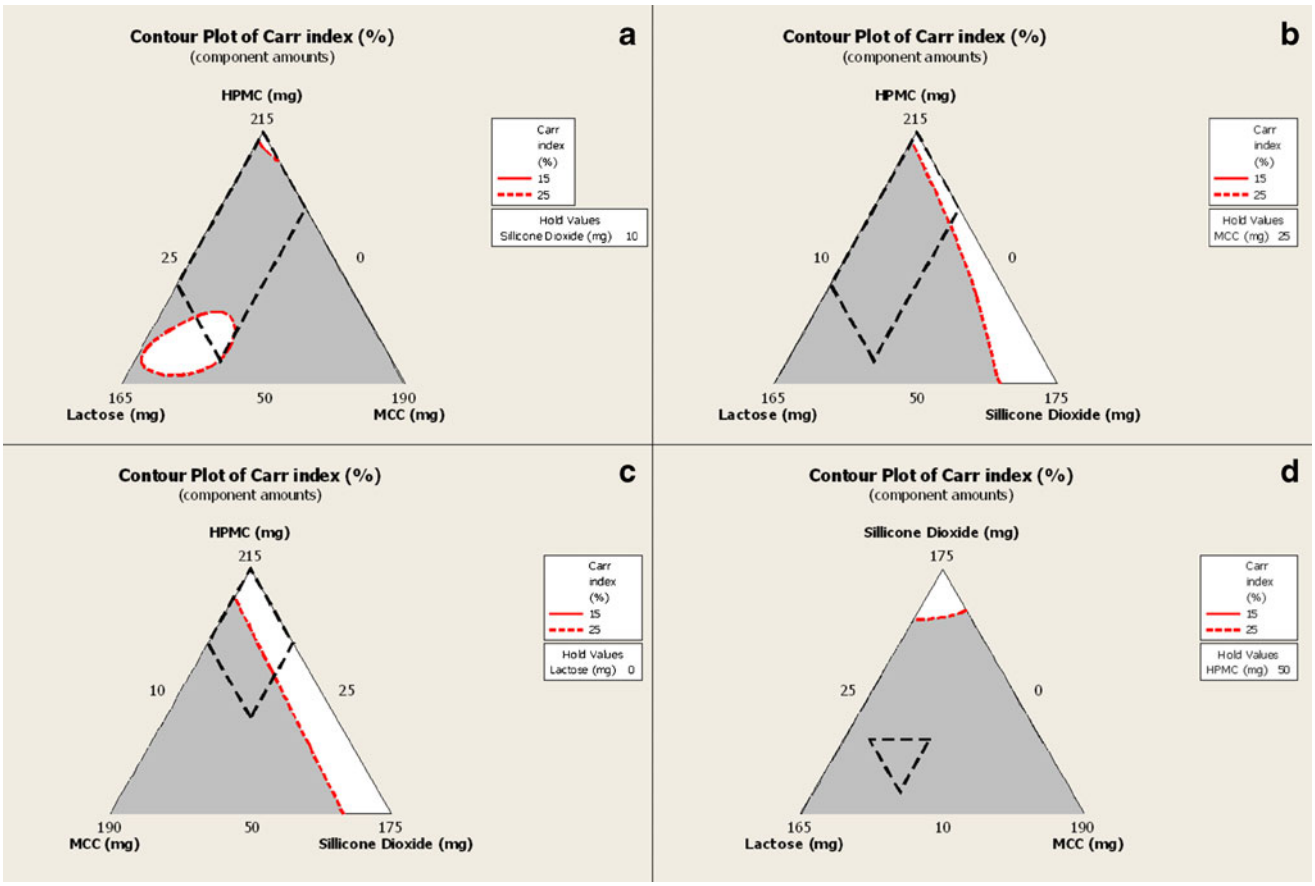

Fig. 5. Overlaid contour plots for Carr's index

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

Where R_t and T_t are the percent drug dissolved at each time point for the sample and reference products, respectively, n is the number of dissolution sample times, and t is the time sample index. The two curves are considered to be similar when f_2 value is close to 100 (50–100). Release profiles are considered to be different when f_1 value is close to 15; generally, f_1 value of less than 15 (0–15) indicates similarity between the profiles.

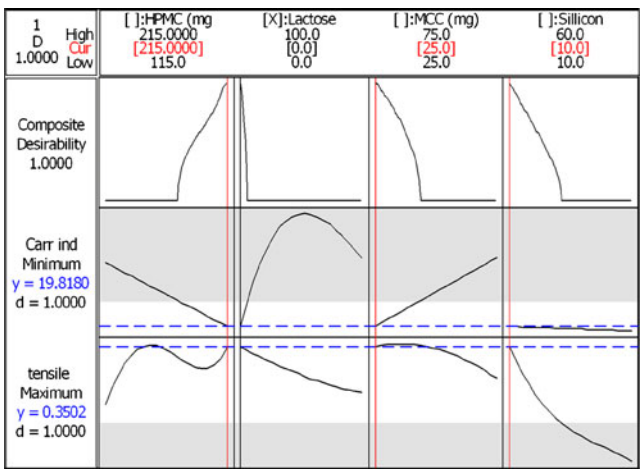

Fig. 6. Optimization plot for the best formulation

ANALYTICAL METHODS

Chromatographic Condition of HPLC Analysis

A Knauer HPLC system consisting of variable wavelength detector set at 210 nm and 20 µl loop injection valve (Knauer, Germany) was used for determination of the drug content. L11 column (Phenyl) 150×4.6 mm was eluted using a mixture of citrate buffer, potassium phosphate buffer, and acetonitrile (35:35:30) adjusted to pH 3 with phosphoric acid as the mobile phase with a flow rate of 2 ml/min and a detection wavelength at 210 nm (18). Quantification of divalproex was carried out by measuring the peak areas in relation to standard chromatograph analyzed under the same conditions.

RESULTS AND DISCUSSION

Formulation Methods

Formulation Design for Matrix Tablet Preparation

Minitab results for formulation compositions have been presented in Table I.

Table III. Similarity and Difference Factors

Selected formulation	Difference factor ($f1$)	Similarity factor ($f2$)
F2	24.96	41.80
F8	21.26	49.67
F11	15.94	54.70
F13	21.16	48.84
F21	12.91	58.40

Evaluation of Flowability

In general, increasing the moisture content of a powder decreases its ability to flow smoothly (19,20). One of the main causes of this phenomenon may be the increased thickness of the adsorbed liquid layer, which increases the strength of liquid bridges formed between particles (21). Divalproex is a hygroscopic powder. This unwanted physicochemical property poses serious problems during manufacturing of pharmaceutical formulations. In this study, it was not possible to measure the flowability of divalproex powder itself and some of the formulation mixtures by flow meter because the powder was too cohesive to flow through the funnel, so the method was changed to Carr's Index calculations (22). Figure 2 depicts the response trace plot indicating the effect of tablet components on calculated Carr's Index of prepared formulations as the response factor.

This type of graphs called components effect plots shows the effect of each formulation component on the desired response. Evaluation of these diagrams in formulations containing three or more components is very useful. Each component in the mixture has a trace, which represents its variation along the relevant axis. According to Fig. 2, lactose decreased Carr's Index and thus results in better flowability. This finding was previously concluded for all types of lactose which had reduced the angle of repose and Carr's Index with the effect on the weight and surface forces of powder (23,24).

In response trace plots, when two traces have the same slope, it can be concluded that the impact of these factors is similar. In Fig. 2, the most dominant effect is related to the HPMC. The figure also shows that the dominant effect of increasing HPMC amount is the decrease of Carr's Index. Research of Shinde and colleagues has shown that increasing the amount of HPMC K100 in the matrix polymeric systems of salbutamol sulphate increased Carr's Index (25).

It is also obvious that MCC incorporation results in unwanted Carr's index values. MCC shows poor flowability due to irregular shape and interlocking. Moreover, it loses a part of its compactability on direct compression, but the blend of MCC and colloidal silicon dioxide showed better flow than that of the original MCC (26).

Small particle size and high porosity of MCC powder (15) increase the cohesion forces between particles and consequently improved compaction of the powder mixture after tapping procedure is achieved. This phenomenon leads to high Carr's Index values (27). It should be noted that silicon dioxide, which appears as a light and soft powder with a very small particle size (15), can be adsorbed to the surface of porous excipients such as MCC and lactose (26,28) and lower the cohesion forces between MCC particles and simultaneously increasing particle density, resulting in Carr's Index value reduction (27,29). In many pharmaceutical investigations, silicon dioxide has been referred as a free-flow agent (12), and it is well known that lubricants can improve the powders' flowability (30).

Physical Properties of Tablets

The physical properties (Carr's Index, thickness, hardness, friability, and tensile strength) of the prepared tablets are presented in Table II. According to Table II, thickness variations are small in all cases and are ranged from 0.573± 0.005 to 0.610±0.010 cm. Descriptive analysis of thickness data shown in Table II revealed equal values for mean, median, and mode (0.59), which indicates normal distribution of data, and calculated CV value (1.62%) showed no significant differences between the thickness data of different tablet formulations. It was observed that increasing polymer concentrations resulted in a slight increase in the thickness of the tablet formulations. These results might be explained by the polymers' low binding properties. The friability of the prepared tablets falls into the range of 0.27% to 0.59% (USP limit<1%), and tensile strength of the prepared tablets ranged from 0.22 to 0.49 Mpa which complies with literature (31).

Hardness data were used as tensile strength in defined response values. Figure 3 shows the response trace plot for tensile strength. According to this figure, lactose which is commonly used as filler increases the hardness and tensile strengths of the prepared formulations. It was previously shown that a higher hardness yield is obtained by mixing lactose and MCC (32).

Chowhan and coworkers showed that hardness of tablets containing different binders like lactose at different moisture levels increased after overnight exposure to ambient room conditions, suggesting the moisture loss from the tablets after compression. The magnitude of the hardness increase is related to the type and concentration of the binder used in direct compression (33).

Table IV. Prediction Power of the Models

	Carr Index			Tensile strength		
	R (sq) (%)	P value	MPE	R (sq) (%)	P value	MPE
Mixture Regression	92.63	0.766	3.22	97.18	0.553	2.576
Stepwise	64.32	0.013	8.29	88.73	0	5.25
Forward	64.32	0.013	8.29	88.73	0	5.25
Backward	92.63	0.766	3.219	97.18	0.553	2.58

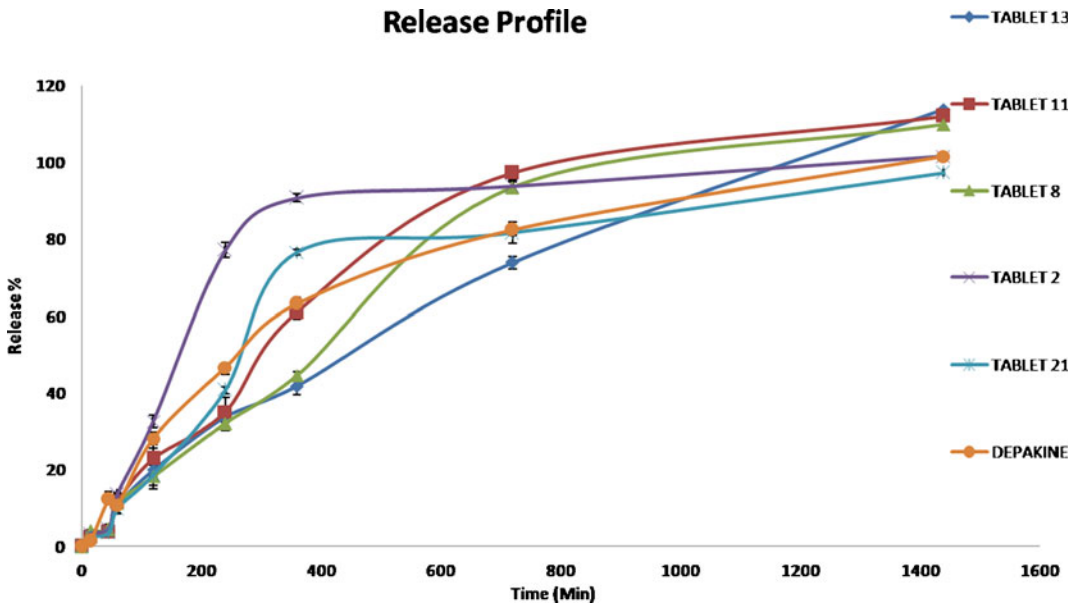

Fig. 7. Comparison of release profiles of selected formulations and commercial product

HPMC incorporation increased the hardness of the prepared tablets which is in accordance with previous observations (34).

Considering the slopes of each trace, the most dominant factors increasing and decreasing the tensile strength values (response) are lactose and silicon dioxide, respectively. Figure 4 shows mixture counter plot for Carr's index. In each plot, one of the components has defined as hold values and is constraint. Prepared formulations region has been surrounded by dotted line in each plot. Each figure is a simple guide to the desired excipient effect on response (Carr's index). According to Fig. 4a, in which lactose is the hold value, increasing silicone dioxide proportion leads to response decrease.

Another useful feature is overlaid contour plot. In these plots, desired region of the response value is being determined manually by the researcher, and the desired region of the excipients proportion is shown by white areas, while the prepared formulations have been shown by dotted line (Fig. 5).

In optimization plot graphs optimal conditions for Carr's Index (19/8%) and tensile strength (0.35) have been defined manually. These graphs suggest the best formulations. **M**initab's Response Optimizer searches for a combination of input variables that jointly optimize a set of responses by satisfying the requirements for each response in the set. Generally, a target value and an allowable maximum response value are defined by the scientists. In minimizing a response, the desirability for the response below the target value is 1; above the maximum acceptable is 0. The closer the response to the target, the closer the desirability is to 1. Composite desirability is the weighted geometric mean of the individual desirabilities for the responses (5). According to Fig. 6, a formulation composed of HPMC, lactose, MCC, and silicone dioxide in 215, 0, 25, and 10 mg, respectively, has a composite desirability equal to 1. This formulation is named as number 13 which was previously introduced in Table I.

As was shown in Table III, this formulation has a release profile which is different from the innovator, but is near zero-

Table V. Kinetic Models Fitting Results for F8 and Depakine (Dep) Release Data

	MPE %		r^2		*K*		*n*		Slope		Intercept	
	F8	Dep	F8	Dep	F8	Dep	F8	Dep	F8	Dep	F8	Dep
Zero order	16.06	141.72	0.996	0.895	0.0013	0.0012			0.001	0.001	0.015	0.079
First order	152.27	50.24	0.911	0.991	0.0037	0.0026			−0.004	−0.003	0.229	0.007
Higuchi	50.81	55.54	0.945	0.978	0.0384	0.0391			0.038	0.039	−0.201	−0.160
Peppas (Power Law)	20.74	26.54	0.923	0.952	0.0031	0.0003	0.836	1.374	0.836	1.374	−5.768	−8.074
Hixson-Crowell	66.45	96.56	0.953	0.970					0.001	0.001	−0.033	0.012
Square root of mass	41.24	112.22	0.970	0.954					0.001	0.001	−0.029	0.026
Three seconds root of mass	26.75	124.46	0.984	0.936					0.001	0.001	−0.017	0.043
Weibull	26.63	21.23	0.927	0.966	0.0021	0.0028	1.085	1.327	1.085	1.327	−6.677	−7.821
Linear probability	26.75	98.22	0.974	0.799	0.0045	0.0041			0.004	0.004	−1.665	−1.552
Log probability	40.64	22.01	0.841	0.981					0.780	0.863	−4.385	−4.740
Reciprocal powered time	36.89	17.42	0.856	0.983					−1.402	−1.580	7.852	8.709
Nonconventional order 1	20.17	134.91	0.993	0.914	0.0012	0.0011	0.150	0.150	0.001	0.001	−0.001	0.062
Nonconventional order 2	215.44	28.79	0.893	0.996	0.001	0.000	1.143	1.143	0.001	0.000	−0.045	−0.005

order kinetics [r^2=0.979 and mean percent error (MPE)=40] with Hixson-Crowell as proposed model (r^2=0.979 and MPE=17.8).

Prediction Power of the Models

The Carr's index and tensile strength as response values for the designed compositions were analyzed using Minitab software and design of experiments analysis option by four models including mixture regression, stepwise, forward, and backward, and the effect of each excipient on tensile strength and Carr's Index were determined.

r^2 and *P* value of each model for Carr's index and tensile strength were estimated by Minitab software. Table IV compares these values. The stepwise as well as forward models were selected for regressions.

In Vitro Drug Release Studies

The HPMC-based hydrophilic matrix systems can prolong the drug release characteristics of matrix tablets. Initial contact with the dissolution medium (0.1 N HCl, phosphate buffer pH 5.5) will release divalproex as a water-soluble drug depositing on the matrix tablet surface, Then, water penetrates the matrix, leading to polymer swelling. The swelling phenomenon along with drug dissolution and matrix erosion determines the drug release from swellable matrices. Drug release from hydrophilic matrix systems such as HPMC has been extensively reviewed and studied (2,35–37). Chopra *et al.* studied the extent of erosion and swelling related to hydrophilic matrix systems containing HPMC in dissolution media using scanning electron microscopy and observed that the hydrophilic matrix tablets underwent both swelling and erosion at the same time (2), and drug dissolution. Therefore, the drug could gradually diffuse from the matrix. With a higher polymer concentration, the resultant gel layer would be more viscous, and the tightness of the swollen hydrogel network will be increased, and consequently, divalproex diffusion through a gel layer to a dissolution medium will decrease.

Figure 7 compares the *in vitro* drug release percentage (dissolution profiles) of prepared tablets with commercial product, Depakine®, in dissolution media (HCL 0.1 N and phosphate buffer pH=5.5).

Dissolution profiles of selected matrix tablets according to their physical properties (tensile strength and friability) were compared to that of the commercial product, Depakine®, and have been presented in Table III.

Depakine® released 30%, 48%, 65%, and 84% of its drug content over 2, 4, 6, and 12 h, respectively. The similarity factor (f_2) values were found to be greater than 50, and difference factor (f_1) values were found to be less than 15 for F11 and F21. Thus, the most suitable formulations were F11 and F21 since the difference factor (f_1) values were 15.94 and 12.91, respectively, and the values of similarity factor (f_2) were 54.70 and 58.40, respectively. So these systems have similar dissolution profiles with Depakine®.

In controlled or sustained-release formulations, the diffusion, swelling, and erosion were the three most important rate-controlling mechanisms. The drug release data were fitted to different release models (38,39). Zero order, first order, Higuchi, Peppas (Power Law), Hixson-Crowell, square root of mass, 3 s root of mass, Weibull, linear probability, log probability, reciprocal powered time, nonconventional order 1, nonconventional order 2 were tested, and the proposed model was selected according to r^2 and MPE results.

The drug release from the polymeric system mostly occurred by diffusion and was best described by the Fickian diffusion. F8 showed zero-order kinetics (r^2=0.996 and MPE=16), but Depakine® release kinetic followed nonconventional order 2 (r^2=0.996 and MPE=29; Table V).

CONCLUSION

It can be concluded that mixture design is an easy method for designing suitable sustained-release divalproex formulations with similar dissolution behavior to innovators.

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