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International Journal of Pharmaceutics 240 (2002) 103–114

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Optimization of a self-nanoemulsified tablet dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients

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Received 15 January 2002; received in revised form 29 March 2002; accepted 29 March 2002

Abstract

The objectives of the present study were (1) to evaluate the effect of formulation ingredients on the release rate of Ubiquinone from its adsorbing solid compact; and (2) to prepare and evaluate an optimized self-nanoemulsified tablet formulation. A three factor, three-level Box–Behnken design was used for the optimization procedure, with the amounts of copolyvidone (X_1), maltodextrin (X_2) and microcrystalline cellulose (X_3) as the independent variables. The response variable was cumulative percent of Ubiquinone emulsified in 45 min with constraints on weight, flowability index, tensile strength, friability and disintegration time of the dry powdered emulsion and the resultant compact. Based on the experimental design, different Ubiquinone release rates and profiles were obtained. Mathematical equations and response surface plots were used to relate the dependent and independent variables. The regression equation generated for the cumulative percent emulsified in 45 min was $Y_6 = 64.10 - 12.32X_1 - 4.36X_2 - 25.53X_3 + 6.99X_1X_2 + 3.97X_1X_3 + 9.70X_2X_3 - 8.98X_1^2 - 16.22X_2^2 + 17.10X_3^2$. The optimization model predicted an 85.4% release with X_1, X_2 and X_3 levels of 66.6, 560.1 and 100, respectively. A new formulation was prepared according to these levels. The observed responses were in close agreement with the predicted values of the optimized formulation.

Keywords: Self-nanoemulsified drug delivery system; Coenzyme Q_{10}; Optimization; Box–Behnken; Response surface methodology

1. Introduction

Large proportions of new drug candidates have poor water solubility. To overcome these problems, various formulation strategies were reported in the literature, including complexation with cyclodextrins, solid dispersions and co-precipitates (Perng et al., 1998; Nazzal et al., 2002a). In recent years, however, much attention has been focused on lipid based formulations, with particular emphasis on self-emulsifying drug delivery systems (Pouton, 2000). Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00130-8

oil-in-water emulsion when introduced into aqueous medium under gentle agitation (Charman et al., 1992; Craig et al., 1993; Gao et al., 1998). Recently, a novel eutectic based self-nanoemulsified drug delivery system (SNEDDS) of Ubiquinone was introduced (Nazzal et al., 2002b). In eutectic-based SNEDDS, the melting point depression method allows the oil phase containing the drug itself to melt at body temperature from its semisolid consistency and disperse to form emulsion droplets in nanometer size range.

Utilizing the eutectic interaction between Ubiquinone (Coenzyme Q_{10}) and essential oils provided an attractive dosage form with high drug loading and small overall dosage size. Therefore, it was possible to incorporate this formulation into a model tablet preparation using a proper blend of excipients (Nazzal et al., 2002c). Formulating liquid medications into solid compacts has been the interest of many studies. Yang et al. (1979), Liao and Jarowski (1984) and later Spireas and Sadu (1998), Spireas et al. (1992) and Spireas et al. (1998) worked on producing solid solutions and 'liquisolids' based on the concept of blending liquid medications with selected powder excipients to produce free flowing, readily compressible powders. Such excipients included cellulose or lactose as the carriers and fine silicates as the coating material.

Adsorbing oils or liquid medications onto powders, however, often result in a blend suffering from poor flow and compaction properties. To overcome these problems, oil loading is reduced or fine particulates, such as silicates, are added in large quantities often exceeding the limits stated by the Code of Federal Regulation (CFR). Aqueous or organic based granulation can also be used to overcome particle cohesion. Using solvents in the preparation of dry emulsion-based solid compacts however was found to degrade the adsorbed eutectic-based SNEDDS and adversely affect the emulsion release rate. It was therefore of interest to prepare directly compressible material.

Eutectic-based SNEDDS of CoQ_{10} was found to form a 'wax-like' paste when mixed with small quantities of copolyvidone (Kollidon VA 64). In a reported study, Kollidon VA 64, a copolymer of vinylpyrrolidone and vinyl acetate, was shown to posses unique dry binding capacity (Kolter and Flick, 2000). Copolyvidone paste ground with a suitable excipient produces granules of good flow properties that are readily available for direct compression. Maltodextrin was found to be a good excipient for its solubility, particle size and acceptable adsorbing properties. When compressed, however, given granules produce soft compacts, therefore, directly compressible microcrystalline cellulose (MCC) was blended with the granules to increase the hardness of the tablets. MCC is often regarded as one of the best excipients for direct compression (Lahdenpaa et al., 1997). Extragranular MCC was shown to increase dissolution rates and compressibility of tablets made by high shear granulation (Li et al., 1996).

An important criterion that governs the quality of the dry adsorbed tablet dosage form is the release rate of the lipid-based formulation. Emulsion release rate is profoundly influenced by the physical and chemical attraction between the formulation and its adsorbing particles. Formulation ingredients, i.e. maltodextrin, copolyvidone and MCC, used in the preparation of the model adsorbed tablet dosage form would have a great effect on emulsion release rate. To optimize the level of these ingredients, response surface methodology was used in this study for its effectiveness in demonstrating the interactions between these factors on producing the optimum dry adsorbed tablet dosage form. The statistical optimization designs have been documented for the formulation of many pharmaceutical solid dosage forms (Karnachi and Khan, 1996; Singh et al., 1996; Wehrle et al., 1996; Sastry et al., 1997).

The objectives of the present work were (1) to evaluate the effect of formulation ingredients on the release rate of the SNEDDS formulation from their adsorbing compacts applying response surface methodology; and (2) to prepare and evaluate an optimized Coenzyme Q_{10} self-nanoemulsified based solid dosage form. As part of the optimization process, the main effects, interaction effects and quadratic effects of the formulation ingredients were investigated.

2. Materials and methods

2.1. Experimental design

A three factor, three level Box–Behnken design was used for the optimization procedure. This design is suitable for exploring quadratic response surfaces and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of each edge of the multidimensional cube that defines the region of interest. The nonlinear quadratic model generated by the design is of the form: $Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E$, where Y is the measured response associated with each factor level combination; A_0 is an intercept; A_1–A_9 are the regression coefficients; X_1, X_2 and X_3 are the factors studied; and E is the error term (Box and Behnken, 1960). The independent factors and the dependent variables used in the design are listed in Table 1.

2.2. Materials

Coenzyme Q_{10} was a generous gift from Kyowa Hakko USA (New York, NY). Polyoxyl 35 castor oil (Cremophor EL) and copolyvidone (Kollidon VA 64) were obtained from BASF Corp. (Mount Olive, NJ). Medium chain mono- and diglycerides (Capmul MCM-C8) was obtained from Abitec Corp. (Janesville, WI). Single fold lemon oil type C.P. Extra FCC was obtained from Citrus and Allied Essences Ltd. (Floral Park, NY). Maltodextrin with a mean particle diameter of 190 microns and a dextrose equivalent of 12.5 (Glucidex IT 12) was obtained from Roquette America, Inc. (Keokuk, IA). Microcrystalline cellulose (Avicel PH-112) was obtained from FMC Corp. (Newark, DE). HPLC grade methanol and *n*-hexane were purchased from VWR Scientific (Minneapolis, MN). All chemicals were used as received.

2.3. Preparation of the solid-state self-nanoemulsified dosage form

The eutectic-based self-nanoemulsified drug delivery system (SNEDDS) of CoQ_{10} was prepared as follows. CoQ_{10} and lemon oil at a ratio of 1:1 were accurately weighed into screw-capped glass vial and melted in water bath at 37 °C. Cremophor EL and Capmul MCM-C8 were added to the oily mix at a final concentration of 26.9% w/w

Table 1
Variables in the Box–Behnken design

	Levels		
	Low	Middle	High
Independent variables			
X_1 = Amount of copolyvidone added (mg)	30	165	300
X_2 = Amount of maltodextrin added (mg)	300	500	700
X_3 = Amount of microcrystalline cellulose added (mg)	100	250	400
	Constraints		
	Low	High	Goal
Dependent variables			
Y_1 = Weight (mg)	695	1000	Minimize
Y_2 = Flowability index (Carr's flow index point)	50	100	Maximize
Y_3 = Tensile strength (MPa)	0.05	0.32	Maximize
Y_4 = Friability (%)	0	1	Minimize
Y_5 = Disintegration time (min)	0	30	Minimize
Y_6 = Cumulative % of CoQ10 released after 45 min (%)			Maximize

Table 2
Observed responses for the Box–Behnken design

Run	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
1	30	500	400	1060	69	0.052	0.1	26.6	61.5
2	165	300	100	695	76.5	0.328	0.09	20.8	84.1
3	300	500	100	1030	67	0.177	0.28	22.8	70.9
4	300	700	250	1380	66	0.127	1.8	27.3	48.5
5	300	500	400	1330	67	0.125	1.6	6.1	49.2
6	30	500	100	760	43.5	0.02	0.08	16.3	91.1
7	165	300	400	995	69.5	0.205	0.11	3.9	49
8	165	500	250	1045	65	0.156	0.19	19.9	63.9
9	300	300	250	980	71	0.169	0.24	18.2	46.1
10	165	500	250	1045	61.5	0.14	0.21	18.1	63.5
11	165	500	250	1045	63	0.162	0.14	22.3	64.9
12	30	700	250	1110	45.5	0.04	0.1	28.8	49.9
13	165	700	100	1095	65	0.152	0.1	23.8	70.4
14	30	300	250	710	30.5	0.051	0.07	21.2	61.5
15	165	700	400	1395	65.5	0.148	0.5	12.3	54.6

each. The resultant emulsion was mixed with a stirring bar until a transparent solution of SNEDDS was obtained. The SNEDDS were then allowed to cool at ambient temperature for 24 h until a viscous paste was obtained. Detailed characterization of the eutectic-based drug delivery system can be found elsewhere (Nazzal et al., 2002b). Nanoemulsion adsorbed granular material was obtained from a mixture of SNEDDS paste, Kollidon VA 64, Glucidex IT 12 and Avicel PH-112. SNEDDS was initially mixed with Kollidon VA 64 using mortar and pestle until a semisolid waxy paste was obtained. The mixture was then ground with Glucidex IT 12 in the mortar for 1 min to obtain the dry microemulsion based granules. Finally, Avicel PH-112 was added to the granules and blended in a V-blender (Patterson-Kelley Co., E. Stroudsburg, PA) for 5 min. The amount of copolyvidone, maltodextrin and MCC, added in each of the 15 formulations, to make a tablet containing 130 mg of SNEDDS are given in Table 2.

2.4. Carr's flowability index

The flow properties of the solid state powdered emulsion were determined by the Carr's method. The following four tests were measured: (1) compressibility; (2) angle of repose; (3) angle of spatula; and (4) uniformity coefficient or cohesion. The flowability index (FI) was then calculated with the point scores as described (Carr, 1965).

2.4.1. Compressibility

The granular powder (10 g) was poured lightly into a 25 ml graduated cylinder. The powder was tapped until no further change in volume was observed. Powder bulk density, ρ_b (g cm^{-3}) and powder tapped density, ρ_p (g cm^{-3}) were calculated as the weight of the powder divided by its volume before and after tapping, respectively. Percentage compressibility was computed from the following equation:

$$\%\ \text{compressibility} = 100(\rho_p - \rho_b)/\rho_p.$$

2.4.2. Angle of repose

Angle of repose was measured using a protractor for the heap of granules formed by passing 10 g of the sample through a funnel at a height of 8 cm from the horizontal surface.

2.4.3. Angle of spatula

Angle of spatula was measured using a protractor and a steel spatula with a $5 \times 7/8''$ blade. The spatula was inserted to the bottom of the heap that was carefully built by dropping the material through a funnel at a height of 8 cm from the horizontal surface. The spatula was then with-

drawn vertically and the angle of the heap formed on the spatula was measured as the angle of spatula.

2.4.4. Uniformity coefficient

Uniformity coefficient was obtained by sieve analysis of 10 g of the powdered material using a Retsch® sieve shaker type AS200 (F. Kurt Retsch GmbH, Germany). The sieve shaker was fitted with eight US standard sieves (Dual mfg. Co., Chicago, IL) ranging in size from 0.075 to 1.7 mm and vibrated at a setting of 80 for 120 s. Uniformity coefficient was measured as the numerical value arrived at by dividing the width of the sieve opening that will pass 60% of the sample by the width of sieve opening that will pass 10% of the sample.

2.4.5. Cohesion

Cohesion is used with powders of very fine particles as a measure of the effective cohesive force when uniformity coefficient cannot be determined. Cohesion was measured for formulations 6, 12 and 14 (Table 2) by determining the retention of the material on three sieves with mesh numbers of 40, 60 and 100. Some 10 g of the powder were placed on top of the 40-mesh screen and the assembly was vibrated at a setting of 80 for 120 s. Based on the amount of the material left on each screen, percent cohesion was measured by giving 5, 3 and 1 points for every 5% of the powder retained on screen 40, 60 and 100, respectively.

2.5. Compaction of the solid state self-nanoemulsified dosage form

Microemulsion adsorbed compacts were prepared using concave elongated punches (Natoli Eng. Co., St. Charles, MO). Tablets were made by compressing the powder between the faces of the punch at a compaction pressure of 31.2 MPa. Punching assembly was mounted between the platens of a Carver® press model C (Carver Inc., Wabash, IN) attached to a semiautomatic compression assembly model 2826 (Carver). Punches were 0.750″ in length and 0.375″ in width and provided tablets with an area of the curved segment equivalent to 0.0083 cubic inches and a height of the curved surface above the central thickness equivalent to 0.06″.

2.6. Determination of tensile strength

Tensile strength provides a measure of the inherent strength of the compacted material independent of tablet dimensions (David and Augsburger, 1974). Tensile strength of the elongated, curve faced tablets was measured in triplicate with a three point flexure test using Instron material testing instrument, model 4442 (Instron Corp., Canton, MA). The load was applied at a rate of 25 mm min^{-1} and the fracture load was obtained from the load–displacement curve recorded using Instron software series IX. Tablets were examined for the mode of failure and only those with the fracture plane running through the center point of the surface of the tablet were used to derive tensile strength values.

The tensile strength was calculated by the following equation (Stanley and Newton, 1980; Newton et al., 2000):

$$\vartheta_f = \frac{3FL}{2d^2}\left(\frac{d+2a}{6A+bd}\right)$$

where ϑ_f is the tensile strength, F is the fracture load in a three point flexure text, b and d are the width and the thickness of the tablet, respectively, a is the height of the curved surface above the central thickness, A is the area of the curved segment and L is the distance between the lower supports.

2.7. Friability and disintegration studies

Friability of the compacts was measured using VanKel Type™, dual chamber drum, friability tester (VanKel, Cary, NC) set at a rotation speed of 25 rpm. Some 5 g of tablets were allowed to rotate for 4 min (100 rotations). At the end of the run, tablets were accurately weighed and percent friability was computed from the weight of tablets before and after the test.

Disintegration time for three replicates was measured using VanKel single basket disintegration testing system at 37 °C according to the USP XXIV specification.

2.8. Dissolution studies

Dissolution profiles of the self-emulsified tablets were determined using USP XXIV rotating basket apparatus (VanKel, model VK7000) at 37 °C. The rotating speed was 50 rpm and the dissolution medium was 900 ml of water. Samples (3 ml) withdrawn at fixed time intervals were filtered using a 10 μm VanKel filter and were assayed for Coenzyme Q_{10} by HPLC at 275 nm. Briefly, coenzyme Q_{10} was analyzed using a C18, 3.9×150 mm reverse phase chromatography column (Nova-Pak; Waters, Milford, MA). The mobile phase consisted of methanol: *n*-hexane (9:1) and was pumped at a flow rate of 1.5 ml min^{-1}. The dissolution experiments were carried out in triplicate. Details of the HPLC method can be found elsewhere (Nazzal et al., 2001).

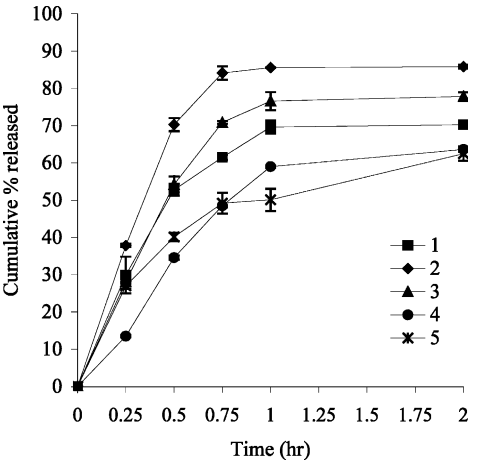

Fig. 1. Dissolution profiles of Coenzyme Q_{10} from the dry self-nanoemulsified solid formulations (Form.) 1–5.

3. Results and discussion

3.1. Experimental design

For the response surface methodology based on the Box–Behnken design, 15 experiments were required. The experimental runs and the observed responses for the 15 formulations are given in Table 2. Based on the experimental design, the factor combinations resulted in different CoQ_{10} release rates. The range of the responses Y_6, the cumulative percent of CoQ_{10} released from the self-nanoemulsified tablet dosage form and emulsified into the dissolution medium within 45 min, were 91.1% in formulation No. 6 (maximum) and 46.1% in formulation No. 9 (minimum). Dissolution profiles of all 15 formulations are shown in Figs. 1–3. Mathematical relationship in the form of polynomial equation for the measured responses obtained with the statistical package Statgraphics *plus* (version 4, Manugistics Inc., Rockville, MD) are listed in Table 3. The confidence that the regression equation would predict the observed values better than the mean for Y_1, Y_2, Y_3, Y_4 and Y_5 were 100, 80.4, 93, 93.2 and 88.4%, respectively. The polynomial equation relating the response Y_6 and the independent variables was: $Y_6 = 64.10 - 12.32X_1 - 4.36X_2 - 25.53X_3 + 6.99X_1X_2 + 3.97X_1X_3 + 9.70X_2X_3 - 8.98X_1^2 - 16.22X_2^2 + 17.10X_3^2$.

The above equation represents the quantitative effect of process variables (X_1, X_2 and X_3) and their interactions on the response (Y_6). The values of the coefficients $X_1 - X_3$ are related to the effect of these variables on the response (Y_6). Coefficients with more than one factor term and those with higher order terms represent interaction terms and quadratic relationships, respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect. The values of $X_1 - X_3$ were substituted in the equation

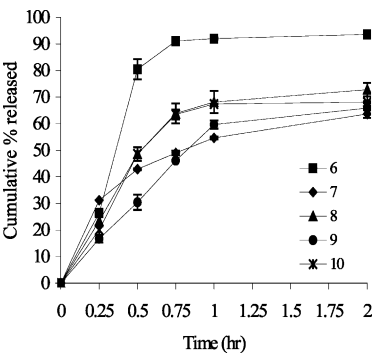

Fig. 2. Dissolution profiles of Coenzyme Q_{10} from the self-nanoemulsified solid formulations (Form.) 6–10.

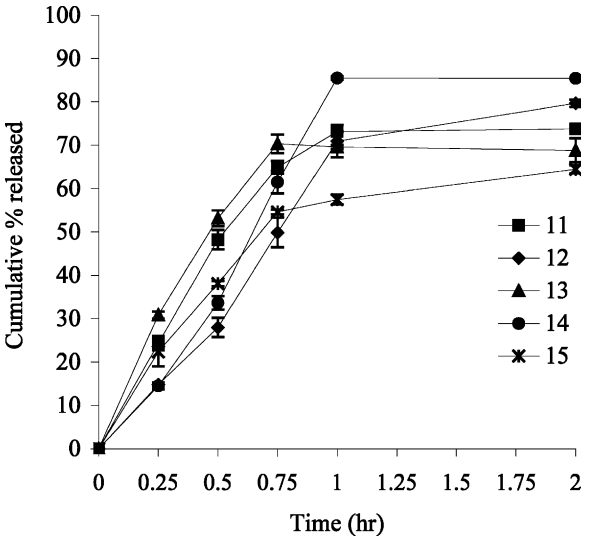

Fig. 3. Dissolution profiles of Coenzyme Q_{10} from the self-nanoemulsified solid formulations (Form.) 11–15.

to obtain the theoretical values of Y_6. The theoretical (predicted) values and the observed values were in reasonably good agreement, as seen from Table 4. The significance of the ratio of mean square variation due to regression and residual error was tested using ANOVA. The ANOVA indicated a significant ($P < 0.05$) effect of factors on response (F cal (41.10) > F crit (19.11)).

3.2. Effect of formulation ingredients on dissolution rate

Emulsion release rate and the cumulative percent of CoQ_{10} dissolved into the aqueous medium are important criteria that govern the quality of the solid-state self-emulsified dosage form. The extent of dissolution, however, is dependent on the reversible attraction and surface adsorption of CoQ_{10} and the oily formulation onto the adsorbing powder. Therefore, physical properties of the ingredients used to prepare the solid compacts have a profound effect on the emulsion release rate. This relationship between the formulation ingredients (independent variables) and emulsion release rates (dependent variables) was elucidated using contour and response surface plots. The effect of X_1 (copolyvidone) and X_2 (maltodextrin) and their interaction on Y_6 (the cumulative percent of CoQ_{10} dissolved in 45 min) at a fixed level of X_3 (250 mg of microcrystalline cellulose) are given in Figs. 4 and 5. At low levels of X_2, Y_6 is increasing from 44.02 to 63.34% when the amount of copolyvidone added (X_1) is decreasing from 300 to 30 mg. Similarly, at high levels of X_2, Y_6 is increasing from 46.66 to 51.98% when X_1 is decreasing from 300 to 30 mg. The decline in the efficacy of the tablets to release the self-emulsified formulation at high levels of copolyvidone can be explained as follows. Copolyvidone holds the oily formulation by forming 'wax-like' granules that entrap the formulation within its matrix base rather than by surface adsorption. This is crucial in preventing emulsion separation, especially when formulating with eutectic based system as in SNEDDS. Eutectic-based delivery systems require a close association of the eutectic agent with the drug. Increasing the amount of copolyvidone (Kollidon VA 64) effectively reduces the concentration of lemon oil, which was used as the eutectic agent, per unit area of the matrix. Besides, as the amount of copolyvidone increases it become less effective in absorbing the oily formulation and becomes incapable of producing matrix granules. This is similar to the aqueous-based granulation. Efficient granulation requires optimum amount of granulating fluid. In this case, the oily formulation acts as the granulating agent in what could be termed an 'oil based granulation'. As a consequence, an increasing amount of the absorbed emulsion becomes exposed to the subsequent layers of excipients and subjected to surface adsorption. Surface adsorption onto maltodextrin particles during the granulation process disrupts

Table 3
Regression equations for the responses[a]

$$Y_1 = 130 + X_1 + X_2 + X_3$$
$$Y_2 = 63.17 + 20.63X_1 + 4.75X_3 - 10.00X_1X_2 - 12.75X_1X_3 - 17.42X_1^2 + 14.33X_3^2$$
$$Y_3 = 0.15 + 0.11X_1 - 0.07X_2 - 0.04X_3 + 0.06X_2X_3 - 0.17X_1^2 + 0.06X_2^2 + 0.05X_3^2$$
$$Y_4 = 0.18 + 0.89X_1 + 0.50X_2 + 0.44X_3 + 0.77X_1X_2 + 0.65X_1X_3 + 0.19X_2X_3 + 0.69X_1^2$$
$$Y_5 = 20.10 + 7.03X_2 - 8.70X_3 - 13.50X_1X_3 - 10.83X_3^2$$

[a] The terms with small magnitude of coefficient are deleted from the equation.

Table 4
Observed and predicted values of the response $Y6$

Run	Observed	Predicted	Residuals	
1	61.5	59.6	1.9	
2	84.1	84.3	−0.2	
3	70.9	72.8	−1.9	
4	48.5	46.7	1.8	
5	49.2	51.2	−2	
6	91.1	89.1	2	
7	49	49.1	−0.1	
8	63.9	64.1	−0.2	
9	46.1	44	2.1	
10	63.5	64.1	−0.6	
11	64.9	64.1	0.8	
12	49.9	52	−2.1	
13	70.4	70.3	0.1	
14	61.5	63.3	−1.8	
15	54.6	54.4	0.2	
ANOVA for Y_6				
Source	DF	SS	MS	*F*-ratio
Total (corrected)	14	2468		
Regression	9	2435	271	
Residual	5	33	6.6	41.1

Confidence that the regression equation predicts the observed values better than the mean = 98.7%.

the emulsion and explains the decline in emulsion release rate. At low levels of X_1, the amount of the formulation emulsified after 45 min is decreasing from 63.34 to 51.98% as X_2 is increasing from 300 to 700 mg. Similar trend was observed for the effect of X_1 and X_3 (amount of MCC added) and their interaction on Y_6. As seen from Figs. 6 and 7, at low levels of X_3, Y_6 is decreasing from 89.07 to 72.78% as X_1 is increasing from 30 to 300 mg. Similarly, at high levels of X_3, Y_6 is decreasing from 59.58 to 51.23 as X_1 is increasing from 30 to 300 mg. A decline in emulsion release rate was also observed with an increase in the amount of MCC (X_3) added to the formulations (Figs. 6 and 7). At low levels of X_1, Y_6 is decreasing from 89.07 to 59.58% as X_3 is increasing from 100 to 400 mg. MCC however, was not used during the granulation process. Rather, it was blended with the granules at a later stage in an attempt to increase the hardness of the compacts. Compaction of the powdered material and the 'squeeze-out' effect explains the decline in emulsion release rate with an increase in either X_2 or X_3. Any traces of the self-nanoemulsified formulation released from the granular matrix during tableting will be adsorbed onto the surfaces of the fine MCC particles added to the formulation. Hydrophobic CoQ_{10} particles that exist in their crystalline form within the eutectic formulation forms tight bonds with the hydrophobic surfaces of the insoluble MCC particles. Irreversible hy-

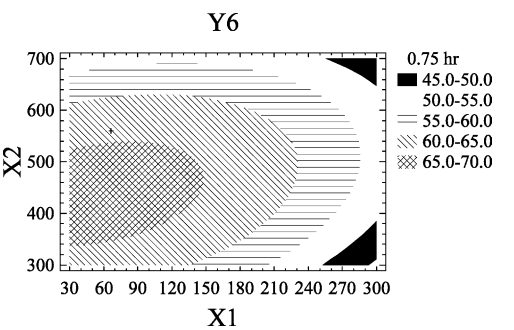

Fig. 4. Contour plot showing the effect of the amount of copolyvidone (X_1) and maltodextrin (X_2) added on the response Y_6.

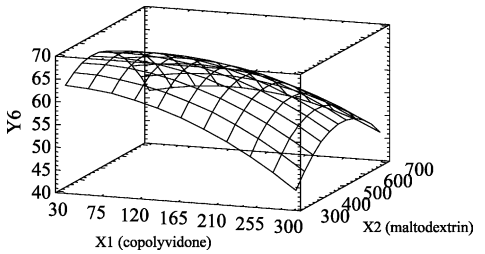

Fig. 5. Response surface plot (3D) showing the effect of the amount of copolyvidone (X_1) and maltodextrin (X_2) added on the response Y_6.

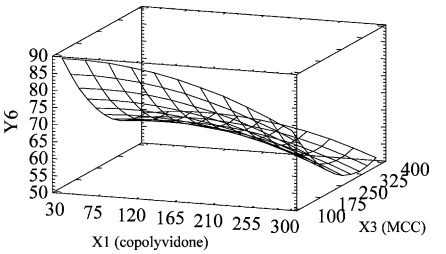

Fig. 7. Response surface plot (3D) showing the effect of the amount of copolyvidone (X_1) and microcrystalline cellulose (X_3) added on the response Y_6.

drophobic attraction between CoQ_{10} and MCC during powder compaction causes variable release rates where the oily components of the formulation are emulsified into the aqueous medium at a faster rate compared to the release of CoQ_{10}. During compaction however, 'squeezed out' formulation will be adsorbed on extragranular maltodextrin as well. This relationship between X_2 (maltodextrin) and X_3 (MCC) and their effect on Y_6 is given in Figs. 8 and 9. As previously discussed, surface adsorption onto insoluble MCC particles explains the decrease in Y_6, at low levels of X_2, from 84.33 to 49.10% as X_3 increases from 100 to 400 mg. Similarly, at high levels of X_2, Y_6 is decreasing from 70.27 to 54.44% as X_3 is increasing from 100 to 400 mg. Maltodextrin, however, is soluble in water. Therefore, the effect of maltodextrin on emulsion release rate is less significant compared to the effect of MCC. This explains the decline in Y_6 at low levels of X_3, from 84.33 to 70.27% as X_2 increases from 300 to 700 mg. At high levels of X_3 however, MCC becomes the dominant adsorbing agent during powder compaction. This explains the release of only 49.10% of the formulation at low levels of X_2. Increasing the amount of maltodextrin added at high levels of X_3 diverts some of the exuded formulation onto the soluble maltodextrin particle, thereby increasing the amount of CoQ_{10} released to 54.44%.

3.3. Optimization of the formulation ingredients

After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the response Y_6. Optimization was performed to obtain the levels of X_1–X_3, which maximize Y_6 at constrained conditions of Y_1 through Y_5. Formulation ingredients were optimized to obtain compacts that would maximize the amount of the self-nanoemulsified

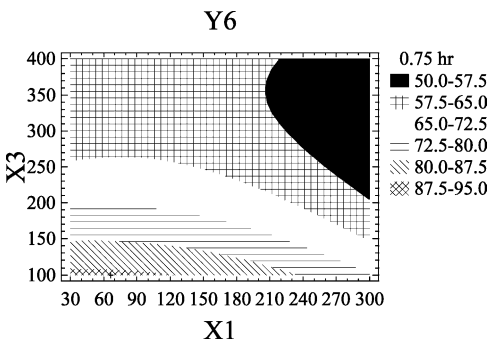

Fig. 6. Contour plot showing the effect of the amount of copolyvidone (X_1) and microcrystalline cellulose (X_3) added on the response Y_6.

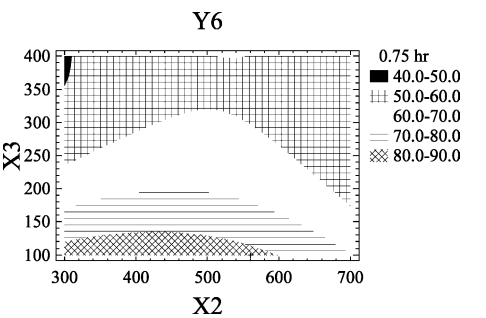

Fig. 8. Contour plot showing the effect of the amount of maltodextrin (X_2) and microcrystalline cellulose (X_3) added on the response Y_6.

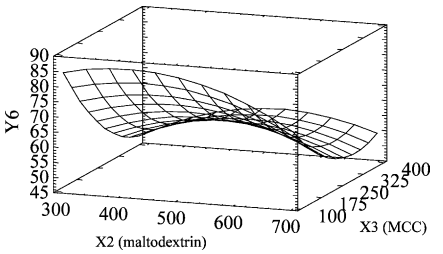

Fig. 9. Response surface plot (3D) showing the effect of the amount of maltodextrin (X_2) and microcrystalline cellulose (X_3) added on the response Y_6.

formulation released within 45 min. Constraints were made in an effort to obtain an optimized formulation with an improved flow, friability, disintegration and compaction properties. The objectives were to obtain a formulation with a final weight < 1 g with a flow index exceeding 50 in a scale method reported by Carr. Percent friability and disintegration time were targeted for $< 1\%$ and 30 min, respectively in order to comply with the USP requirements for the nutritional supplements (USP24 $< 1216 >$ and $< 2040 >$). The optimized levels of the formulation ingredients that would achieve the desired dissolution and compaction properties and their predicted $Y_1 - Y_6$ responses are given in Table 5. To verify these values, a new formulation was prepared according to the predicted levels of X_1, X_2 and X_3. A representative dissolution profile of the optimized formulation is given in Fig. 10. Obtained Y_6 was in a close agreement with the predicted value. The predicted and observed values are shown in Table 5. The given results demonstrate the reliability

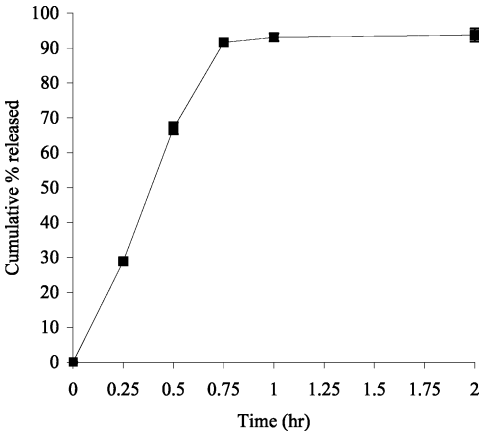

Fig. 10. Dissolution profile of the optimized Coenzyme Q_{10} self-nanoemulsified tablet dosage form.

of the optimization procedure in predicting the dissolution behavior of solid-state self-nanoemulsified drug delivery systems.

4. Conclusion

Optimization of the solid self-nanoemulsified formulation of Coenzyme Q_{10} was performed using Box–Behnken design. The amount of added copolyvidone (X_1), maltodextrin (X_2) and microcrystalline cellulose (X_3) showed a significant effect on the dissolution and release rate of the self-nanoemulsified formulation from their solid compacts, as well as on the physical and compaction properties of the dry emulsion-based tablet dosage form. The quantitative effect of these factors at different levels was predicted by using polynomial equations. Response surface

Table 5
Optimized values obtained by the constraints applied on $Y1$–$Y6$

Variable	Nominal values	Response	Expected values	Observed values
X_1	66.6	Y_1	856.7	856.7
X_2	560.1	Y_2	51.4	61
X_3	100	Y_3	0.082	0.094
		Y_4	0.01	0.04
		Y_5	18.15	18.21
		Y_6	85.36	91.6

methodology was then used to predict the levels of the factors X_1, X_2 and X_3 required to obtain an optimum formulation with minimum weight, friability and disintegration time and with a maximum tensile strength and flowability index value. A new formulation was prepared according to these levels. Observed responses were in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing self-nanoemulsified based tablet dosage forms.

Acknowledgements

Part of this work was supported by the Texas ATP/ARP Grant No. 010674-0110-1999. The authors wish to thank Dr Quentin Smith and Dean Arthur Nelson for their support in establishing the Center for Drug Delivery and Formulations at Texas Tech. University School of Pharmacy.

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