AAPS PharmSciTech, Vol. 9, No. 1, March 2008 (© 2007)
DOI: 10.1208/s12249-007-9008-6

Research Article

Effect of Eudragit® RS 30D and Talc Powder on Verapamil Hydrochloride Release from Beads Coated with Drug Layered Matrices

Yasser El-Malah[1] and Sami Nazzal[1,2]

Received 2 July 2007; accepted 7 September 2007; published online 9 January 2008

Abstract. The aim of this study was to investigate the effect of Eudragit® RS 30D, talc, and verapamil hydrochloride on dissolution and mechanical properties of beads coated with "drug-layered matrices". This was accomplished with the aid of a three-factor multiple-level factorial design using percent drug release in 1 and 2 h, T_{50}, tensile strength, brittleness, stiffness and toughness as the responses. Beads were coated in a fluidized-bed coating unit. Surface morphology and mechanical properties were evaluated by surface profilometry and texture analysis, respectively. No cracks, flaws and fissures were observed on the surfaces. The mechanical properties were dependent on the talc/polymer ratio. The release of verapamil from the beads was influenced by matrix components. Increasing the level of both talc and Eudragit decreased the percent drug released from 67% to 4.8% and from 80.7% to 6.7% in 1 and 2 h, respectively, and increased T_{50} from 0.8 to 25.7 h. It was concluded that beads could be efficiently coated with "drug-layered matrices". The release of drug, however, depends on a balance between the levels of drug, talc, and polymer, whereby desired dissolution and mechanical properties could be controlled by the talc/polymer ratio and the level of drug loading.

KEY WORDS: drug layered matrix; Eudragit RS 30D; fluid bed coating; talc powder; verapamil hydrochloride.

INTRODUCTION

Multiparticulate dosage forms, such as beads or pellets, offer several advantages over conventional dosage forms. For example, their gastric emptying rate is more predictable and they are less likely to experience dose dumping (1,2). When manufacturing a multiparticulate dosage forms, the drug is either incorporated within the beads through a process of extrusion and spheronization (3,4) or simply adhered to the surface of the beads by a fluidized bed coating process (5,6). When the drug is layered on the surface of the beads, it is subsequently coated with a control release membrane that would allow the beads attain the desired drug release profile. Alternatively, both the drug and the polymer required for controlled release could be coated on the beads simultaneously in a single step using a single coating dispersion (7). While less common, coating beads with a film forming material incorporating the drug, i.e., a layered drug matrix around the beads, is economic. It reduces the number of steps involved in the coating process meanwhile it provides flexibility in attaining the desirable drug release profile (8). Very few studies; however, were reported in the literature that address this alternative coating approach. A notable example is a study by Wu and McGinity (9) in which beads were coated with a blend of ibuprofen and Eudragit RS 30 D as the film forming material. While ibuprofen was evaluated for its plasticizing effect, it was concluded that the release rate of ibuprofen was influenced by both the amount of ibuprofen in the polymeric film and the thickness of the coating layer. Another factor that is seldom considered for its effect on layered matrices is the presence of an anti-tacking agent. The addition of an anti-tacking agent such as talc to the film-forming material is often recommended to expedite processing by avoiding the agglomeration problems caused by polymeric particles during the coating process. The importance of talc, however, is more prominent in aqueous-based coating systems as the mechanism by which films are formed using these systems is more complex than those encountered with the organic-solvent based systems. In aqueous systems the coalescence of individual colloidal particles and the interdiffusion of polymeric particles must occur to form a continuous film (10). This is accomplished during the coating process as a result of water evaporation, which generates surface tension effects and capillary forces among polymer particles (11). The slow rate of water evaporation coupled with its high latent heat of vaporization, however, is also responsible for the tackiness problems experienced with these systems (12). Therefore, talc powder has been frequently used as an inert anti-tacking agent in aqueous-based acrylic colloidal dispersions when coating either single unit dosage forms (tablets) or multiparticulate units (3,11,13). Maejima and McGinity (11) reported that high levels of talc powder up to 200%, based on dry polymer weight, however, had a stabilizing effect on the release rate of

[1] Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, Louisiana 71209-0497, USA.
[2] To whom correspondence should be addressed. (e-mail: nazzal@ulm.edu)

Table I. Independent and Dependent Variables of the Full Factorial Design

Independent Factors	Levels		
Coded values	−1	0	1
X_1: drug level (g)	1	NA	3
X_2: talc level (g %)[a]	50	150	250
X_3: polymer level (g)	7.5	NA	13

[a] Amount of talc based on dry polymer weight.
Dependent factors are Y_1: percent drug released in 1 h, Y_2: percent drug released in 2 h, Y_3: tensile strength (g/mm^2), Y_4: distance to fracture force (taken as an opposite indication to brittleness; mm), Y_5: stiffness (g/mm), Y_6: toughness (g/mm), T_{50}: time to 50% release (h)

theophylline from coated beads after storage at different conditions. This study implied that talc at higher levels might exhibit an effect other than its intended use as an anti-tacking agent. Talc was also shown to act as a thickness building agent in matrices (8,14). Therefore, talc is expected to have a profound effect on the release rate of drugs from beads coated with drug layered matrices.

Based on the preceding discussion, the overall objective of this study was therefore to evaluate the dissolution and physical properties of Nu-Pareil® beads directly coated with an aqueous dispersion consisting of a blend of verapamil HCL, Eudragit® RS 30 D, and talc. More specifically the goals of this study were to evaluate the effect of the level of verapamil HCL as a model drug, Eudragit® RS 30 D as the film forming material, and talc powder on the mechanical strength of the beads and the dissolution rate of the drug. To accomplish this goal a three-factor, multiple-level full factorial design was used to evaluate the significance of each factor and their interaction effect on the responses.

MATERIALS AND METHOD

Materials

The aqueous dispersion of Eudragit® RS 30D [poly (ethyl acrylate, methyl methacrylate) trimethylammonioethyl methacrylate chloride] was obtained from RÖhm America Inc. (Piscataway, NJ). Triethyl citrate (TEC) was obtained from Morflex Chemical Co. (Greensboro, NC). Talc was purchased from Spectrum Quality Products (Gardena, CA). Verapamil HCL was supplied by BASF (Mount Olive, NJ). Nu-pareil sugar spheres NF mesh size 14/18 (1,000–1,410 μm diameter) was provided by CHR Hansen (Mahwah, NJ). Nu-pareil Sugar Spheres NF are approximately spherical granules composed of sucrose and starch used as inert cores upon which the drug is coated. All chemicals and raw materials were used as received without further processing. Water used in this study was purified by Nanopure® Water System (Barnstead/Thermolyne, Dubuque, IA).

Experimental Design

In this study a three factor multiple level full factorial design was used to construct the response surface and the mathematical model for the tested variables. Full factorial design is commonly used to reveal the main effects and interaction effects between the independent variables of the experiment. For completely randomized factorial design with three factors at multiple levels, second order polynomial equation was generated using response surface methodology (RSM), which includes quadratic terms and two factor interaction that explain the non-linear nature of the response (15). A second order polynomial equation that describes the effect of independent factors on the response is expressed in the following form:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_1X_3 + A_6X_2X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E \quad (1)$$

Where Y is a response, X_1–X_3 are the independent factors, A_o is a constant, A_1–A_9 are the coefficients of the respective variables and their interaction terms, and E is an error term. Results of statistical analysis are usually considered significant if their corresponding P values are less than 0.05. In this study the levels of the independent factors that were used to construct a full factorial design is given in Table I. A total of 12 experimental runs were prepared and tested according to the full factorial design.

Preparation of Beads Coated with Drug Layered Matrices

A total of 12 coating dispersions were prepared according to the amounts specified by the experimental design. The

Table II. The Randomized Runs of the Full Factorial Design and the Observed Responses

Run	Drug Level	Talc Level	Polymer Level	Y_1 (%)	Y_2 (%)	T_{50} (h)	Y_3	Y_4	Y_5	Y_6	R_q (nm)	R_a (nm)	Bead Diameter (mm)
1	1	0	−1	83.3	86.1	0.40	1,599	0.299	9,759	496.7	353	293	1.53
2	1	1	−1	78.6	82.0	0.40	1,443	0.284	9,077	398.8	505	381	1.51
3	−1	1	−1	8.50	12.8	12.4	1,059	0.281	8,019	357.6	788	621	1.64
4	−1	0	1	8.96	12.2	16.2	1,076	0.394	8,959	782.4	1,155	894	2.04
5	1	0	1	40.3	72.4	1.42	1,261	0.402	7,699	664.1	387	316	1.77
6	1	−1	−1	98.0	99.0	0.25	799.6	0.158	8,720	127.3	517	419	1.48
7	−1	0	−1	14.5	36.3	2.88	1,511	0.257	9,991	349.0	357	280	1.47
8	1	1	1	37.1	68.5	1.42	1,125	0.367	9,428	706.1	698	569	1.97
9	−1	1	1	4.80	6.72	25.7	1,408	0.342	8,668	562.5	913	723	1.65
10	−1	−1	1	16.3	29.2	3.02	1,409	0.279	8,978	333.7	440	346	1.49
11	1	−1	1	90.9	98.2	0.25	1,468	0.316	8,639	416.4	568	415	1.54
12	−1	−1	−1	67.0	80.7	0.83	1,080	0.178	9,735	146.7	744	555	1.43

composition of the coating dispersions is given in Table II. Briefly, talc powder was first homogenized with a blend of water and 20% triethyl citrate, based on the dry polymer weight, for 10 min. Then it was added to the Eudragit® RS 30D aqueous dispersions under agitation. Verapamil HCL was dissolved in purified water and then added to the coating dispersion. Masterflex® Digi-Static® pump (Cole-Parmer Instrument Company, Veronon Hill, Illinois) was used to feed the formulations to the fluidized-bed coater (MFL.01, Vector Corporation, Marion, IA). To ensure that only dry air is flowing into the system, a Hankison air trap and several in-line filters were placed between the fluid-bed and the compressor. Loading charge of 20 g Nu-pareil® sugar spheres, of mesh size 14/18 (1,400–1,000 μm in diameter), was used in this study. Processing parameters (Table III) were kept constant for all runs. The coating suspension was agitated during the coating process to maintain homogeneity in the formulation. At the end of the coating process, coated beads were cured in an oven at 40°C for 24 h.

Morphology of Beads Coated with Drug Layered Matrices

The surface view of the intact and divided beads was recorded using a VHX-600 Digital Microscope with an optical diffused lighting source (KEYENCE Corp., Woodcliff Lake, NJ). Surface roughness of the beads coated with a "film matrix" was measured using Alpha-Step 1Q stylus contact surface profiler (model AS-1Q, KLA-Tencor Corporation, San Jose, CA). The instrument was adapted with a diamond stylus which was programmed to scan a length of 750 μm of the pellet surface at a scanning speed 20 μm/s. In each experiment, the R_q (RMS) and R_a (Average) surface parameters were determined.

Content Uniformity

To extract verapamil HCL, an accurately weighed sample of the beads (1.5 g), from each run, was ground and transferred to a 500 ml volumetric flask containing purified water. The flask was sonicated for 30 min. After 24 h of storage at room temperature, the aqueous dispersion was then filtered, diluted, and analyzed spectrophotometrically at 275 nm (Cary 50 probe UV spectrophotometer, Varian Inc, Cary, NC). All assays were carried out in triplicate and the mean value was reported.

Table III. Coating Process Parameters

Parameters	
Nozzle diameter	0.029 mm
Wurster insert	Bottom spray
Atomization air pressure	25 psi
Preheating temperature	32°C
Preheating time	5 min
Batch size	20 g
Spray rate	0.6 ml/min
Inlet temperature	38°C
Bed temperature	29–30°C
Inlet air	220 LPM

Dissolution Study

Dissolution studies on a fixed weight of 1.5 g of the beads were performed in triplicates using a USP type II (paddle) dissolution apparatus (VK 7000, Varian Inc., Cary, NC). The dissolution medium consisted of 900 ml of purified water, which was maintained at 37°C and agitated at 75 rpm. Samples (5 ml) were withdrawn at predetermined time intervals, filtered and analyzed spectrophotometrically at 275 nm. From the result, the cumulative percent drug release-time profiles were determined. Dissolution experiments were performed in triplicates, unless otherwise stated.

Mechanical Properties of an Individual Pellet

The mechanical properties of a single pellet were determined in terms of tensile strength, brittleness, Young's modulus and toughness using a TA.XTPlus texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) fitted with a 1 mm^2 flat stainless steel probe. Beads were compressed at a rate of 0.10 mm/s whereby mechanical properties were estimated from the generated force–displacement profiles.

RESULTS AND DISCUSSION

Statistical Design and Analysis

Full factorial multiple levels experimental design was used in this study to evaluate the main effects and the interaction terms of the test independent factors. The levels of each independent factor evaluated and the investigated responses are listed in Table I. Verapamil and polymer effect were evaluated at two levels only whereas talc was evaluate at three levels. This was based on preliminary studies (unpublished data), which showed that polymer and verapamil exert linear effect on the responses. A 12-run factorial design was generated using STATGRAPHICS plus 5 statistical experiment design software (Manugistics Incorporation, Rockville, MA). The 12 runs in the experimental design along with the observed responses are shown in Table II. A standard significance level of α=0.05 was selected in this study. This indicates that the effect of the test variable will be considered significant if its P value is less than 0.05. Table IV shows the model parameters obtained from analysis of variance (ANOVA) for the responses Y_1–Y_6 and T_{50}. Table IV was used to construct the models that describe the effect of the test variables on the responses (Y_1–Y_6 and T_{50}). Regression equations for the fitted models are presented in Table V. The magnitude and direction of the factor coefficient in the equations explains the nature of effect of factors (X_1–X_3) on the response. Factors with coefficients of greater magnitude show high effect on the response. The sign of the coefficient indicates the direction by which the factor influences the response. The effect of factors on the responses is further elucidated in subsequent sections.

Morphology of Beads Coated with Drug Layered Matrices

To investigate the effect of X_1 (amount of verapamil HCL), X_2 (amount of talc powder) and X_3 (amount of Eudragit RS 30D) on the surface topography and roughness

Table IV. Model Parameters for the Dependent Responses

	Y_1		Y_2		T_{50}		Y_3		Y_4		Y_5		Y_6	
Term	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value
Constant	36.4		57.0		5.21		1362		0.338		9102		573.1	
X_1	25.7	0.006	27.4	0.001	−4.73	0.003	12.76	0.900	0.008	0.218	−85.91	0.727	23.13	0.376
X_2	−17.9	0.038	−17.1	0.010	4.40	0.007	34.88	0.779	0.043	0.003	−110.3	0.715	125.1	0.012
X_3	−12.6	0.058	−9.15	0.040	2.57	0.022	21.23	0.834	0.054	0.001	−244.3	0.348	132.4	0.005
X_2^2	13.4	0.258	7.90	0.289	−4.11	0.009	40.44	0.746	−0.062	0.844	−194.2	0.712	−191.9	0.018
X_1X_2	−0.40	0.948	5.45	0.218	−2.23	0.035	−19.22	0.850	0.001	0.522	396.0	0.232	15.19	0.622
X_1X_3	−2.64	0.610	4.47	0.216	0.32	0.844	−137.7	0.532	0.004	0.006	−54.57	0.824	−5.120	0.836
X_2X_3	1.58	0.801	4.08	0.336	1.52	0.154	−120.7	0.358	−0.014	0.097	229.5	0.461	4.500	0.882

Table V. Regression Equations of the Fitted Models

Regression Equations
$Y_1 = 36.7 + 25.7X_1 - 17.9X_2 - 12.6X_3 - 0.4X_1X_2 - 2.6X_1X_3 + 13.4X_2^2 + 1.6X_2X_3$
$Y_2 = 51.8 + 27.4X_1 - 17.1X_2 - 9.2X_3 + 5.5X_1X_2 + 4.5X_1X_3 + 7.9X_2 \wedge 2 + 4.1X_2X_3$
$T_{50} = 5.21 - 4.73X_1 + 4.4X_2 + 2.57X_3 - 4.11X_1X_2 - 2.23X_1X_3 + 0.32X_2^2 + 1.52X_2X_3$
$Y_3 = 1,361.8 - 12.76X_1 + 34.88X_2 + 21.23X_3 + 40.44X_1X_2 - 19.22X_1X_3 - 137.68X_2^2 - 120.69X_2X_3$
$Y_4 = 0.3 + 0.01X_1 + 0.04X_2 + 0.05X_3 + 0.001X_1X_2 + 0.004X_1X_3 - 0.06X_2^2 - 0.014X_2X_3$
$Y_5 = 9,101.7 - 85.9X_1 - 110.3X_2 - 244.4X_3 + 396.02X_1X_2 - 54.6X_1X_3 - 194.2X_2^2 + 229.5X_2X_3$
$Y_6 = 573.1 + 23.1X_1 + 125.1X_2 + 132.4X_3 - 191.9X_2^2 + 15.2X_1X_2 - 5.1X_1X_3 + 4.5X_2X_3$

of the beads, microscopic imaging and contact profilometry were carried out on intact and scalpel-divided beads. A representative microscopic image is given in Fig. 1. It was observed that an increase in the level of study factors resulted in an increase in the thickness of the matrix layer around the core. At any factor-level combination, the layer around the core homogenously surrounded the core indicating the efficiency of the coating process. No cracks or fissures were observed at any combination levels of the study factors. When the amount of verapamil HCL was increased, at a constant level of Eudragit® RS 30D and talc, microscopic white particles of verapamil HCL were observed on the surface of the beads. These particles would serve as entrance or exit points for the dissolution medium to the deeper region of the matrix after the release of the drug from the surface of the beads.

The effect of the study factors on the surface roughness of the beads coated with the film matrix was determined by measuring the surface parameters R_q (RMS) and R_a (Average). R_q (RMS) is the Root-Mean-Square or geometric average deviation of the profile from the mean line measured in the sampling length. R_a (Average) is the arithmetic average deviation of the absolute values of the roughness profile from the mean line or center line. Measured R_q and R_a values for all beads were in the nano-meter range (Table II), which indicates smoothness of the surfaces and absence of cracks. Figure 2 shows the effect of increasing the amount of X_2 and X_3 on R_q and R_a roughness parameters. Both R_q and R_a increased with an increase in the levels of X_2 and X_3 which

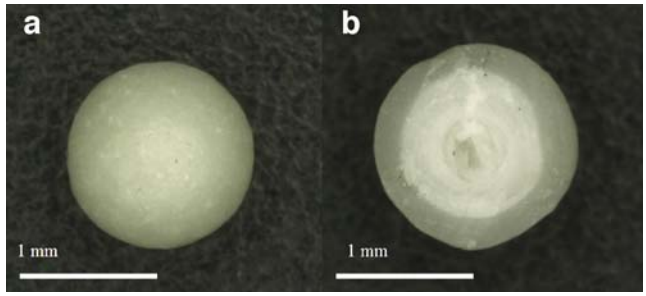

Fig. 1. Microscopic image of the **a** external surface of intact pellet and **b** internal surface of divided pellet

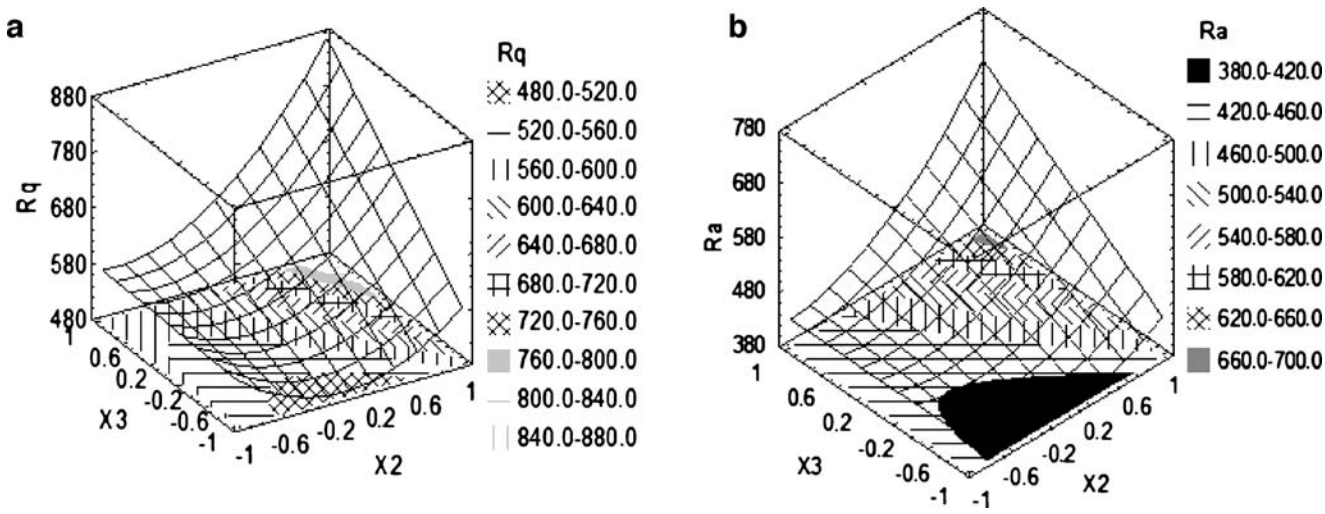

Fig. 2. Response surface plots showing the effect of talc level (X_2) and polymer level (X_3) on **a** R_q roughness parameter and **b** R_a roughness parameter

indicates that an increase in the amount of talc powder and Eudragit® RS 30D increases the surface roughness of the beads coated with film matrices.

Effect of Study Factors on Verapamil HCL Release

The influence of the level of Eudragit® RS 30D, talc and verapamil HCL on the release properties of verapamil HCL from the beads coated with drug layered matrices was determined from their dissolution profiles, which are given in Fig. 3. The effect of each factor on the responses is discussed in the following sub-sections. Table IV shows the model parameters obtained from analysis of variance (ANOVA) for the responses. The models as fitted explain 92.15%, 96.72%, and 96.75% of the variability in Y_1, Y_2, and T_{50}, respectively, which were the primary responses considered in this study.

Effect of Eudragit® RS 30D

Eudragit® RS 30D is a methacrylic ester copolymer available as a latex-like aqueous dispersion. The commercial aqueous dispersion, with 30% polymer content is referred to as 30 D (16). Due to its ability to form a continuous film upon spraying and drying, Eudragit® RS 30 D has been frequently used as a release controlling film (3, 16–19). In the present study Eudragit® RS 30 D was used as a film and matrix forming material. Statistical analysis was carried out to evaluate the effect of Eudragit® RS 30D on the dissolution responses Y_1, Y_2 and T_{50}. Analysis of variance showed that Eudragit® RS 30D had an insignificant effect on Y_1 but a negative and significant effect on Y_2 and a positive and significant effect on T_{50}. At low levels of talc and verapamil HCL, increasing the amount of Eudragit® RS 30D from 7.5 to 13 g decreased the percent cumulative amount of drug released in 1 h [Y_1] from 67.02% to 16.29%. However, at high level of verapamil HCL, an increase in the amount of Eudragit® RS 30D only slightly decreased Y_1 from 98.01% to 90.89%. These findings indicated that the effect of Eudragit® RS 30D is only predominant at low levels of verapamil HCL. This could be explained by the fact that verapamil HCL is a water soluble drug. Upon dissolution, the drug on the surface of the beads dissolves and leaches out creating a porous

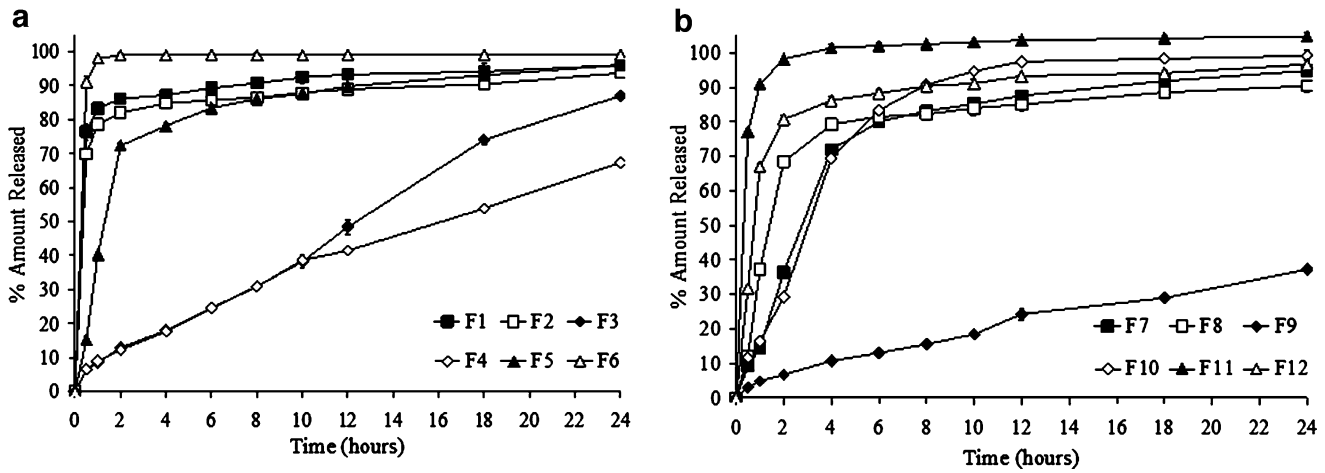

Fig. 3. Dissolution profiles of verapamil HCl from pellets coated with drug-layered matrices: **a** runs 1–6 and **b** runs 7–12

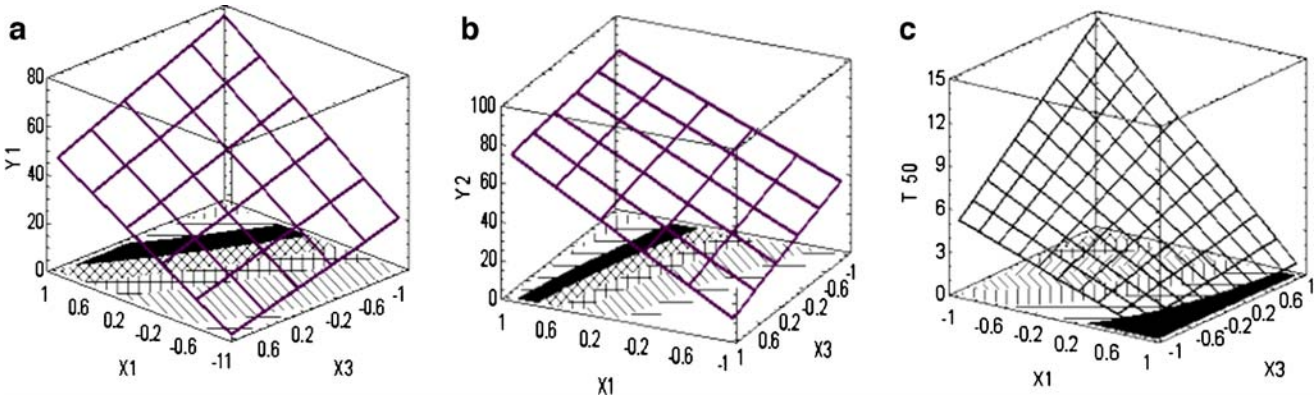

Fig. 4. Response surface plots showing the effect of verapamil HCl level (X_1) and polymer level (X_3) on responses **a** Y_1, **b** Y_2, and **c** T_{50}

matrix through which remaining drug readily diffuses into the dissolution medium. Increasing the level of Eudragit® polymer, however, forms a rigid matrix, which decreases the mobility of drug molecules. This in turn decreases the number of pores through which the drug could diffuse into the dissolution medium. This decrease in porosity was observed in the dissolution profiles by the decrease in the cumulative percent verapamil released. The effect of Eudragit® RS 30D was insignificant in the first hour, during which the drug is mainly released from the surface of the beads. In the second hour (Y_2), however, drug primarily diffused from the interior of the matrix, which was affected by the decreasing number of pores due to the increase in Eudragit® RS 30D amount. Therefore increase in the level of Eudragit® RS 30D had a negative and significant effect on Y_2. The overall effect of Eudragit® RS 30D level on dissolution process is further observed by the increase in time required to release 50% of verapamil HCL (T_{50}).

Effect of Verapamil HCL

The level of verapamil HCL in the drug layered matrix was found to have a significant effect on the responses Y_1 [percent amount released in 1 h], Y_2 [percent amount released in 2 h] of verapamil HCL and T_{50} [time required to 50% verapamil HCL release]. The effect of verapamil HCL [X_1] and Eudragit® RS [X_3], at mid level of talc [X_2], on Y_1, Y_2 and T_{50} are shown in Fig. 4. At low polymer level [X_3], increasing verapamil HCL [X_1] from 1 to 3 g increased Y_1 from 14.5% to 83% and Y_2 from 36% to 86% while; T_{50} was decreased from about 5 h to less than half hour. At high levels of X_3, as the level of X_1 increased from 1 to 3 g, Y_1 increased from 9% to 40% and Y_2 increased from 12.2% to 72.3% while T_{50} decreased from 14 h to only 1 h. Increasing the amount of verapamil HCL, at fixed levels of X_2 and X_3, also decreased the average time required to release at least 90% of the drug from 8 h to less than 2 h. The significant effect of verapamil HCL on Y_1, Y_2, and T_{50} demonstrates that soluble drugs, such as verapamil HCL (solubility 1 g/16 ml), act as pore formers in film matrices. When coated beads are exposed to the dissolution medium, the drug dissolves and leaches out of the matrix, which creates pores in the matrix through which more drug continue to diffuse into the dissolution medium. This effect, however, is more pronounced at high drug levels, which explains the increase in the cumulative amount released with time.

Effect of Talc Powder

Traditionally talc powder is used as an anti-tacking agent at concentrations ranging from 25% to 100%, based on the weight of dry polymer, to facilitate the coating process (11). Talc has the ability to decrease the agglomeration tendency of pellets when coated with aqueous polymeric dispersions. In addition to its effect as an anti-adherent, talc was used as a matrix-forming material in this study. Talc powder had a significant negative effect on both Y_1 and Y_2, and a significant positive effect on T_{50}. The effect of talc powder [X_2] and Eudragit® RS

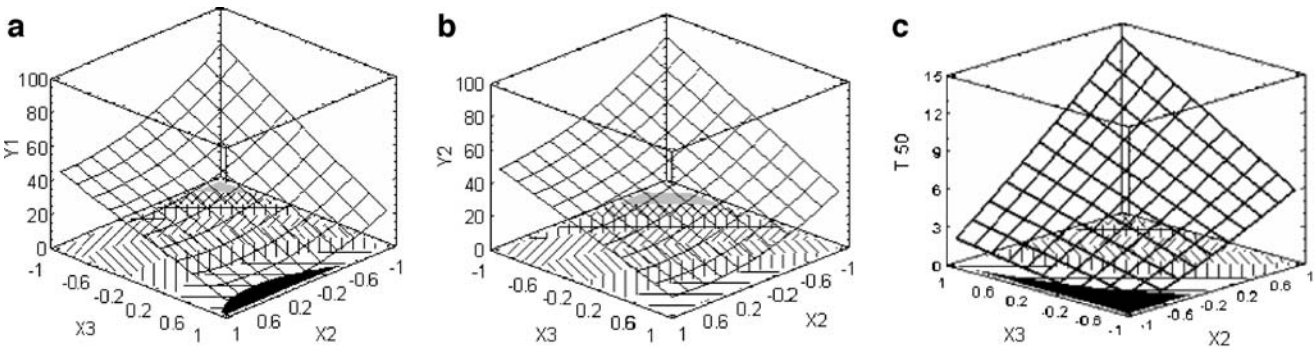

Fig. 5. Response surface plots showing the effect of talc level (X_2) and polymer level (X_3) on responses **a** Y_1, **b** Y_2, and **c** T_{50}

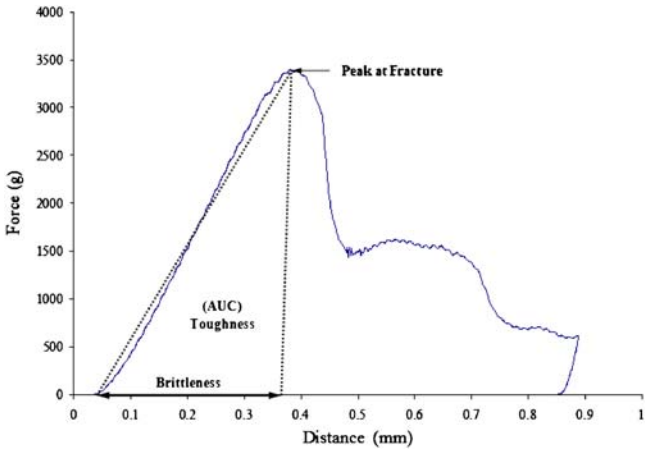

Fig. 6. A representative force–displacement profile obtained from the texture analyzer

[X_3] on Y_1, Y_2, and T_{50} is shown in Fig. 5. At mid level of verapamil HCL [X_1] and low level of X_3, increasing X_2 from 50% to 250%, based on dry polymer weight, decreased Y_1 from 80% to 40% and Y_2 from 87% to 47% while T_{50} was increased from less than 1 to 6 h. Increasing talc content from 50% to 250% also extended the time required to release at least 90% of verapamil HCL from 8 to 24 h. This finding illustrates the ability of talc powder to modulate the release profile of the drug. The coefficient of talc effect on both responses Y_1 and Y_2 was approximately the same which indicates that talc influenced both responses by a similar mechanism. At high levels of talc, the matrix would consist primarily of talc and polymer latex. As the particle size of the polymer latex is much smaller than that of talc, consequently talc at higher levels would form the skeleton of the drug-layered matrix (12,20), thereby creating a diffusing barrier to verapamil HCL.

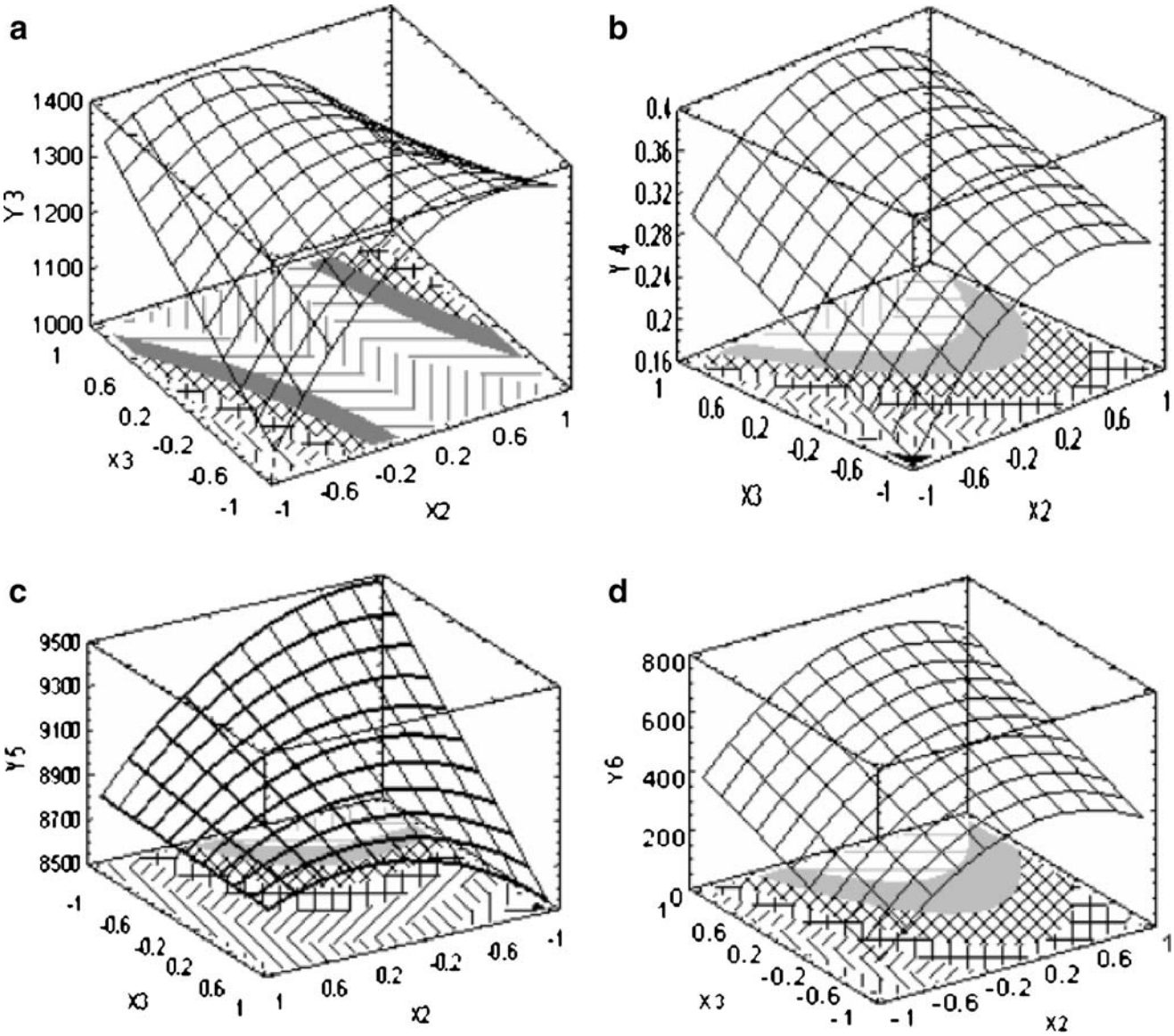

Fig. 7. Response surface plots showing the effect of talc level (X_2) and polymer level (X_3) on **a** tensile strength (Y_3), **b** distance to fracture force (Y_4), **c** stiffness (Y_5), and **d** toughness (Y_6)

Effect of Study Factors on the Mechanical Properties of the Beads

Beads coated with a drug matrix must be resistant to physical stresses exerted by both external force, such as those experienced during shipping and packaging, and internal pressure due to osmosis and peristaltic movement within the gastro-intestinal tract. Such forces could rupture the matrix and result in dose dumping. The mechanical properties of the coated beads could be therefore used as an indirect measure of their ability to withstand such pressures. When investigating the mechanical properties of a single bead, it was assumed that the bead is spherical to avoid scatter in the data and have no crack, flaws or fissures. Also the bead was assumed to be isotropic, which means the properties of the pellet do not change by changing its direction (21). Texture analyzer was utilized to investigate the mechanical properties of a single pellet. All beads coated with verapamil HCL matrix showed plastic deformation. A representative force–distance curve obtained from the instrument is depicted in Fig. 6. From the plot four parameters were determined; fracture force, distance to fracture force, stiffness, and toughness. The two main parameters that were investigated in greater detail were the maximum force at fracture and the distance to fracture force. Distance to fracture force was taken as an indication of brittleness. The less the distance to fracture forces, the more the brittleness of the bead. Tensile strength of a single bead was calculated using Kuno's equation (22):

$$\mathrm{TS} = 4P/\pi D^2 \qquad (2)$$

Where P is the maximum force at fracture and D is the diameter of the pellet. Stiffness was obtained from the slope of the regression line to fracture force. Stiffness is defined as the ability of the bead to resist deformation. The fourth parameter which was estimated in this study was toughness, which is defined as the total work required for the pellet to undergo deformation (21). Toughness was measured from the area under force–distance curve from zero to maximum force as illustrated in Fig. 6.

Effect of Talc and Eudragit® RS on Y_3 and Y_4

Figure 7 (a and b) show the effect of talc powder [X_2], and Eudragit® RS 30 D [X_3], on the responses, Y_3 (tensile strength) and Y_4 (distance to fracture force). None of study factors had significant effect on Y_3, whereas both talc [X_2] and Eudragit® RS [X_3] had a significant positive effect on Y_4, therefore they had a negative significant effect on brittleness. The least tensile strength values were observed at low levels of X_2 and X_3. The effect of increasing X_3 on tensile strength depends on the level of X_2. It increases tensile strength at low and mid levels of X_2, while decreases tensile strength at high level of X_2. On the other hand, at any level of X_2 increase level of X_3 led to a linear increase in the distance to fracture force therefore, decrease brittleness. Talc however had a non-linear effect on Y_3 and Y_4. Initially Y_3 andY_4 increased with an increase in talc content and then gradually declined with further increase in talc content. This finding could be explained as follow. At low level of talc powder, the matrix would consist mainly of bonded polymer particles. Plasticization of Eudragit® RS 30D with 20% triethyl citrate; based on dry polymer weight, however, results in soft thin matrix, which results in low tensile strength and high brittleness. As the talc level increases, thickness of the matrix increases, and the bonds between the polymer and talc increases, this leads to an increase in tensile strength and decreases brittleness. Further increase in the talc level, however, results in a thick matrix, which is formed mainly of talc with dispersed polymer particles sufficient to bind the matrix. This decreases the tensile strength and distance to force at fracture i.e. increase brittleness of the beads. These findings illustrate that both tensile strength and brittleness are dependent on thickness and the balance between Eudragit® RS and talc in the matrix.

Effect of Talc and Eudragit® RS on Y_5 and Y_6

Figure 7 (c and d) illustrate the effect of talc powder [X_2] and Eudragit® RS 30D [X_3] on the responses Y_5 (stiffness) and Y_6 (toughness) of the pellets coated with the drug layered matrix. Within the limits of this study, none of the factors had a significant effect on Y_5. Maximum stiffness; however, was observed at low levels of X_2 and X_3. Increasing X_2 or X_3 led to a decrease in Y_5. X_2 and X_3 however had a significant positive effect on pellet toughness [Y_6]. Lowest toughness value was observed when beads were coated with a matrix at low levels of X_2 and X_3. As X_2 and X_3 increased the toughness increased. These findings could be explained on the basis of the balance of bonds formed between the matrix components as mentioned above.

CONCLUSION

Controlled drug release could be achieved at lower drug loading by manipulating the levels of talc and polymer. The effect of talc/polymer ratio on the dissolution process was evident by its impact on T_{50}. Mechanical properties of the beads were also influenced by the talc/polymer ratio. Within the limits evaluated in this study, increasing talc and or polymer resulted in improved mechanical properties, which further supports the idea that the dissolution and mechanical properties of beads coated with a drug-layered matrix could be readily manipulated by balancing the matrix-forming ingredients.

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