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EVALUATION OF A RAPIDLY DISINTEGRATING, MOISTURE RESISTANT LACQUER FILM COATING

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ABSTRACT

Simplex optimization was used during the development of a rapidly disintegrating, moisture resistant lacquer film coating. A hygroscopic anionic exchange resin with the capability of adsorbing four to five times its weight in water was used as the model drug. The coating variables investigated included levels of magnesium stearate, talc, hydroxypropylmethylcellulose (5 cps), polyethylene glycol 8000, Opaspray, and Eudragit E30D. Response parameters monitored included disintegration time, percent weight gain after 48 hours in a 30 deg C 75% relative humidity chamber and physical appearance.

The effect of the core tablet on the performance of the coated tablet was also investigated. This study illustrates the use of the simplex design in the development of a film coating formula. It also examines the interaction between the core tablet and the film coating.

INTRODUCTION

Development of a rapidly disintegrating, moisture resistant lacquer film coating provides a means of protecting a moisture sensitive active ingredient from its environment. A moisture resistent lacquer film coating containing a neutral copolymer based on poly(meth)acrylic acid esters (Eudragit E30D) can be used to protect the product from moisture while retaining desirable disintegration characteristics. The Eudragit E30D coatings are permeable to water, buffer solutions and gastric fluid, but are not soluble in them. The permeability of the films can be increased by the addition of water soluble polymers such as hydroxypropylmethylcellulose and polyethylene glycols. These substances increase the permeability of the films to the point at which they rapidly disintegrate. Incorporation of color pigment, talc and magnesium stearate reduce the tendency of the lacquer substance to become tacky and enhance the protective abilities of the lacquer coating at higher atmospheric moisture levels.

The characteristics of the core tablet may also effect the properties of the final coated product. Core tablet weight, composition and disintegration time may all have an effect on the performance of the coated tablet.

A geometrical simplex design was used in order to obtain an optimal coating formulation in a limited number of experimental trials.

EXPERIMENTAL

Materials and Methods

The qualitative formulation for the core tablets used in the simplex study is shown in Table 1. Three separate

TABLE 1

Qualitative Core Tablet Formulation
used in Simplex Study Coating Trials

Material (Source)
Hygroscopic Anionic Exchange Resin (HAER) (The Upjohn Co.)
Microcrystalline Cellulose NF Medium Powder (FMC)
Hydroxypropylmethylcellulose (HPMC) 2208 USP 100 cps (Dow Chemical)
Colloidal Silicone Dioxide NF (Cabot)
Magnesium Stearate NF Food Grade V (Witco)

lots of tablets (1A, 1B and 1C) were made from the formula shown Table 1. All materials, except the magnesium stearate, were screened (#20 mesh) and mixed for 30 minutes in a PK mixer. The magnesium stearate was then screened (# 20 mesh), added to the mixer and mixed for three minutes. The mixture was directly compressed to the desired weight on a 30 station Kilian TX30A press with 125 lbs. precompression and 6800 lbs. final compressional force using .6875 x .4062 full oval tooling. A summary of the physical characteristics of the tablets is presented in Table 2.

The tablets were coated using continuous film coating techniques in a 24 inch Accela Cota. The tablet charge totaled five kilograms for each coating trial. Approximately one kilogram of hygroscopic anionic exchange resin (HAER) tablets were combined with four kilograms of 15/32 full oval tablets.

Coating dispersions were prepared in a similar fashion for each coating trial. The components of the coating dispersions (coating variables) are shown in Table 3. A

TABLE 2

Physical Characteristics of the Core Tablets Used in the Simplex Study

	Lot Number 1A	1B	1C
Disintegration Time (min)[a]	30	30	25
% Weight Gain[b]	21.1	19.5	20.2
Friability[c]	LT 0.3	LT 0.3	LT 0.3

a. USP method in 0.1 N HCl

b. % weight gain of 6 tablets placed in an open petri dish after 48 hours at 30 deg C 75% relative humidity in an Espec humidity chamber

c. % weight loss of 10 tablets after 4 minutes in Erweka friablator

TABLE 3

Coating Variables and Ranges used in the Simplex Study

Variable (Supplier)	Range (G/2000 g suspension)
Magnesium Stearate NF Food Grade V (Witco)	40-120
Talc NF bolted (Whittaker, Clark & Daniels)	40-120
Polyethylene Glycol 8000 (Sargent Welch)	15-45
Opaspray K-1-2506-B (Colorcon)	116-349
Eudragit E30D (Rohm Tech)	46-232
Hydroxypropylmethylcellulose 2910 USP 5 cps (Dow Chemical)	2.5-10
Purified Water USP	qs 2000

portion of the total water content was used to prepare the polymer solution. The polymer solution was prepared one day prior to coating to insure full hydration of the hydroxypropylmethylcellulose (HPMC) 2910 USP 5 cps. On the day of coating, the talc, magnesium stearate, polyethylene glycol (PEG) 8000, and Opaspray were added to the polymer solution and mixed for ten minutes with a disc shaped impeller. The Eudragit E30D and remaining water were combined in a separate container and mixed for five minutes. The two dispersions were then combined and mixed for and additional five minutes. The coating dispersion was passed through a 60 mesh screen prior to application to the tablets.

The coating dispersion was delivered continuously to the spray gun at 25-30 cc/minute by a Masterflex (Digi-Staltic) peristaltic pump. A pneumatic atomizing spray gun from Spraying Systems was used with fluid cap number 2850ss and air cap number 67228-45ss. The spray gun was supplied with 60 psi of atomizing air. The distance of the gun from the moving tablet bed was nine inches. The drying air was supplied to the pan at 190-220 cfm at approximately 65 deg C. The exhaust temperature was maintained at approximately 40 deg C. The tablet bed was rotated at 12-13 rpm and small baffles were used to maintain adequate tablet movement in the pan. The coating dispersion was manually agitated every four to five minutes during the coating run to prevent sedimentation of the solids. The coating dispersion was applied until a five percent weight gain (based on initial core weight of HAER tablets) was obtained. Tablets were removed from the pan and stored in closed containers with three gram desiccant packets (Davison Chemical).

Physical Testing

Percent Weight Gain

Six tablets were placed in an open petri dish and stored in an Espec humidity cabinet at 30 deg C and 75% relative humidity for a period of 48 hours. The amount

of moisture absorbed was determined gravimetrically using the difference between the initial weight and the weight immediately after exposure to the humidified environment. The results were reported as a percentage increase from initial tablet weight.

Disintegration Time

Disintegration testing of six tablets was performed using standard USP testing methods. Disintegration fluid used was 0.1 N HCl. Results were reported as the time required for complete disintegration of the last tablet.

Physical Appearance

Coated tablets were examined for structural defects using a Nikon HFX Microscope at 0.66 magnification. The tablets were examined prior to their placement into and immediately after their removal from the high humidity cabinet for color uniformity, cracking, splitting or peeling of the coat, incomplete edge covering and pinholes in the coating at the tablet edge.

Simplex Optimization: Experimental Design

The experimental design used during the study was a Geometrical Variable Size Simplex design (1,2). A simplex is a geometric figure defined by a number of points equal to one more than the number of variables. The variable size simplex method is a logical algorithm consisting of reflection, expansion and contraction rules. The algorithm can be used with any number of dimensions (variables).

The vertices for the initial simplex (Table 4) were determined using the CHEOPS software package (version 1.1 Elsevier Science Publishers).

To illustrate the rules of the simplex design, a flow diagram of the potential moves in a six variable simplex is presented in Figure 1. The initial simplex is first evaluated by physically testing the coated tablets. A rating is assigned to each vertex (trial) based on a rating system (Table 5). A total score is calculated by

TABLE 4
INITIAL SIMPLEX

Vertex	Factor Levels (G/2000 g Suspension)					
	Talc	Mag. Stearate	HPMC	PEG 8000	Opaspray	Eudragit
1	40.0	40.0	2.5	15.0	116.0	184.0
2	58.0	43.9	2.9	16.5	125.3	193.2
3	43.9	58.0	2.9	16.5	125.3	193.2
4	43.9	43.9	4.2	16.5	125.3	193.2
5	43.9	43.9	2.9	21.8	125.3	193.2
6	43.9	43.9	2.9	16.5	167.0	193.2
7	43.9	43.9	2.9	16.5	125.3	226.3

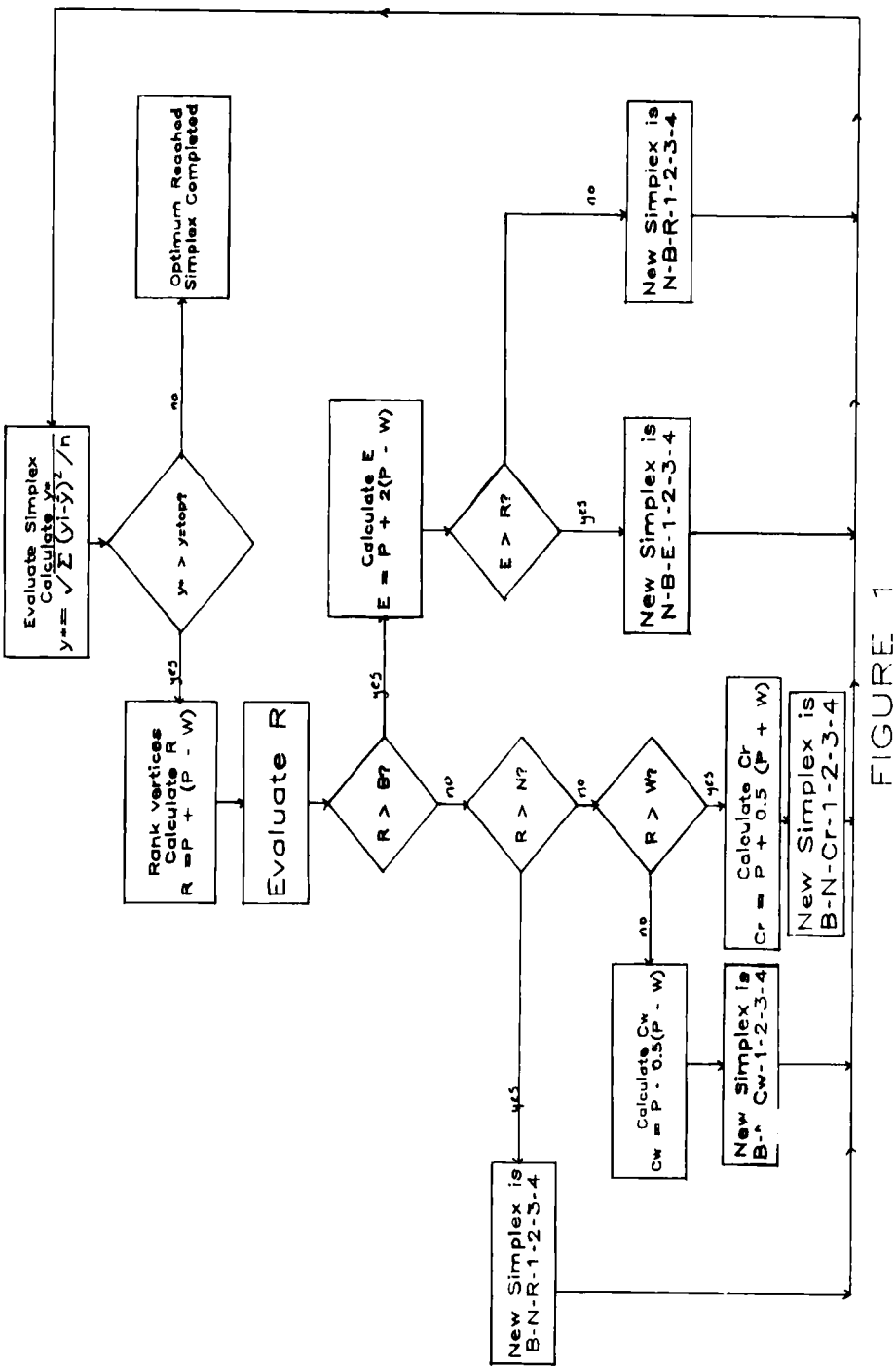


FIGURE 1
Possible Moves in a Simplex Algorithm

TABLE 5

Rating System for Coating Quality

Disintegration Time (min) (DT)	score	% Weight Gain (WG)	score
DT ≤ 15	45	WG ≤ 4	45
15 < DT ≤ 30	40	4 < WG ≤ 5	41
30 < DT ≤ 45	35	5 < WG ≤ 6	37
45 < DT ≤ 60	30	6 < WG ≤ 7	33
60 < DT ≤ 75	25	7 < WG ≤ 8	29
75 < DT ≤ 90	20	8 < WG ≤ 9	25
90 < DT ≤ 105	15	9 < WG ≤ 10	21
105 < DT ≤ 120	10	10 < WG ≤ 11	17
120 < DT ≤ 135	5	11 < WG ≤ 12	13
135 < DT	0	12 < WG ≤ 13	9
		13 < WG ≤ 14	5
		14 < WG ≤ 15	1
		15 < WG	0

Physical Appearance	score
No Defects	10
One Defect	5
Multiple Defects	0

summing of the partial scores given for Disintegration Time, Percent Weight Gain and Physical Appearance. A perfect score is 100. The vertices are ranked with B equaling the vertex with the best response, W being the vertex with the worst response and N being the vertex with the next-to-worst response. The remaining vertices are labeled 1, 2, 3 and 4 for convenience.

Before initiating a reflection, expansion or contraction, the standard error of the response value (y^*) is calculated using the following equation: $y^* = \sqrt{\Sigma (y_i - \bar{y})^2/n}$, where y_i is the individual vertex response value, $\bar{y}$ is the average response value for the simplex and n is the number of vertices in the simplex.

Termination of the optimization process occurs when the standard error of the response value (y^*) becomes less than a predetermined stopping value (y_{stop}). The

TABLE 6

Critical Tablet Characterisitcs of Core Tablets Used in Evaluation of the Optimized Coating Formulation

	Lot Number 2	3	4
Disintegration Time (min)	6	14	53
% Weight Gain (48 hr 30°C 75% RH)	19.8	22.5	20.8
Friability (%)	LT 0.3	LT 0.3	LT 0.3

stopping value (y_{stop}) should be at least as large as the standard error associated with the test methods used to evaluate the vertex response. The stopping value is the maximum standard error acceptable to the investigator.

In this study, the simplex was considered completed when the standard error of the simplex was less than ten, i.e. $y^* < y_{stop} = 10$. The estimated standard error associated with the test methods used to evaluate the trials was 8.2.

If $y^* > y_{stop}$, then P, the centroid of the face remaining when the worst vertex is eliminated must be calculated ($P = \sum$ vertex coordinates/n-1). The simplex algorithm consisting of the reflection, expansion and contraction rules is then followed (Figure 1).

Evaluation of the Optimal Film Coating using Different Substrates

After the initial simplex study was completed, three additional lots of HAER tablets (2, 3, 4) were coated to evaluate the effect of the different core tablets on the

TABLE 7

Factor Levels for all Vertices Used in Simplex Experimental Design

Vertex	Factor Levels (G/2000 g Suspension)					
	Talc	Mag. Stearate	HPMC	PEG 8000	Opaspray	Eudragit
1	40.0	40.0	2.5	15.0	116.0	184.0
2	58.0	43.9	2.9	16.5	125.3	193.2
3	43.9	58.0	2.9	16.5	125.3	193.2
4	43.9	43.9	4.2	16.5	125.3	193.2
5	43.9	43.9	2.9	21.8	125.3	193.2
6	43.9	43.9	2.9	16.5	167.0	193.2
7	43.9	43.9	2.9	16.5	125.3	226.3
8	43.7	43.7	2.9	16.8	145.5	195.0
9	40.0	40.0	2.5	15.0	116.0	45.0
10	47.3	47.3	3.2	17.7	139.2	158.2
11	46.5	46.5	3.1	17.5	134.6	174.8
12	48.2	48.2	3.3	18.1	83.5	184.0
13	45.0	45.0	3.0	16.9	145.2	191.4
14	45.1	45.1	3.0	16.9	125.3	207.9

TABLE 8

Results of Physical Testing of Simplex Vertices

Vertex	Disintegration Time (0.1 N HCl)	% Weight Gain	Physical Appearance	Rating
1	45 min	14.1	cracking along sidewalls, some splitting around logo	46
2	44 min	11.5	cracking limited to seams	58
3	97 min	7.2	little to no cracking, limited to seams	54
4	53 min	9.5	cracking along seams	61
5	32 min	7.6	little to no cracking, limited to seams	74
6	70 min	13.3	cracking along sidewalls	40

7	150 min	10.1	cracking along seams	27
8	30 min	13.6	cracking along sidewalls and around logo	55
9	24 min	17.3	cracking over entire coating surface, uneven color, chipped at logo	40
10	35 min	16.6	cracking along sidewalls and logo, pinholes at seams	40
11	32 min	17.4	cracking along sidewalls and logo, pinholes at seams	40
12	37 min	16.1	cracking along sidewalls and logo, pinholes at seams, picking around logo, dusty appearance	35
13	37 min	16.0	cracking along sidewalls, pinholes at seams	45
14	34 min	15.2	cracking along sidewalls and logo, pinholes at seams	45

TABLE 9

Optimized Coating Formula

Material (Source)	G/2000g Suspension
Talc USP, bolted (Whittaker, Clark & Daniels)	43.9
Magnesium Stearate NF Powder Food Grade-V (Witco)	43.9
Hydroxypropylmethylcellulose 2910 USP 5 cps (Dow Chemical)	2.9
Polyethylene Glycol 8000 (Sargent Welch)	21.8
Opaspray K-1-2506-B (Colorcon)	127.4
Eudragit E30D (Rohm Tech)	209.8
Purified Water	1550.4

performance of the optimized coating formulation. Core tablet formulas selected had different disintegration times so that the effect this core property had on the coated tablet performance could be evaluated. Critical core tablet physical characteristics are presented in Table 6.

Results and Discussion

Simplex Optimization

A total of fourteen trials were run in the simplex study. A summary of all coating trials formulations is presented in Table 7. The results of physical testing are presented in Table 8.

The final simplex in the study had a standard error of 9.1 thereby meeting the stopping criteria of $y^* < y_{stop} = 10$. The optimal formula was trial number 5 and is shown in Table 9. The procedures used to prepare and evaluate the optimal coating formulation were

TABLE 10

Reproducibility of Optimal Coating Formulation

Trial	Disintegration Time (0.1 N HCl)	% Weight Gain	Physical Appearance	Rating
Initial	32 min	7.6	little to no cracking, limited to seams	74
Repeat 1	44 min	10.2	cracking limited to seams	62
Repeat 2	37 min	10.9	limited cracking along sidewalls	62

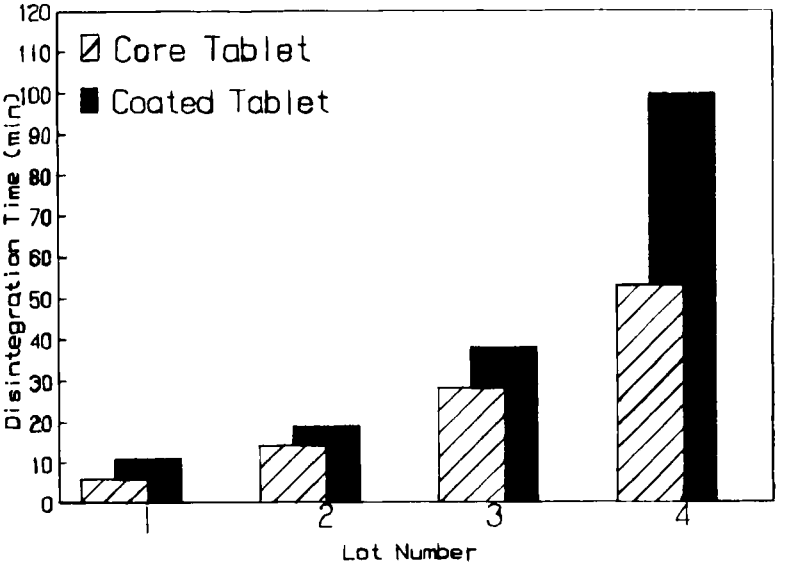


FIGURE 2

Effect of Core Tablet Disintegration Time on Coated Tablet Disintegration Time

repeated two times to verify the results obtained were reproducible. The results of testing these formulations are shown in Table 10. The disintegration time for repeated trials was longer and the percent weight gain was greater than the initial trial, but the overall rating was still higher than for any other vertex. The optimized formula produced an elegant film coated tablet. The functional film coating allowed less than half of the moisture adsorbed by the uncoated core tablet to penetrate the coating, yet slowed disintegration by only ten minutes.

Effect of Coating Substrate on Performance of Finished Coated Tablet Quality

The optimal coated formula was applied to three different HAER tablets (2, 3 and 4) to determine the

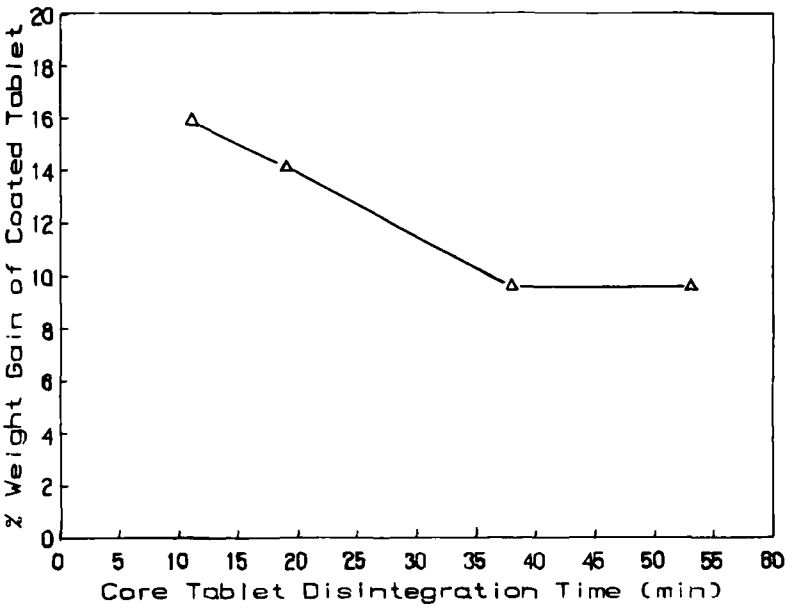


FIGURE 3
Effect of Core Tablet Disintegration Time on Coated Tablet % Weight Gain

effect of core tablets with different disintegration times on the coated tablet quality. Figure 2 illustrates as core tablet disintegration time increased, the disintegration time of the film coated tablet increased to a much greater extent than would be explained by the film coating alone. These results suggest that a rapidly disintegrating core tablet serves to weaken the film during disintegration of the film coated tablet whereas a slowly disintegrating core tablet allow the coating to "self-protect" the tablet from disintegration.

In general, the percent weight gain of the coated tablet is inversely proportional to the disintegration time of the core tablet as shown in Figure 3. A slow disintegrating core tablet permits the film to remain intact longer and provide superior barrier properties. However, delaying the core tablet disintegration time beyond 30 minutes does not appear to improve the barrier

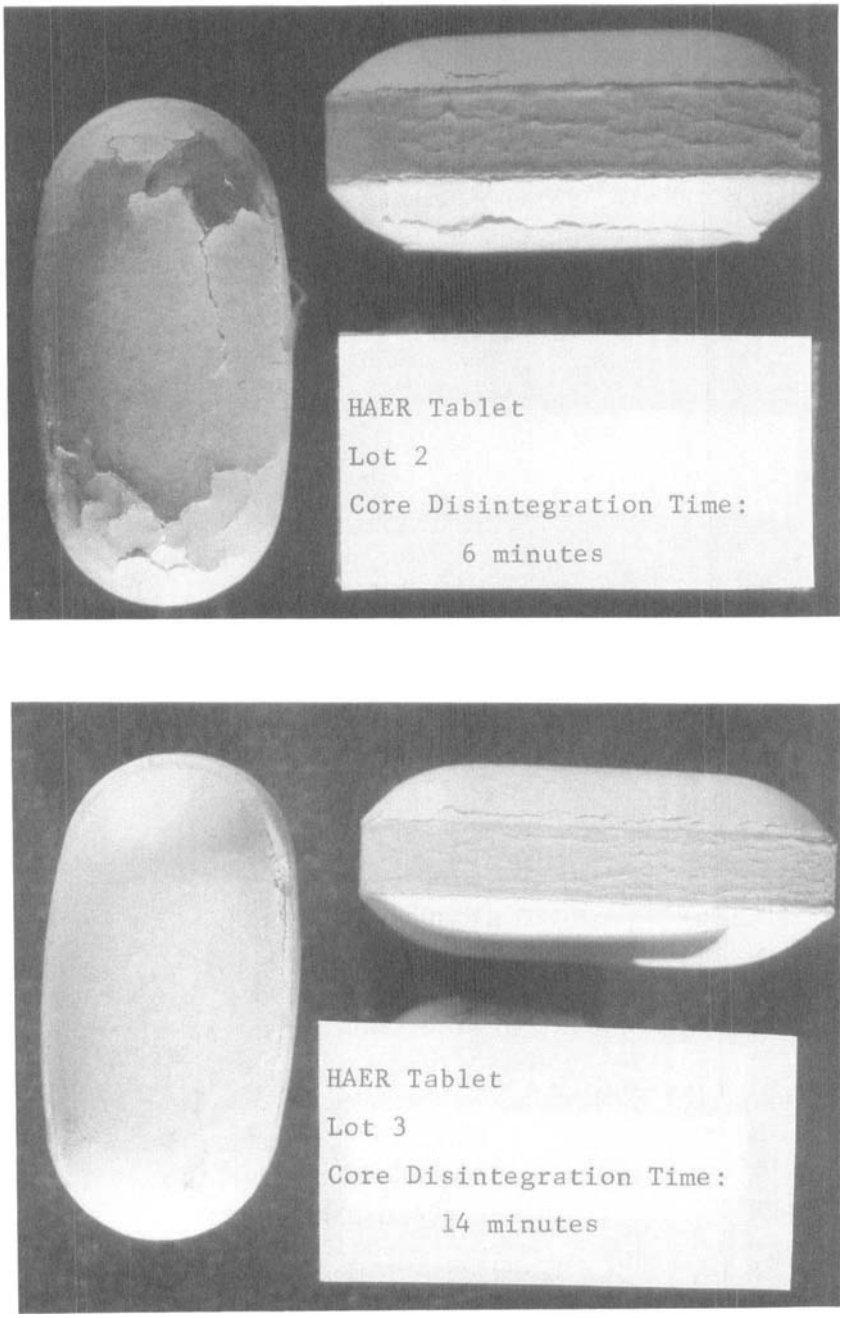
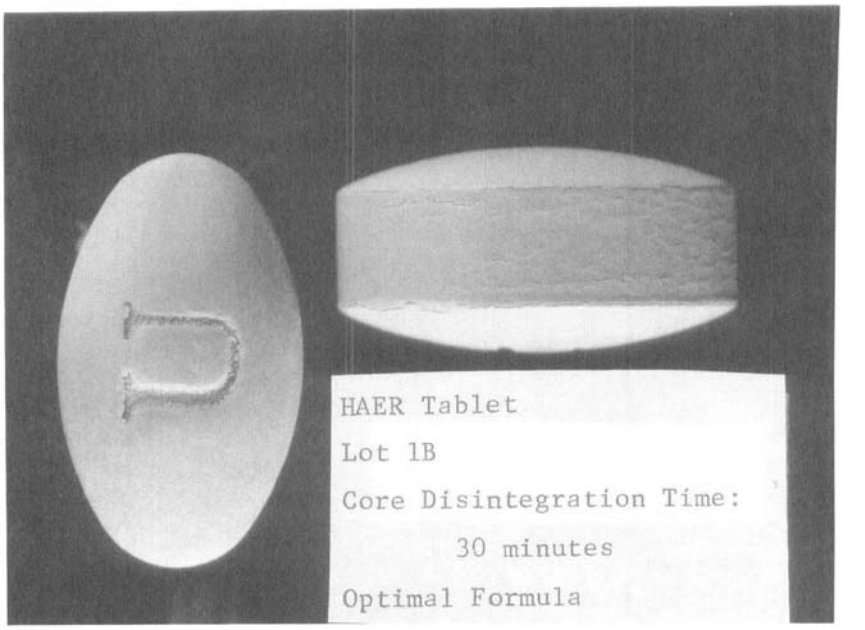


FIGURE 4
Effect of Core Tablet Disintegration Time on Film Coating Integrity



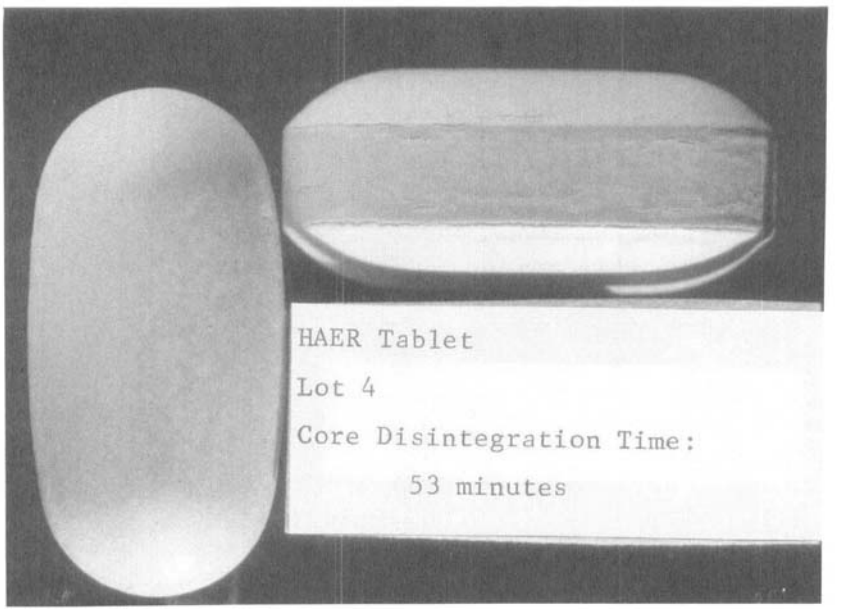


FIGURE 4 (Continued)
Effect of Core Tablet Disintegration Time
on Film Coating Integrity

properties of the film coated tablet. These results illustrate the trade-off that must occur in order to develop a rapidly disintegrating, moisture resistant, film coated tablet. Disintegration time of the core tablet must be delayed to provide a sufficient degree of film integrity to moisture.

The degree to which a tablet absorbs water also affects the integrity of the coating. The greater the percent weight gain, the greater the damage to the coating. This may be attributed to the fact that as the tablets pick up a greater percentage of moisture, they begin to disintegrate and place stress on the coating and fracture the film. The varying degrees of this disruption can be seen in the photographs contained in Figure 4 (tablets stored for 48 hours at 40°C/75% RH). As the disintegration time of the core tablet decreases, i.e. the tablet is formulated to absorb water at a more rapid rate, the extent of disruption increases. The core tablets formulated to provide moderate to slow disintegration (lots 1B and 4) had minimal fracture along the tablet sidewalls and coating seams. The core tablets formulated to provide a rapid disintegration (lots 2 and 3) fractured extensively along the face and sidewalls of the tablet. Once the film coating loses its integrity, the hygroscopic drug is no longer protected from the environment and rapidly absorbs moisture causing further disruption of the tablet core.

CONCLUSIONS

Simplex is an efficient means of developing an optimal coating formulation. In the present study, six coating formulation factors required only fourteen trials to develop the optimal formula. If a second order experimental design such as a central composite design had been used, a minimum of 64 trials would have been required. The advantage of a second order design is that a predictive mathematical model would be generated for each response parameter. In simplex experiments,

mathematical models are generally not developed. The sequential simplex method rapidly located the region of the optimum by varying all factors simultaneously. The coating developed was resistant to environmental moisture while maintaining desirable disintegration properties.

The disintegration time and extent of resistance to environmental moisture was affected by properties of both the film coating and the core tablet. For the model drug used in this study, tablets formulated with an intermediate disintegration time, approximately 25-30 minutes, performed better than did those formulated to disintegrate more rapidly. The relationship observed between the core tablet and the film coating indicates the importance of simultaneous development of both the core and the film coating formulations when both may affect the performance of the final product.

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