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Evaluation of Different Fast Melting Disintegrants by Means of a Central Composite Design

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ABSTRACT Fast-disintegration technologies have encountered increased interest from industries in the past decades. In order to orientate the formulators to the choice of the best disintegrating agent, the most common disintegrants were selected and their ability to quickly disintegrate direct compressed tablets was evaluated. For this study, a central composite design was used. The main factors included were the concentration of disintegrant (X_1) and the compression force (X_2). These factors were studied for tablets containing either Zeparox® or Pearlitol 200® as soluble diluents and six different disintegrants: L-HPC® LH11 and LH31, Lycatab PGS®, Vivasol®, Kollidon CL®, and Explotab®. Their micromeritics properties were previously determined. The response variables were disintegration time (Y_1), tensile strength (Y_2), and porosity (Y_3). Whatever the diluent, the longest disintegration time is obtained with Vivasol® as the disintegrant, while Kollidon CL® leads to the shortest disintegration times. Exception for Lycatab PGS® and L-HPC LH11®, formulations with Pearlitol 200® disintegrate faster. Almost the same results are obtained with porosity: no relevant effect of disintegrant concentration is observed, since porosity is mainly correlated to the compression force. In particular, highest values are obtained with Zeparox® as the diluent when compared to Pearlitol 200® and, as the type of disintegrant is concerned, no difference is observed. Tensile strength models have been all statistically validated and are all highly dependent on the compression force. Lycatab PGS® concentration does not affect disintegration time, mainly increased by the increase of compression pressure. When Pearlitol 200® is used with Vivasol®, disintegration time is more influenced by the disintegrant concentration than by the compression pressure, an increase in concentration leading to a significant and relevant increase of the disintegration time. With Zeparox®, the interaction between the two controlled variables is more complex: there is no effect of compression force on the disintegration time for a small amount of disintegrant, but a significant increase for higher concentrations. With Kollidon CL®, the main factor influencing the disintegration time is the compression force, rather than the disintegrant concentration. Increasing both the compression force and the disintegrant concentration leads to an increase of the disintegration time.

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For lower Kollidon CL® percentages, the compression pressure increases dramatically the tablet disintegration. With the Explotab®, whatever the increase of compression force, the disintegrant concentration leads to an increase of the disintegration time. According to Student's t-test, only the compression force significantly and strongly influences the disintegration time when Pearlitol 200® is used. A slight interaction and some trends nevertheless appear: above 150 MPa, increasing the disintegrant concentration leads to a shortened disintegration time, below this limit the opposite effect is observed.

KEYWORDS Fast melting, Disintegrants, Direct compression, Central composite design

INTRODUCTION

Fast-dissolving tablets are continuously gaining great success in the pharmaceutical market. Many patients have difficulty swallowing tablets and hard gelatin capsules, so that they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy (Seager, 1998). The pediatric and geriatric populations are of particular concern. Working patients who are busy or traveling, especially those who have no access to water, but also patients who prefer a readily administered dosage form, greatly appreciate this fast-dissolving form. It can indeed dissolve/suspend in water, be chewed, or rapidly dissolve in the mouth. In addition, the bioavailability of this form is undoubtedly greater than conventional tablets or hard gelatin capsules. Another advantage, interesting for pharmaceutical industries, is cost savings, particularly when these solid dosage forms are compared with similar fast-dissolving tablets such as effervescent tablets, which require particular care to maintain very low relative humidity percentage during the entire tablet production and to guarantee an appropriate first packaging choice.

Different are the technologies for fast-melting tablets: freeze-drying, molding (either by compression or by heating), and direct compression (Dobetti, 2000). Each approach shows advantages and disadvantages. Lyophilized tablets are characterized by a very porous structure, which causes quick penetration of saliva into the pores, when placed in the oral cavity (Virley & Yarwood, 1990; Kearney & Wong, 1997). The main disadvantages of this dosage form are, in addition to the cost intensive production process, the lack of physical resistance in standard blister packs and their limited ability to incorporate high concentrations of active drug (Schiermeier & Schmidt, 2002). Molded tablets reveal rapid disintegration, but weaker mechanical strength, and higher manufacture costs than other forms (Schiermeier & Schmidt, 2002). Therefore, direct compression appears to be a convenient and cheap way to produce tablets with sufficient structural integrity (Cousin et al., 1995). So far there have been many patents for fast disintegrating tablets, but only a few publications dealing with this dosage form (Bi et al., 1999; Habib et al., 2000; Mattsson et al., 2001; Schiermeier & Schmidt, 2002; Shu et al., 2002).

The aim of this work is to provide a first step in this subject by comparing the disintegrating properties of six different agents with respect to different formulation and process variables, considering direct compression. This contribution can be useful to orientate the formulators to the correct choice of the best disintegrating agent for their own solid dosage forms.

MATERIALS AND METHODS

Materials

All materials were kindly supplied by the manufacturers: Lactose (Zeparox®, Borculo Domo, Borculo, Holland), Mannitol (Pearlitol 200®, Roquette, Lestrem, France), low-substituted hydroxypropyl cellulose (L-HPC LH 11®, L-HPC LH 31®, ShinEtsu, Tokyo, Japan), pregelatinized maize starch (Lycatab

P.G.S.®, Roquette, Lestrem, France), croscarmellose sodium (Vivasol®, J. Rettenmaier & Söhne, Rosenberg, Germany), crospovidone (Kollidon CL®, Basf, Ludwigshafen, Germany), sodium starch glycolate (Explotab®, Penwest Pharmaceuticals Co., Surrey, UK).

Magnesium stearate was purchased from ACEF (Fiorenzuola D'Arda, Italy).

Tablet Preparation and Characterization

A typical mixture is composed of one diluent (Zeparox® or Pearlitol 200), one disintegrant in a percentage (w/w) defined by the experimental design, and of 0.5% (w/w) of magnesium stearate as lubricant. The disintegrant concentration varies according to the experimental design, and the percentage of diluent is adjusted to reach 100%. Diluent was added to disintegrant by geometrical dilution and by mixing them in a "V-shaped" mixer (Divisione Artha, Laboratori Mag, Carbagnate Milanese, Italy) for 20 minutes. Magnesium stearate was mixed for the last 3 minutes. The apparent powder density needed to calculate tablet's porosity was measured by a helium pychnometer (Accupyc 1330, Micromeritics, UK) equipped with a cell of 10 cm^3. Results are the mean of 10 measurements.

Tablets were produced on a mini rotary press (Ronchi, Piccola 10, Italy) equipped with 10 flat 11.28 mm diameter punches. Compression parameters such as applied and ejection forces were measured with strain gages, and the obtained signals were treated and analyzed with a computerized control system. Mixes were manually introduced in one die. Die and punches were prelubricated with a 1% magnesium stearate suspension (A.C.E.F., Italy) in ethanol 96% (v/v) (PRS, Panreac, Spain). The mass, added in the die and then compressed, was varied in order to obtain the different compression pressure levels defined by the experimental design (pressure value ±0.2 MPa). Results for each compression pressure were the mean of five measurements.

Thickness and diameter of ejected tablets were measured with a manual micrometer (Mitutoyo, Japan) immediately after ejection. Tablet porosity was calculated from tablet dimensions, mass, and apparent powder density. Crushing force was measured immediately after compression with a tablet strength tester (Erweka, type TBH30, Germany). Tensile strength Q (Fell & Newton, 1970) was calculated according to Eq. 1:

$$Q = 2H/\rho * d * t \qquad (1)$$

where H=the tablet crushing strength, d the diameter, and t the thickness of the tablet. Tablet disintegration time was measured in accordance with European Pharmacopoeia (4th ed.), monograph "Dispersible Tablets," without discs, in demineralized water, thermostated at 37°C. Only one tablet at a time was tested and considered disintegrated when completely dispersed fragments were obtained. Results are the mean of 10 tablets.

Experimental Design and Statistics

Modern statistical methods have been used in this work to study the influence of formulation and operating factors on tablet characteristics formulated with different disintegrants and diluents. The response surface methodology using a central composite design is particularly interesting to estimate second order polynomial equations appropriate to find out optimal operating conditions and formulations. In addition, the use of this experimental design is efficient to collect the maximum information with the minimum of required runs. The analysis of the estimated models helped by the use of three dimensional response surfaces (and their corresponding isoresponse curves) is exploited to improve the knowledge of the six studied disintegrants.

The central composite design allows estimating a second-order polynomial design with only $2^K+2.k+n$ central experiments with k the number of controlled variables or factors. For two variables, the design is built with four experiments at the corners of the experimental field, four axial points at a distance± alpha to the center, and three center points. The number of central points and the distance alpha are calculated in order to meet orthogonality and rotatability criteria, which confer great efficiency to this type of design. Orthogonality implies that the estimations of the regression coefficients of the polynomial (in direct relation to the factors effects) are independent of each other, giving therefore an unbiased value of the associated effect. The quality of

prediction of the response within the experimental domain depends on rotatability. Once this property is considered, the variance of prediction of the response only depends on the alpha distance from the center and not on the direction in which one moves from the center; no direction is favored above another (Box & Draper, 1987; Lewis et al., 1999). Two main factors are included in the experimental design: the concentration of disintegrant (X_1) and the compression force (X_2). These factors are studied for tablets containing Zeparox® or Pearlitol 200® as diluents and six different disintegrants. The three studied response variables are disintegration time, tensile strength, and porosity.

The runs of the experimental design and the composition of the 11 batches are shown in Table 1. The design and results are given for each of the six disintegrants and each of the two diluents. Experiments were carried out in a random order to avoid systematic error incidence. This statistical design provides a second order polynomial describing linear and quadratic effect as well as the interactions of each of the studied factors on the considered response variable. The general model corresponding to the following equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$

is calculated by multiple regression. Analysis of variance (ANOVA) is run for each model, the significance of each of the model terms (corresponding to the factors effects) is determined using Student's t-test, and finally, the models are fully tested by additional calculation of the coefficient of determination. The software Nemrod® LPRAI Ver. 3.1. (Marseille le Merlan, France) was used for generating the experimental design, modeling the response surface and calculating the statistical evaluation.

RESULTS AND DISCUSSION

Statistics and General Analysis

Models and statistical evaluations are reported in Table 2. The levels of significance are represented in the conventional manner: $p<0.001$ (0.1%); $p<0.01$ (1%); $p<0.05$ (5%). Almost all the models have been validated, highlighting the effects of factors on the studied tablet characteristics. General results (mean, minimal, and maximal measured values for each experimental design) are given in Fig. 1 for the response variable: disintegration time. Whatever the diluent, the longest disintegration time is obtained with Vivasol® as the disintegrant, varying from 35s to 146s (Zeparox®) and from 25s to 72s (Pearlitol 200®). Kollidon CL® leads to the shortest disintegration times, the range of variation being from 23s–41s (Zeparox®) to 12s–43s (Pearlitol 200®). Exception for Lycatab PGS® and L-HPC LH11®, formulations with Pearlitol 200® disintegrate faster. The information collected for the disintegration time is quite rich and complex, and will be analyzed in detail in the next section for each of the studied disintegrant.

Tensile strength models have been all statistically validated and are all highly dependent on the compression force. The concentration of disintegrant displays effects statistically validated for almost all the designs but appears to be of small amplitude and therefore not relevant. Only for L-HPC LH31® it can be noticed (data not detailed) that the concentration shows no effect on the tensile strength for small compression forces, but an increase in the concentration leads to an increase of the tensile strength for higher compression force. This is true for Zeparox® and more pronounced for Pearlitol 200®. In addition, when Pearlitol 200® is used as the diluent, a decrease of the tensile strength is observed for the smallest compression forces when the disintegrant concentration is increased. In the experimental field, the hardness of Pearlitol 200® tablets is higher compared to Zeparox® tablets. No differences appear between the disintegrants (Fig. 2). Almost the same results are obtained with porosity, no relevant effect of disintegrant concentration is observed, and porosity is mainly correlated to the compression force. The highest values are obtained with Zeparox® as the diluent when compared to Pearlitol 200®. Where the type of disintegrant is concerned, no difference is observed (Fig. 3). No further results and deeper analysis need to be provided for these last two response variables.

Lycatab PGS®

Lycatab PGS® (pregelatinized maize starch) is a starch that has been chemically and mechanically

TABLE 1 Central Composite Design (Coded and Operating Levels) and Obtained Results for the Disintegration Time

Batch #	Disintegrant concentration (X_1)		Compression force (X_2)		Disintegration time (s)											
					(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)	(k)	(l)
1	−1	2.00%	−1	100.0 MPa	27.7	31.3	27.6	22.0	33.8	20.8	37.9	24.5	26.4	12.2	26.7	19.7
2	+1	8.00%	−1	100.0 MPa	27.0	12.8	22.5	17.6	32.3	19.8	82.3	59.2	25.3	13.6	45.0	28.7
3	−1	2.00%	+1	200.0 MPa	47.3	99.0	45.8	66.3	55.9	70.6	54.1	37.8	32.3	35.1	46.0	64.0
4	+1	8.00%	+1	200.0 MPa	38.6	55.9	41.1	44.0	60.6	46.2	145.8	63.8	40.9	21.1	71.1	53.4
5	−1.414 (−alpha)	0.76%	0	150.0 MPa	42.2	68.4	36.2	52.8	43.1	59.5	34.8	43.1	31.1	43.1	34.8	43.1
6	+1.414 (+alpha)	9.24%	0	150.0 MPa	32.1	37.7	27.4	27.5	36.3	27.5	142.3	71.6	34.2	13.4	50.4	41.0
7	0	5.00%	−1.414 (−alpha)	79.3 MPa	26.9	12.9	23.3	15.6	28.0	16.8	57.2	44.1	23.2	12.4	28.0	26.4
8	0	5.00%	+1.414 (+alpha)	220.7 MPa	42.1	76.7	51.3	68.2	59.6	52.1	108.7	58.6	41.4	17.5	53.7	68.0
9	0	5.00%	0	150.0 MPa	33.9	43.1	34.4	32.2	45.7	29.7	86.1	48.1	32.8	15.1	45.6	39.9
10	0	5.00%	0	150.0 MPa	33.6	45.1	32.6	32.9	45.4	30.0	83.4	54.1	31.9	15.2	46.5	42.6
11	0	5.00%	0	150.0 MPa	34.3	49.2	32.7	34.3	46.4	28.8	84.9	50.7	31.0	15.1	47.1	40.9

(a): Disintegrant Lycatab®. Diluant: Zeparox®.
(b): Disintegrant Lycatab®. Diluant: Pearlitol®.
(c): Disintegrant LHPC LH11®. Diluant: Zeparox®.
(d): Disintegrant LHPC LH11®. Diluant: Pearlitol®.
(e): Disintegrant LHPC LH31®. Diluant: Zeparox®.
(f): Disintegrant LHPC LH31®. Diluant: Pearlitol®.
(g): Disintegrant Vivasol®. Diluant: Zeparox®.
(h): Disintegrant Vivasol®. Diluant: Pearlitol®.
(i): Disintegrant Kollidon CL®. Diluant: Zeparox®.
(j): Disintegrant Kollidon CL®. Diluant: Pearlitol®.
(k): Disintegrant Explotab®. Diluant: Zeparox®.
(l): Disintegrant Explotab®. Diluant: Pearlitol®.

TABLE 2 Statistical Evaluation of Models for the Response Variable: Disintegration Time

Model term	Regression coefficient (s)		Level of significance	
	Zeparox®	Pearlitol®	Zeparox®	Pearlitol®
Lycatab®				
b_0	33.91	45.80	*a*	*a*
b_1	−2.96	−13.13	*b*	*a*
b_2	6.60	25.14	*a*	*a*
b_{11}	1.44	3.84	*b*	11.5%
b_{22}	0.13	−0.29	51.5%	88.6%
b_{12}	−2.00	−6.14	*b*	5.1%
ANOVA	F=597.9	F=57.66	*b*	*a*
Error	F=35.07	F=3.24	*c*	43.6%
R^2	0.965	0.983		
LHPC LH11®				
b_0	33.24	33.12	*a*	*a*
b_1	−2.77	−7.80	*a*	*a*
b_2	9.55	18.12	*a*	*a*
b_{11}	−0.80	2.62	8.8%	7.6%
b_{22}	1.94	3.50	*b*	*c*
b_{12}	0.11	−4.47	81.9%	*c*
ANOVA	F=202.5	F=83.4	*a*	*a*
Error	F=0.68	F=10.1	64.2%	9.2%
R^2	0.995	0.988		
LHPC LH31®				
b_0	45.79	29.50	*a*	*a*
b_1	−0.80	−8.81	*c*	*a*
b_2	11.89	15.78	*a*	*a*
b_{11}	−2.09	7.09	*b*	*a*
b_{22}	−0.01	2.57	96.7%	*b*
b_{12}	1.56	−5.86	*c*	*b*
ANOVA	F=914.0	F=1576.3	*a*	*a*
Error	F=71.83	F=117.42	*c*	*b*
R^2	0.955	0.957		
Vivasol®				
b_0	84.81	50.96	*a*	*a*
b_1	36.02	12.64	*a*	*b*
b_2	19.08	4.80	*a*	8.3%
b_{11}	0.43	1.19	83.0%	67.2%
b_{22}	−2.36	−1.80	28.2%	53.2%
b_{12}	11.82	−2.18	*b*	52.5%
ANOVA	F=128.8	F=7.64	*b*	*c*
Error	F=18.96	F=6.65	5.0%	13.4%
R^2	0.992	0.997		
Kollidon CL®				
b_0	31.90	15.16	*a*	*a*
b_1	1.48	−6.83	*c*	*a*
b_2	5.90	4.69	*a*	*a*
b_{11}	0.06	6.27	92.0%	*a*
b_{22}	−0.12	−0.38	83.1%	*b*
b_{12}	2.44	−3.87	*c*	*a*
ANOVA	F=38.6	F=29534	*b*	*a*
Error	F=0.73	F=10188	62.3%	*a*
R^2	0.975	0.828		

(continued)

TABLE 2 Continued

Model term	Regression coefficient (s)		Level of significance	
	Zeparox®	Pearlitol®	Zeparox®	Pearlitol®
Explotab®				
b_0	46.37	41.15	[a]	[a]
b_1	8.17	−0.57	[a]	58.1%
b_2	10.24	15.99	[a]	[a]
b_{11}	−0.51	−0.34	25.2%	77.2%
b_{22}	−1.41	2.22	[c]	10.9%
b_{12}	1.69	−4.92	[c]	[c]
ANOVA	F=482.2	F=59.0	[b]	[a]
Error	F=73.49	F=5.99	[c]	14.7%
R^2	0.916	0.983		

[a] $p<0.001$.
[b] $p<0.01$.
[c] $p<0.05$.

processed to rupture starch granules in order to improve flowability and direct compressibility. As a disintegrant, starch is generally used in a concentration of 5–10% (Wade & Weller, 1994). The mechanism of disintegrant action has been explained by Rudnic et al. (1982).

The "disintegration time" models have been validated for both diluents, Zeparox® and Pearlitol 200®. The corresponding response surfaces (Figs. 4 and 5) show that the disintegrant concentration has no relevant effect on the disintegration time except for the highest compression forces. Pearlitol 200® is more sensible to the factor variations as is demonstrated by the highest regression coefficients (Table 2). For this diluent, there is no interaction between compression force and disintegrant concentration in opposition to Zeparox®. Here again, the effect of the concentration of disintegrant appears only for the highest compression force.

Disintegration time increases when increasing the compression pressure, and no quadratic effect is observed. A significant but not relevant quadratic effect of disintegrant concentration occurs when Zeparox® is used.

L-HPC LH11® and L-HPC LH31®

L-HPC LH11® and L-HPC LH31® (low-substituted hydroxypropyl cellulose) is a partially substituted hydroxypropyl ether of cellulose in which a small proportion of the three hydroxyl groups contained in the β-o-glucopyranosyl ring of the cellulose is etherified with propylene oxide. While a

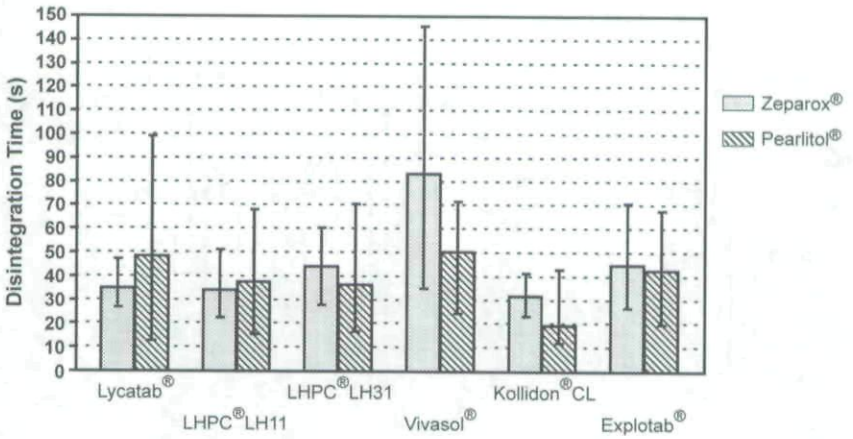

FIGURE 1 Disintegration Time (Mean, Maximal Value, Minimal Value), From Experimental Design Data.

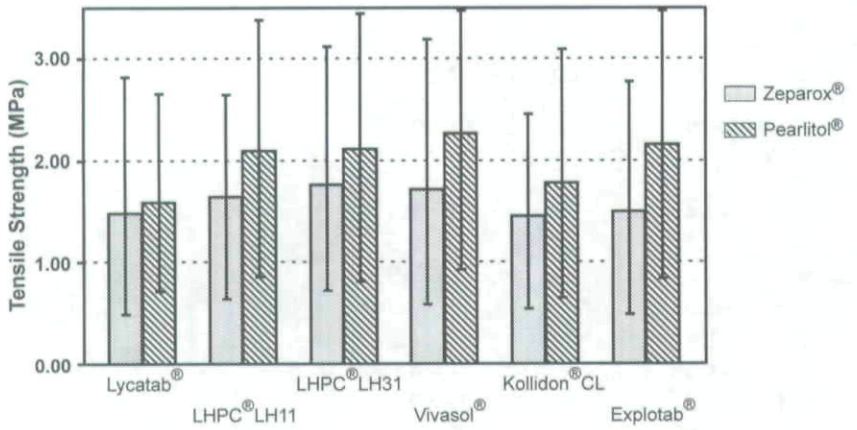

FIGURE 2 Tensile Strength (Mean, Maximal Value, Minimal Value), From Experimental Design Data.

highly substituted hydroxypropyl ether of cellulose is soluble in both water and alcohols, L-HPC® is insoluble in these solvents, but it swells in water. Several grades are available that differ in hydroxypropoxyl content and in particle size. Two different grades were selected, L-HPC LH11® and L-HPC LH31®, both of average hydroxypropoxyl content. The first one is a coarser powder, when the second one is a finer powder (ShinEtsu, Technical Bulletin, Tokyo, Japan, 1998).

L-HPC LH11® behaves almost like Lycatab PGS®, and the studied factors display almost the same effects but with a smaller amplitude when Pearlitol 200® is used. There is no interaction between the compression force and the concentration of disintegrant (Figs. 5 and 7).

Considering L-HPC LH31®, tablet disintegration time is both influenced by compression pressure and L-HPC LH31® percentage. These effects are statistically significant but not relevant for the concentration of disintegrant when Zeparox® is used; the corresponding effect (in direct relation with the regression coefficient) is only $-0.8\times2=-1.6$ s when varying the concentration from the lower limit to the upper limit. On the contrary, the effect of the compression force is $+11.89\times2=23.78$ s when this controlled variable is varied within the experimental limits. For Zeparox®, a slight decrease of the disintegration time is observed for small compression forces when the disintegrant concentration increases, but an increase occurs for higher pressions (Fig. 6). The amplitudes of variation of the studied factors are greater with Pearlitol 200®, but globally, the disintegration time is shorter with this diluent (Fig. 7). A significant positive quadratic effect of the concentration of disintegrant highlights the location of an optimal disintegrant concentration dependent on the compression force: for each compression force an optimal disintegrant concentration exists, leading to the shortest disintegration time. For an 80 MPa compression force, the shortest disintegration time (12.5 s) is

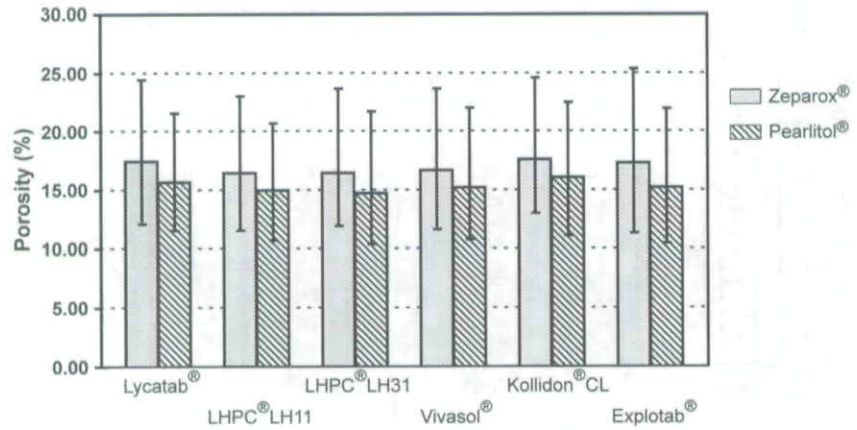

FIGURE 3 Porosity (Mean, Maximal Value, Minimal Value), From Experimental Design Data.

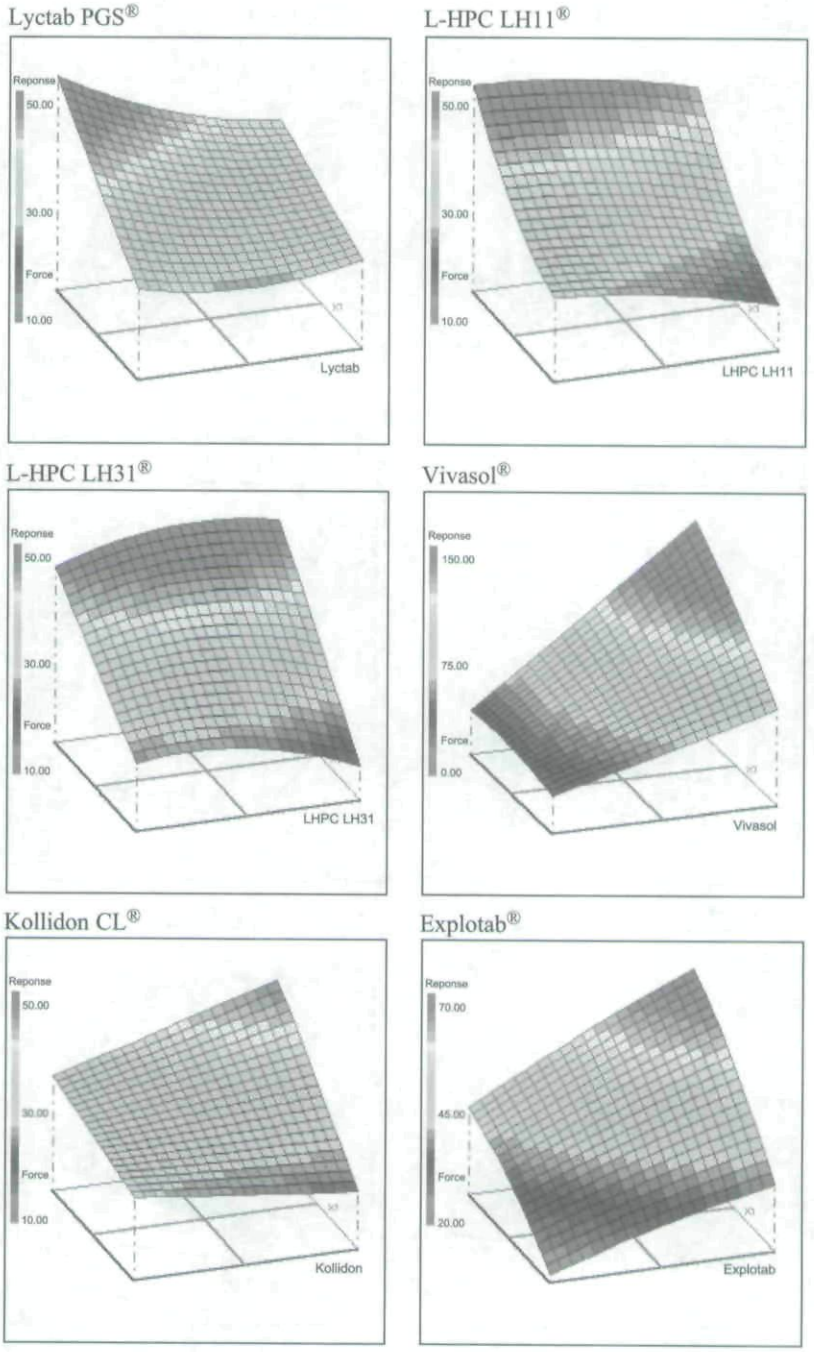

FIGURE 4 **Response Surfaces—Disintegration Time—Diluent: Zeparox®.**

reached with 5% of disintegrant; for 150 MPa, the optimal concentration is 7% of disintegrant, leading to the minimal disintegration time of 28.6 s. A small negative quadratic effect appears with Zeparox®, showing an opposite behavior.

Disintegration time for tablets obtained from L-HPC LH31®-Pearlitol 200® mixtures, a particular response can be detailed. Considering for example a compression pressure of 110 MPa, the increase in L-HPC LH31® concentration until approximately 6% permits a decrease in tablet disintegration time. An additional increase leads to an opposite effect, that is, an increase in disintegration time.

Vivasol

Vivasol® (croscarmellose sodium) is a cross-linked polymer of carboxymethylcellulose sodium. It is

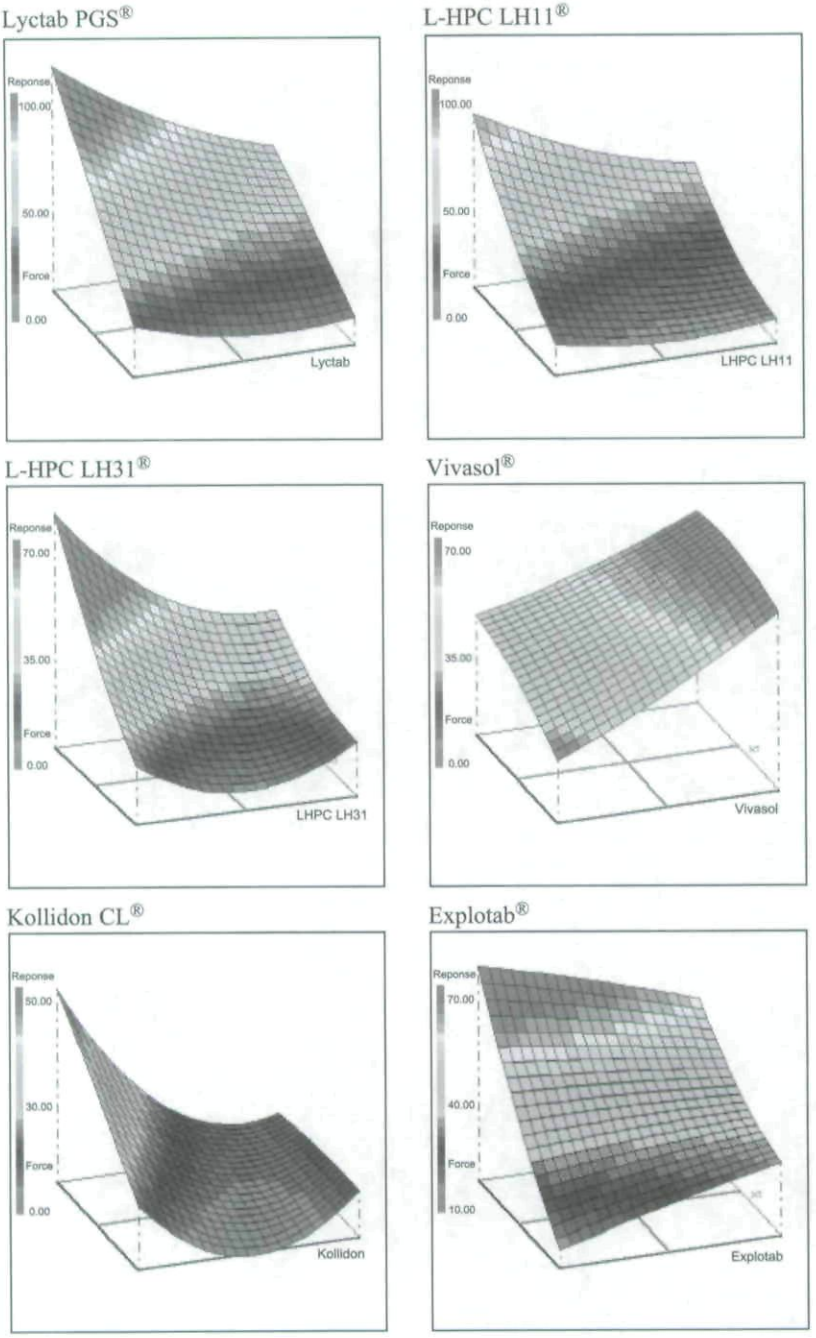

FIGURE 5 **Response Surfaces—Disintegration Time—Diluent: Pearlitol 200®.**

insoluble in water, in which it rapidly swells to four to eight times its original volume (Wade & Weller, 1994). All models have been validated but show, particularly for the disintegration time, completely different effects with this disintegrant when compared with the other excipients. Indeed, tablet disintegration time is mainly influenced by the disintegrant concentration rather than by the compression pressure. Only linear effects are observed. For Pearlitol 200® as the diluent, the compression force does not display any significant effect on the tablet disintegration time. The only significant variation of the disintegration time is due to the variation in disintegrant concentration; more precisely, increasing the disintegrant concentration leads to a significant and relevant increase of the disintegration time. For Zeparox®, an additional interaction occurs between the two controlled variables:

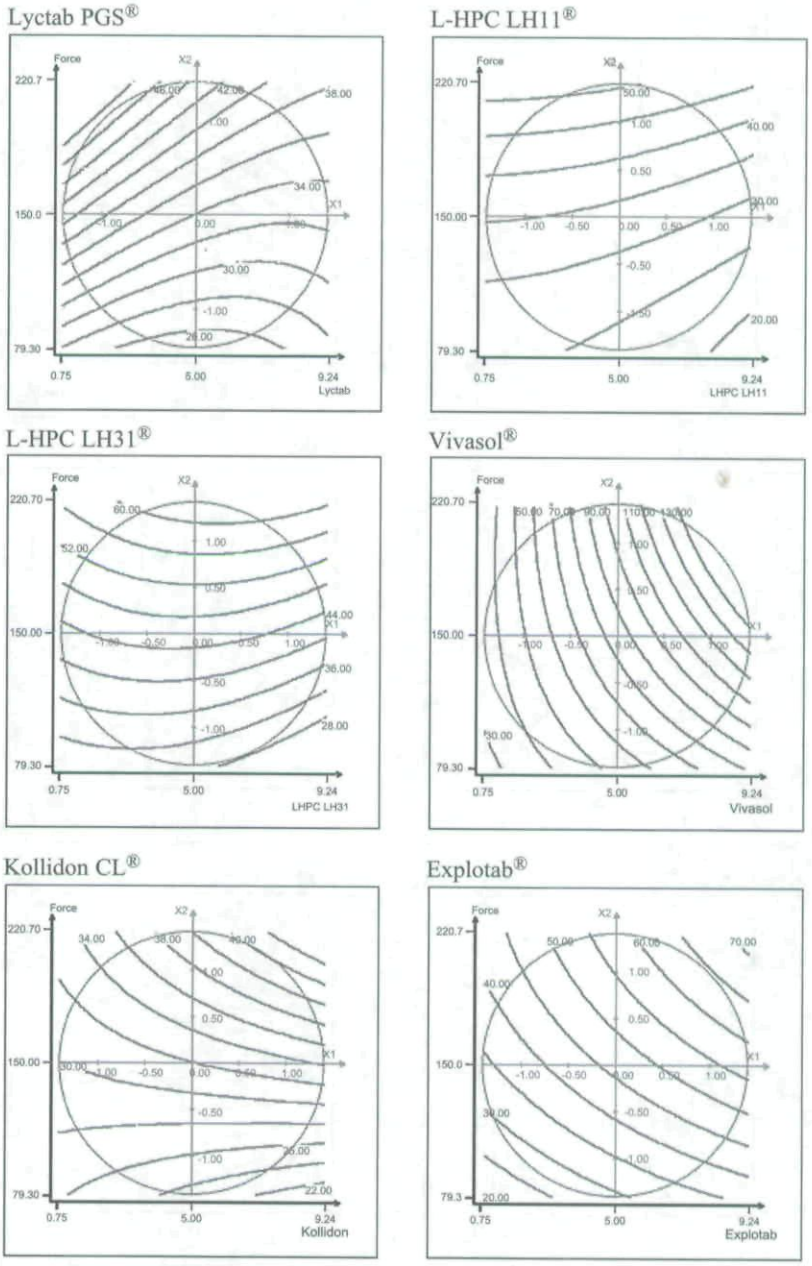

FIGURE 6 **Isoresponse Curves—Disintegration Time—Diluent: Zeparox®.**

no effect of compression force on the disintegration time for a small amount of disintegrant, significant increase for higher concentration (Figs. 4 and 6).

Kollidon CL®

Kollidon CL® (crospovidone) is a water-insoluble synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. It is an insoluble tablet disintegrant used at 2–5% concentration. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to gel formation (Wade & Weller, 1994). For Zeparox®, the model reveals only linear effects and interaction of the two studied controlled variables. The main factor influencing the disintegration time is the compression force. The effect of the disintegrant concentration is statistically significant but small. Increasing both the compression force and the disintegrant concentration leads to an increase of the disintegration time. When Pearlitol 200® is introduced as the diluent, the highest effects are due to the concentration of disintegrant, but all

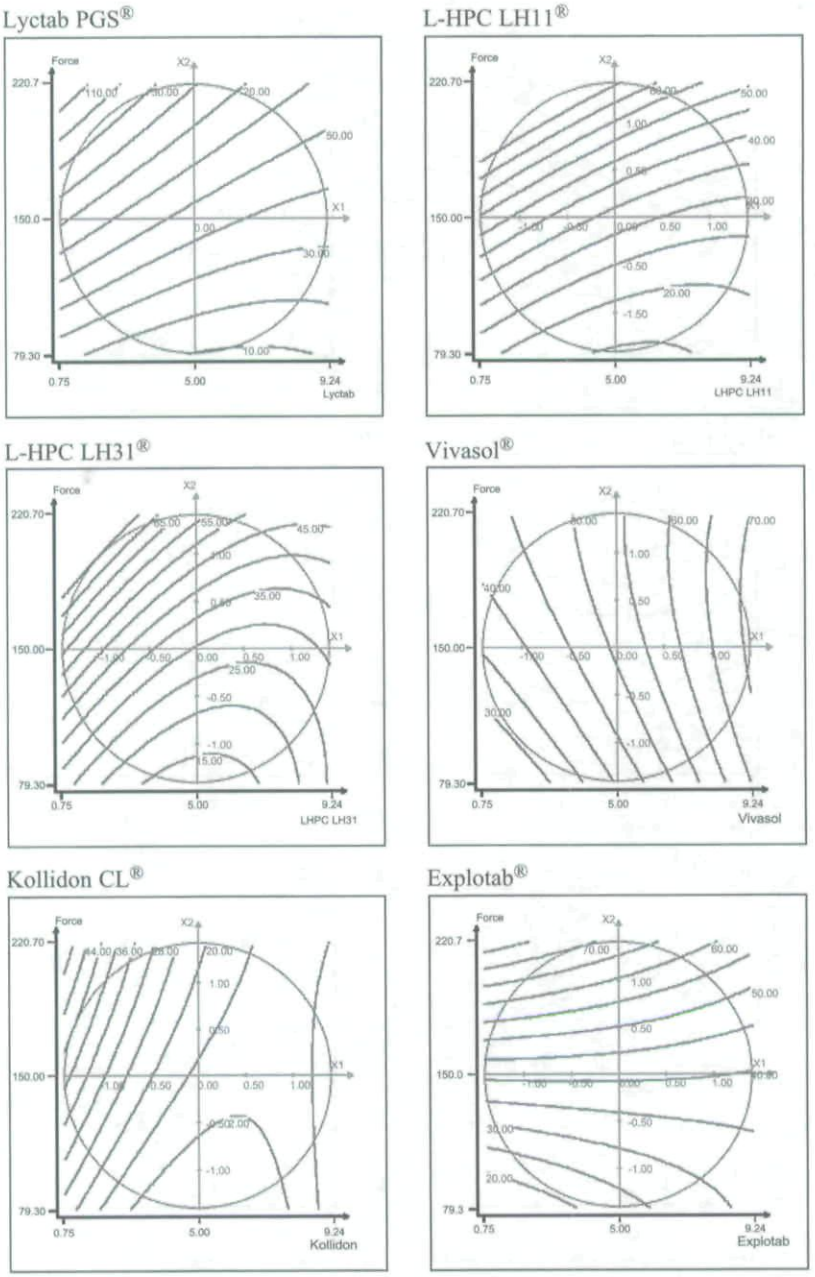

FIGURE 7 **Isoresponse Curves—Disintegration Time—Diluent: Pearlitol 200®.**

terms of the model are statistically significant, leading to a complex response surface characterized by a remarkable stationary region (Figs. 5 and 7). Stable disintegration times (13±2s) are obtained with a disintegrant concentration varying from 6% to 7% and a compression force from 130 to 190 MPa (Fig. 7). The smallest disintegration time (7.8 s) is reached with 5.5% of disintegrant and a compression force of 80 MPa. For lower Kollidon CL® percentages, the compression pressure dramatically increases the tablet disintegration (Fig. 7).

Explotab®

Explotab® (sodium starch glycolate) is the sodium salt of a carboxymethyl ether of starch (USPNF XVII). Explotab is characterized by the degree of substitution and cross-linking. The usual concentration is between 2–8%, with an optimal concentration at 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water, followed by rapid and enormous swelling (Wade & Weller, 1994).

For Zeparox®, both studied factors produce a linear effect on the disintegration time, the compression force influencing the response with higher amplitude. The interaction is not relevant; whatever the increase of compression force, the disintegrant concentration leads to an increase of the disintegration time (Figs. 4 and 6). According to Student's t-test, only the compression force significantly and strongly influences the disintegration time when Pearlitol 200® is used. A slight interaction effect and some trends nevertheless appear: above 150 MPa, increasing the disintegrant concentration tends to shorten the disintegration time, below this limit the opposite effect is observed.

At 150 MPa the disintegration time is no more dependent on the disintegrant concentration. This behavior clearly appears on the iso-response curves representation in which an axis of symmetry is observed at a compression force of 150 MPa (Fig. 7).

CONCLUSION

The disintegration time of tablets obtained by direct compression is highly influenced by the type of disintegrant used: it is generally lower with Vivasol® and faster with Kollidon CL®, whatever the diluent. However, this last one can strongly modify tablet disintegration time. Apart from the specific behaviors with the two different diluents, disintegrants such as Lycatab®, L-HPC LH11®, and Kollidon CL® are more sensitive to the compression force than to the concentration, so that an increase in compression pressure can dramatically increase disintegration time. On the contrary, Vivasol® and Explotab® are more particularly influenced by the disintegrant concentration. Concerning L-HPC LH31®, it is influenced both by disintegrant concentration and compression pressures.

All the collected results can help the formulators to select a disintegrating agent adapted to the requirements for the produced tablets, such as hardness and disintegration time, with optimal operating conditions for the disintegrant concentration and the compression force. The next step of the work will be to study the influence of different actives on optimized, fast-dissolving tablet formulations.

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