RESEARCH ARTICLE

Lubricant Efficiency of Magnesium Stearate in Direct Compressible Powder Mixtures Comprising Cellactose® 80 and Pyridoxine Hydrochloride

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Lubricant Efficiency of Magnesium Stearate in Direct Compressible Powder Mixtures Comprising Cellactose® 80 and Pyridoxine Hydrochloride

Piridoksin Hidroklorür ve Cellactose®80 içeren Doğrudan Basılabilir Toz Karışımlarında Magnezyum Stearat'ın Lubrikant Etkinliği

Summary

The purpose of the present study was to investigate lubricant efficiency of magnesium stearate in a model powder mixture of Cellactose®80 and pyridoxine HCL. A two-factor, three-level full factorial design (3^2) was created to observe the effects of lubricant on the flow properties, consolidation, and compressibility behaviors of the resulting powders and quality of the directly compressed tablets from the powders. The level of lubricant and the length of lubricant mix time were the independent factors. The dependent factors were the measured responses from the powder mixtures before compression such as angle of repose, flow rate, Carr's index, Hausner index, and the intercept and mean yield pressure (P_y) of Heckel equation. The measured responses from tablets were the percentage of friability, disintegration, and percent drug dissolved in 45 min. Nonlinear regression analysis indicated a good correlation ($R^2=0.999-0.844$) between the measured responses and the independent factors. Lubricant amount had a statistically significant effect on all the evaluated properties ($p<0.05$ or $p<0.10$). Lubrication time affected the angle of repose, the intercept of Heckel equation and, to a lesser extent, P_y values of the powder mixtures. Optimum responses were obtained from the medium level of lubricant amount (2%) and medium level of lubricant mix time (6 min).

Key Words: *Magnesium stearate, lubricant efficiency, direct compression, factorial design, pyridoxine HCL.*

Özet

Bu çalışmada, magnezyum stearatın Cellactose®80 ve piridoksin HCl'den oluşturulan model bir toz karışımı içinde lubrikant etkinliğinin araştırılması amaçlanmıştır. Lubrikantın toz karışımlarının akış özellikleri, konsolidasyon ve basılabilirlik davranışları üzerine ve bu toz karışımlarından doğrudan tabletleme yöntemi ile basılan tabletlerin kalitesi üzerine etkisini gözlemek için iki-faktörlü, üç-düzeyli bir faktöriyel tasarım oluşturulmuştur. Toz karışımına ilave edilen lubrikantın miktarı ve lubrikant ile karıştırma süresi bağımsız faktörler olarak belirlenmiştir. Bağımlı faktörler, basım öncesinde toz karışımının yığın açısı, akış hızı, Carr indeksi, Hausner indeksi, Heckel eşitliğinin uygulanmasından elde edilen kesişim ve Py değerleri olarak ölçülen cevaplardır. Tabletlerden ölçülen cevaplar ise yüzde aşınma değeri, dağılma süresi ve 45dak içinde tabletlerden çözünen etkin madde miktarı olmuştur. Nonlineer regresyon analizinin sonuçları, ölçülen cevaplar ile bağımsız faktörler arasında iyi bir korelasyon olduğunu göstermiştir ($R^2=0.844$-0.999). Lubrikant miktarı, değerlendirilen tüm özellikler üzerinde istatiksel olarak önemli derecede etkili bulunmuştur ($p<0.05$ or $p<0.10$). Lubrikant ile karıştırma süresi ise toz karışımlarının yığın açıları, Heckel eşitliğinin kesişim değerleri ve daha az derecede Py değerleri üzerinde etkili olmuştur. En uygun cevaplar, lubrikantın orta düzeyde ilave edildiği (%2) ve orta düzeyde karıştırıldığı (6dak) toz karışımı için elde edilmiştir.

Anahtar kelimeler: *Magnezyum stearat, lubrikant etkinliği, doğrudan basım, faktöriyel tasarım, piridoksin HCL.*

INTRODUCTION

Tablet dosage forms are the most popular and preferred drug delivery systems in terms of precision of unit dose, low cost, patient compliance, and good physical and chemical stability. Tablets account for 70%-80% of all pharmaceutical dosage forms (1-3). The simplest method of tableting is direct compression, in which drugs and excipients are dry-mixed and then compressed without applying any further operation. Direct compression offers advantages over wet granulation and dry granulation, e.g. it is a cost-effective method since the number of unit operations and process time are reduced and it is the method preferred for heat- and/or moisture-sensitive

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compounds. Additionally, validation of the method is easier and contamination risk is lower (2,4-7).

A simple formula includes an active ingredient, a diluent and a lubricant. However, development of a formulation for direct compression might be very complex and requires increased performance from the diluents. An ideal directly compressible agent should have good flow properties, low segregation tendency, and suitable compression behavior. Co-processed excipients are the combinations of two or more existing excipients formed by an appropriate process such as spray drying, blending, milling, or wet and melt granulation, providing them with advanced physico-technical properties, without any associated chemical change. These products are single-bodied excipients acting as filler, binder and disintegrant and offering optimal particle size, shape, distribution, density, and morphology, thus enabling direct compression (2,6,8). The dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material (8). It is also expressed in terms of percentage of noncompressible material or as optimum drug to diluent ratio (2). The dilution potential is especially important for direct tableting of high-dose and poorly compressible drugs. A directly compressible excipient needs to have high dilution potential so that the final dosage form has a minimum possible weight (9,10). Co-processed excipients have been stated to have higher dilution potential than a physical mixture of its constituent excipients (6,8,11).

Among the tablet excipients, lubricants are extremely important for improving the quality and manufacturing productivity of the tablets. Lubricants reduce the friction between the tablet edge and the die wall during compression and facilitate ejection by forming a film of low shear strength between the die wall and tableting mass (12,13). Lubricants can act as a glidant, improving the flow of the powder blend within the hopper and die cavity (7,14,15). Of all the lubricants in use, magnesium stearate (MS) is the most widely used. It has low friction coefficient and high covering potential. The lubricant efficiency and extent of surface coverage depend on the mixing time of the tablet mass with MS because of its laminar structure (16). Introduction of the high-speed tableting machine requires the use of higher concentrations of MS, but increasing concentration of MS can adversely affect the flow properties of the tableting mass and the

quality properties of tablets (1,15,17). Therefore, the concentration of the lubricant in the formulations and the lubrication time should be balanced in terms of the adverse effects of the used lubricant. Generally, lubricants are added to the premixed powder mixture as a final step and mixed for only a few minutes. But even small changes in mixing time and lubricant amount can significantly affect the product performance and quality properties. As a result of over-lubrication, the mechanical strength of the tablets can decrease and the dissolution of the drug may worsen. Therefore, experiments should be performed to define lubricant use level and optimize the mixing process.

One objective of this work was to evaluate the effects of the concentration of MS and the time of lubrication: (i) on the flow properties, consolidation, and compressibility behaviors of powder mixtures consisting of Cellactose®80 and a model drug, pyridoxine HCL (PDH), and (ii) on the quality properties of the directly compressed tablets from the powder mixtures. We also aimed to determine the relationships correlating the assessed properties of powder mixtures and tablets to concentration and mixing time of MS using a factorial design. PDH is an almost white powder and its aqueous solubility is 0.1 mg/ml at 20°C. The particle size distribution of the drug was determined by sieving analysis: 84% of the drug was smaller than 0.110 mm and 16% of the drug was smaller than 0.038 mm; geometric mean size of the drug (50%) was 0.060 mm. PDH has fair flowability; its measured angle of repose was 38.3±1.38. It is inferred from these data that PDH would be indicative of the effect of MS on dissolution behavior of a drug without interfering with the other assessed properties.

MATERIALS and METHODS
Materials
Pyridoxine HCL was kindly supplied by Abbott Laboratories (Istanbul, Turkey). Cellactose®80 (Meggle GmbH, Wasserburg, Germany) was used as a direct compressible agent and MS (Riedel-de Haën AG Seelze, Hannover, Germany) was used as a lubricant. All other materials and solvents were of analytical grade.

Methods
Preparation of Powder Mixtures
For each batch of powder mixture of 800 g, 94 g of PDH and 706 g of Cellactose®80 CL were mixed at 25 rpm for 10 min by a cube mixer (Erweka, Munich, Germany) at

room temperature. Each batch was lubricated with MS (particle size less than 0.250 μm), which was added at the amounts given in Table 1, by additional mixing at 25 rpm in a cube mixer for the times given in Table 1. Total batch number was nine (Table 2).

Table 1. Levels and range of the independent factors with the assigned codes

	Independent Factors			
Levels	Amount of magnesium stearate (%)		Mixing time (min)	
	X_1	Code	X_2	Code
Low	0.5	- 1	3	-1
Medium	2.0	0	6	0
High	8.0	+1	9	+1

Evaluation of Powder Mixtures

Determination of the flow properties of powder mixtures
The flow rate was determined using a glass funnel with an orifice 10 mm in diameter by weighing the same quantity (25 g) of powder mixtures (n=3) each time. The value of the angle of repose was calculated by the static angle of repose method using 50 mL of the powder mixtures (n=3) (18,19).

Determination of consolidation behavior of powder mixtures
Ten milliliters of the powders were gently poured into a 10 ml graduated cylinder through a funnel. The weight of 10 ml was then determined and the bulk density (BD) was calculated. The graduated cylinder was tapped from

a height of 25 mm and the resulting reduction in volume was measured after repeating this procedure 5, 10, 20, 50, 75, 100, 120, 200, 300, 400, and 500 times until achieving constant volume, and then the tapped density (TD) was calculated. Carr's index (CI) was estimated from the bulk and tap volumes (V_{bulk} and V_{tap}) according to Eq.1 (20).

$$CI\% = \frac{V_{bulk} - V_{tap}}{V_{bulk}} * 100\% \qquad (Eq.1)$$

Hausner index (HI) was calculated from the BD and TD values (Eq.2) (21).

$$HI = TD / BD \qquad (Eq.2)$$

Determination of compressibility behavior of powder mixtures
For this purpose, a 10-mm flat face punch and a hand-operated hydraulic press (Ucler, Istanbul, Turkey) were used. The appropriate amounts of granules were pressed at 54.16, 108.31, 162.47, 216.63, 324.94, and 433.26 MPa. When the desired pressure was reached, it was kept at this value for 20 sec. The height of the compact was measured accurately and the volume was calculated (n=3). The data were analyzed by the Heckel equation (22,23). The equation may be written as:

$$\ln \frac{V_p}{V_p - V_\yen} = KP + \ln \frac{V_0}{V_0 - V_\yen} \qquad (Eq.3)$$

$$\ln \frac{V_p}{V_p - V_\yen} = KP + I \qquad (Eq.4)$$

Table 2. Compositions of the studied formulations and the measured responses for 3^2 full factorial design

Code	Independent factors												
							Measured responses						
	Powder mixtures								Tablets				
	X_1	X_2	AOR	FR	CI	HI	Py	I	R^2	AW	H	FRI	DI	DIS
F1	- 1	-1	24.3±0.306	3.13±0.023	19	1.24	95.2	0.777 ± 0.326	0.893	0.344±0.647	7.19±0.065	0.667	1.07±0.01	86.6±2.81
F2	0	-1	26.5±0.783	3.00±0.022	19	1.24	67.1	0.568 ± 0.418	0.911	0.347±0.293	7.33±0.083	0.523	2.48±0.159	86.1±2.45
F3	+1	-1	32.9±0.677	0	27	1.37	123	0.839 ± 0.281	0.871	0.366±0.219	7.80±0.056	0.511	>60	37.6±0.64
F4	- 1	0	28. 6±0.515	3.22±0.056	20	1.25	103	0.756 ± 0.202	0.949	0.343±0.442	7.53±0.077	0.433	1.22±0.050	93.1±0.087
F5	0	0	28.6±0.985	2.64±0.009	16	1.19	76.3	0.441 ± 0.135	0.987	0.346±0.391	7.10±0.046	0.586	2.53±0.146	84.8±0.410
F6	+1	0	34.8±0.484	0	27	1.37	87.0	0.896 ± 0.383	0.879	0.368±0.362	7.43±0.083	0.526	>60	41.6±0.542
F7	- 1	+1	28.7±0.654	3.33±0.026	18	1.22	142	1.09 ± 0.397	0.719	0.344±0.519	7.70±0.111	0.541	1.64±0.158	87.8±3.98
F8	0	+1	27.2±1.58	2.64±0.009	18	1.22	97.1	0.957 ± 0.306	0.879	0.350±0.862	7.93±0.066	0.306	3.75±0.303	89.0±1.06
F9	+1	+1	33.1±1.01	0	20	1.25	96.2	1.75 ± .0973	0.903	0.368±0.194	7.35±0.053	0.532	>60	28.9±3.61

AOR : Angle of repose (degree) ± SE (standard error)	R² : Determination coefficient of Heckel equation
FR : Flow rate (g/sec) ± SE	AW : Average weight (g) ± RSD (relative standard deviation)
CI : Carr index (%)	H : Hardness (Kg) ± SE
HI : Hausner index	FRI : Friability
Py : Mean yield pressure (MPa) from Heckel equation	DI : Disintegration (min) ± RSD
I : Intercept of Heckel equation ± SE	DIS : Percent drug dissolved in 45min±SE

Table 3. Results of regression analysis and p values obtained from analysis of variance (ANOVA)

Measured responses	Coefficients												
	B_1	p	B_2	p	B_{11}	p	B_{22}	p	B_{12}	p	B_0	p	R^{2***}
AOR	3.19	< 0.001*	0.872	0.0289*	2.935	<0.01*	-1.87	0.0163*	-1.04	0.0312*	28.7	<0.0001*	0.991
FR	-1.09	0.0538**	0.509	0.246	-0.6	0.4	0.6	0.421	0.729	0.191	2.35	0.0356*	0.844
CI	2.83	0.055**	-1.5	0.204	4.167	0.0806**	-0.833	0.639	-1.5	0.278	18.2	<0.01*	0.874
HI	0.0477	0.052**	-0.025	0.199	0.0687	0.08**	-0.0163	0.579	-0.026	0.257	1.23	<0.0001*	0.878
Py	-3.00	0.551**	8.33	0.160	24.9	0.0491*	20	0.0821**	-18.4	0.0441*	66.8	<0.0001*	0.914
I	0.144	0.0444*	0.269	<0.0001*	0.363	0.0166*	0.299	0.0278*	0.149	0.0658*	0.456	0.0102*	0.970
FRI	-0.012	0.831	-0.0534	0.376	0.0633	0.531	-0.00167	0.986	0.0368**	0.602	0.473	0.0153*	0.396
DI	29.4	<0.0001*	0.307	0.147	27.7	<0.0001*	0.24	0.445	-0.143	0.515	2.76	<0.01*	0.999
DIS	-26.6	< 0.001*	-0.793	0.694	-24.1	<0.01*	-3.82	0.314	-2.45	0.354	89.2	< 0.0001*	0.989

* : p<0.05, significant parameters   ** : p<0.10, significant parameters   ***: Determination coefficient

where Vp is the volume of the compact at each pressure applied, V_∞ is the true volume of the compact (without pores), V_0 is the initial granule volume, and P is the applied pressure. K is determined from the slope and I from the intercept of a plot of $\ln(Vp/(Vp - V_\infty))$ vs. P.

Preparation of Tablets

A 10–mm single punch eccentric tablet press machine (Korsch, Erweka, Berlin, Germany) was used for pressing round tablets containing 40 mg PDH from the powder mixtures.

Evaluation of Tablet Properties

Weight variation test

The mass of 20 tablets from each batch was weighed using Mettler P1200 balance (Mettler-Toledo (Schweiz) GmbH, Im Langacher, Switzerland), and the average mass was determined. The percentage deviation from the average mass was calculated (24).

Hardness determination

Twenty tablets taken randomly from each batch were tested for hardness using Monsanto hardness tester (Penwalt Stokes, PA, USA). The average hardness (Kg) and standard error were calculated for each batch.

Friability test

Twenty tablets were taken randomly and weighed accurately and placed in a friabilator (Erweka, Germany). After 100 rotations (25 rotations per minute, for 4 min), the tablets were removed and re-weighed accurately. The loss in mass was determined (24).

Disintegration test

One tablet was placed in each tube of the basket rack assembly and a disc was added on each tube. The rack was immersed in distilled water at 37 ± 2ºC and the apparatus (Aymes, Istanbul, Turkey) was operated at a frequency rate between 29-32 cycles per minute. The time (min) to disintegrate and fall of the tablets through the screen was recorded (24).

Dissolution test

Dissolution studies on the tablets of PDH were conducted in USP Apparatus 2 (paddle method) (Aymes D96D, Istanbul, Turkey) with three replicates, according to the USP monograph (25). The dissolution medium was 900 mL of distilled water at 37 ± 0.5ºC. The paddle rotation speed was kept at 50 rpm. In all experiments, 5 mL of dissolution sample was withdrawn at 5, 10, 15, 30, and 45 min and replaced with an equal volume of the fresh medium at 37 ± 0.5ºC to maintain a constant total volume. Samples were assayed by UV spectrophotometry at 292 nm (Shimadzu UV-1202, Tokyo, Japan). Cumulative percentages of the drug dissolved from the tablets were calculated.

Experimental design

The amount of lubricant (X1) added to powder mixtures and the length of lubricant mix time (X2) were the independent factors. The dependent factors were the measured responses (Y) from powder mixtures before tableting, that is, angle of repose, flow rate, compressibility index (CI), HI, and intercept (I) and mean yield pressure (P_y) of Heckel equation. The measured responses from tablets were percent friability, disintegration and percent

drug dissolved in 45 min. A two-factor, three-level full factorial design (3^2) was formed to clarify the effects of independent factors on measured responses (26,27). The levels and range of the independent factors with the assigned codes are given in Table 1. The levels of the factors were selected with the intention that their relative difference was enough to present a measurable effect on the response. A polynomial equation was employed to quantify the effects of independent factors on the measured responses.

$$Y = B_0 + B_1 X_1 + B_2 X_2 + B_{11} X_1 X_1 + B_{22} X_2 X_2 + B_{12} X_1 X_2$$
(Eq.5)

where Y is the measured response, X_i is the level of the independent factors, B_i represents coefficients, and B_0 is the intercept. B coefficients with their standard errors and descriptive statistics of regression for the model were calculated by the nonlinear regression module of Statistica 5.0 for Windows (Statsoft, Tulsa, OK, USA). In nonlinear regression analysis, the quasi-Newton method minimized the least squares. The studied batches and the measured responses are shown in Tables 2 and 3.

RESULTS and DISCUSSION
Determination of the Flow Properties of Powder Mixtures

Several pharmaceutical processes, including blending, transportation, storage, feeding, compaction, and fluidization entail powder handling. The flow of powder during manufacturing dictates the quality of the product in terms of weight, hardness, and content uniformity of the tablets. Therefore, the measurement of the flow properties of powder mixtures is essential before tableting and capsule filling (28,29). The flow property of bulk material results from the cohesive forces acting on individual particles such as van der Waals, electrostatic, surface tension, interlocking, and friction (28). The methods commonly reported for testing powder flow are angle of repose, flow rate through an orifice, CI, or HI (24).

Effects of MS amount and lubrication time on the angle of repose and flow rate of powder mixtures are shown in Table 2. The flow rates of the powder mixtures were substantially decreased depending on the amount of MS, and powder flow was interrupted at the highest level of MS (F3, F6, and F9 formulations). The lubrication time did not exert a clear

effect on the flow rates of the powder mixtures. Angles of repose of the powder mixtures ranged between 24.3°-34.8°. Values for angles of repose ≤30° generally indicate a free-flowing material and angles ≥40° suggest a poorly flowing material. An aid was needed to sift formulations F3, F6, and F9, showing flow stoppages from the funnel orifice during the measurements. Increasing levels of MS and lubrication times caused increasing values of angle of repose of the powder mixtures. The increase in magnitude of the angle of repose was associated with a decrease in flow rate (30). A negative correlation (R= -0.897) was observed between angles of repose and flow rates of the powder mixtures (Fig. 1). Fine particles of MS (<0.250 µm) have a large surface area. During flow, the friction surfaces would be abundant at a high level of MS, and thus, as angle of repose increases, the powder flow deteriorates. In this case, a powder rheometry might be suggested for investigating the flow properties of cohesive powders (31).
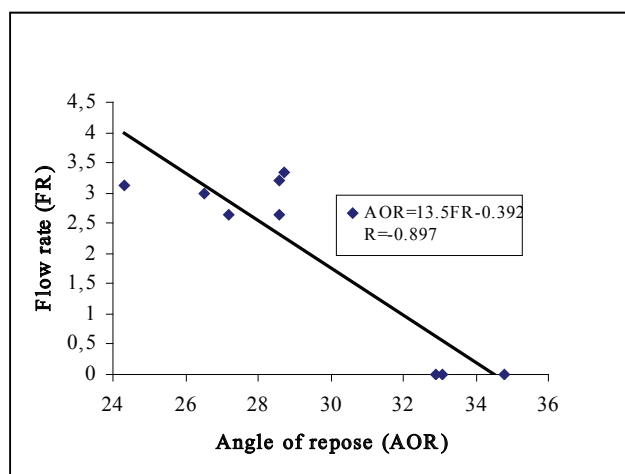

Figure 1: Relationship of angle of repose to flow rate for powder mixtures.

The results of the nonlinear regression analysis (B coefficients and R^2 values) and analysis of variance (p values) are shown in Table 3. Determination coefficients (R^2 values) obtained for angles of repose and flow rates of powder mixtures were 0.991 and 0.844, respectively. These values reveal a good correlation between the dependent factors and the measured responses besides representing the performance of the polynomial equation (Eq.3). Coefficients with one factor describe the linear effects of the factors while the coefficients with more than one factor indicate an interaction between the factors. The coefficients of the factors squared represent the quadratic (nonlinear) nature of the relationship, signifying a curvature

in the response. Negative signs of the coefficients indicate negative quantitative (antagonistic) effect of the factor on the measured response just as positive signs indicate positive quantitative (synergistic) effect (26,27,32).

Two independent factors (X_1: amount of MS and X_2: lubricant mix time) were found to be significantly effective on the angle of repose (p<0.05) (Table 3). The level of MS and the lubrication time increased the values of angle of repose (Table 3, Fig. 2). The relationships between the

Figure 2: Response surface plot for angle of repose of the powder mixtures as a function of the amount of MS (X1) and mixing time with lubricant (X2). C points show the measured responses.

amount of MS and the angle of repose and between the lubrication mix time and the angle of repose were quadratic. Interaction of MS-lubrication time (p<0.05) (Table 3) was found to be statistically significant. Interaction is thought of as a lack of additivity of factor effects; that is, the effect of one factor at each level on the measured response is not parallel with that of other factors. Lack of parallelism suggests interaction (Bolton, 1997). The decreasing effect of MS level on the flow rates of the powder mixtures was found to be significant (p=0.0538) at the 10% level.

Determination of Consolidation Behavior of Powder Mixtures

Granule flowability and compactability are important properties for tableting because they affect uniform die filling and tablet mechanical characteristics. The HI and

CI are the indicators of the flowability and consolidation properties of the powder mixtures. When the CI and HI ratio are adequate, the powder flows at minimum bulk density and consolidates to maximum density inside the die, prior to compression (33). A high bulk density, i.e. a low porosity, will result in a low deformation potential: a lack of space for deformation during compression will cause less intimate contact between the particles within the tablets, resulting in weaker tablets (34).

The HI values of the powder mixtures increased with the increase in MS amount (Table 2). The HI values of the powder mixtures excluding F3 and F6 were between 1.19-1.25, pointing out the fair flow characteristic (Table 2) (Fig. 3). The HI values for both F3 and F6 powder mixtures containing MS at the high level were 1.37, indicating poor flow properties (24). However, the long mixing time (9 min) influenced the total volume reduction of powder mixture (F9), and lowered the HI value from 1.37 to 1.25. MS has a large covering potential, and thus the long mixing time improves the lubricant distribution at the particle level to assist the particle rearrangement under tapping by reducing the interparticulate friction (1,21).
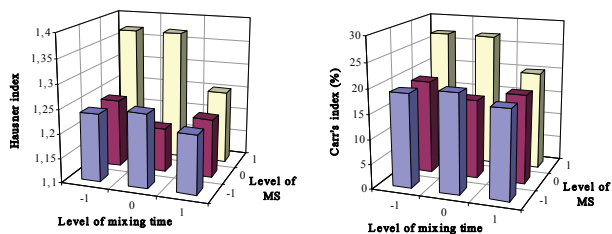

Figure 3: Hausner indexes and Carr's indexes as a function of the amount of MS (X1) and mixing time with lubricant (X2).

The CIs of the powder mixtures were changed in the same way as HIs, depending on the factors investigated, as seen in Figure 3. The values of CIs varied from 16 to 20%, indicating fair flow properties of the powder mixtures, excluding F3 and F6. The CIs of powder mixtures of F3 and F6 were 27%, showing passable flow character due to high level MS in their compositions (Table 2). The long mixing time lowered the CI values from 27% to 20%.

The analysis of variance of HI and CI values is presented in Table 3. The most important effect was the level of MS (p=0.052 for HI and p=0.055 for CI) with a significance level of 10%. The relationships between the amount of

MS and HI, and between the amount of MS and CI were quadratic and significant (p=0.08 for HI and p=0.0806 for CI) at 10% level. Determination coefficients (R^2 values) for HI and CI values of powder mixtures were 0.878 and 0.874, respectively.

Determination of Compressibility Behavior of Powder Mixtures

The Heckel equation describes the relationship of the compact density to the applied pressure. The rate of density increase with applied pressure is proportional to the volume fraction of pores (22). In our study, volume reduction of the compacts was used instead of density increase under the applied pressure in Heckel equation. The reciprocal value of the slope of Eq.(4) ($P_y=1/K$) represents the mean yield pressure by which a substance resists the deformation process. The value of intercept (I) is related to the die filling and particles slipping over each other during rearrangement before deformation and bonding of the separate particles at the beginning of the compression (2,22,35,36).

The constants for Heckel equation (Eqs. 3,4) are given in Table 2. The Heckel plots of the powder mixtures evaluated are shown in Figure 4. Various stages of a compression process can be described through a Heckel plot (2): the first curvature point indicates the particle rearrangement before a plastic deformation begins. A linear part in the plot means plastic deformation and a plateau is reached. The plateau is explained by the work of hardening and change of crystal density. This part of the Heckel plot also indicates the elastic deformation of the powder mass.
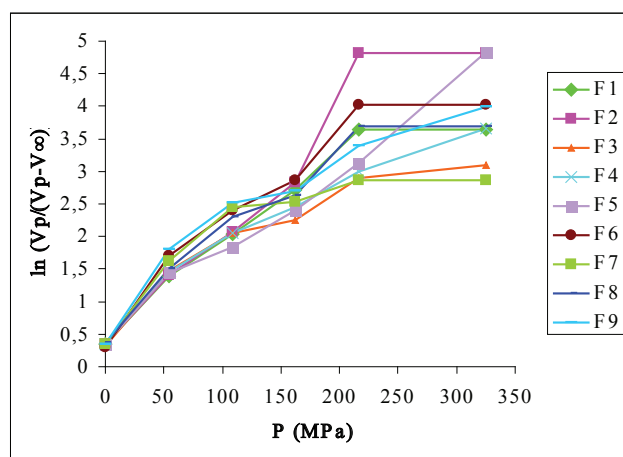

Figure 4: Heckel plot derived from relative volume and compaction pressure.

The level of MS (p<0.05) and lubricant mixing time (p<0.0001) were significantly effective on I values of Heckel equation (Eq.4) with a determination coefficient (R^2=0.970). The relationships between the amount of MS and I (p<0.05) and between the lubricant mixing time and I (p<0.05) were quadratic and significant. Interaction of the MS level - lubrication time (p=0.0658) (Table 3) was found to be statistically significant at the 10% level. The highest I values were observed for the powder mixtures blending with the lubricant for longer periods of time (9 min) (F7, F8, and F9 formulations), indicating the difficulty in powder packing before plastic deformation. The lowest I values were noticed for the powder mixtures containing MS at the medium level and blending with the lubricant for the shorter time periods (F2 and F5 formulations) (Fig. 5).
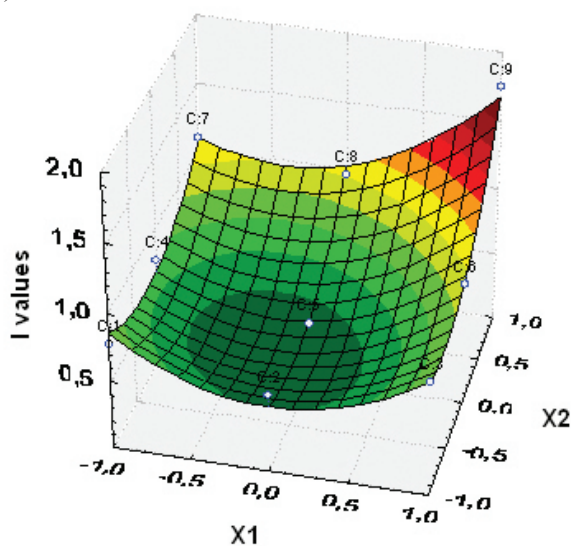

Figure 5: Response surface plot for I values of Heckel equation as a function of the amount of MS (X1) and mixing time with lubricant (X2). C points show the measured responses.

As seen in Table 3, determination coefficient of the Heckel equation fitted for Py values is 0.914. The level of MS was an important factor with a significance level of 10% (p=0.551) and its effect on Py values was quadratic (p<0.05). The quadratic effect of lubricant mixing time is also important at a level of 10% (p=0.0821). The interaction between MS level and lubrication time was significant (p<0.05).

Cellactose®80 is a co-processed spray-dried compound consisting of 75% α-lactose monohydrate and 25% cellulose. The compactibility is attributed to a synergistic

effect of consolidation by fragmentation of lactose and plastic deformation of cellulose (10,37). Arida and Tabakha (37) investigated the compressibility properties of Cellactose®80 and reported that the presence of MS at a concentration of 1.0% has insignificant influence on the consolidation of Cellactose®80 because the fragmenting behavior predominates as many new surfaces of lactose are generated under compression and, therefore, the effect of the lubricant would be at a minimum. The Py values of Cellactose®80 powder alone have been found to be 50-60 MPa depending on the compression speeds. In our study, all the powder mixtures included 88.25% of Cellactose®80. Py values of the powder mixtures (F2 and F5 formulations) containing MS at medium level and blending with the lubricant for 3 min and 6 min were found to be 67.1 and 76.3 MPa, respectively. In general, a low Py value (higher slope) reflects low resistance to pressure, good densification, higher plastic deformation ability, and easy compression. Higher Py values were determined for the powder mixtures blending with the lubricant for longer time periods (9 min) (Table 2, Fig. 6).

The lubrication efficiency originates from the monomolecular film formed by MS over the surface of each particle of other tablet components. The extended mixing times increase the coating effect of MS. This

phenomenon has a strong negative effect on interparticle bonding under pressure (38,39) because the compression behavior of the powder mixture changes and the inherent property of MS, that is, its elastic deformation, dominates the fragmentation during plastic deformation. A satisfactory compression could not be achieved and the Py values became higher.

Evaluation of Tablet Properties

Hardness of the tablets was controlled by the upper punch adjusting knob while weights of the tablet were controlled using the lower punch adjustment. The adjustments were kept constant during the compression run. The exact compression forces could not be determined since the tablet press is not an instrumented press. Powder mixtures of nine formulations were compressed by direct compression method. The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, and dissolution of PDH (Table 2). Average tablet weights of all the batches met the pharmacopeial limits regarding the relative standard deviations within the limit of 5% (24). The values of tablet hardness were found to be between 7.10 to 7.93 kg. Friability of the tablets was less than 1.0%, which was considered acceptable to indicate sufficient mechanical integrity and strength of the prepared tablets (24,40). The determination coefficient obtained from the polynomial equation was 0.396, indicating that the level of MS and lubrication time did not significantly affect the friability of tablets (Table 3).

The tablets including MS at the low and medium level disintegrated within 1.07-3.75 min while those including high level of MS had not disintegrated at the end of 60 min (Table 2). The disintegration times of these formulations were assumed as 60 min for the nonlinear regression analysis. Determination coefficient (R^2 value) obtained for disintegration time of the tablets was 0.999. The increasing level of MS extended the disintegration time significantly ($p<0.0001$), and the relationship between the amount of MS and disintegration time was quadratic ($p<0.0001$) (Table 3, Fig. 7). The hydrophobic film formed by MS on the surface of the particles prevented the penetration of the water into the tablet structure and delayed the tablet disintegration (3,41). The lubrication time insignificantly increased the disintegration time of the tablets (Table 3, Fig. 7).
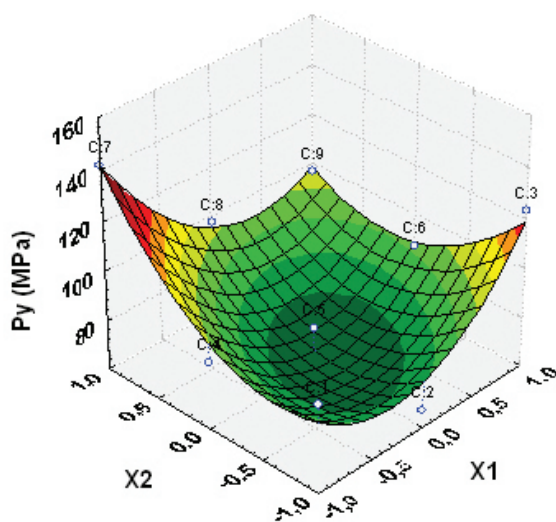

Figure 6: Response surface plot for P_y values of Heckel equation as a function of the amount of MS (X1) and mixing time with lubricant (X2). C points show the measured responses.
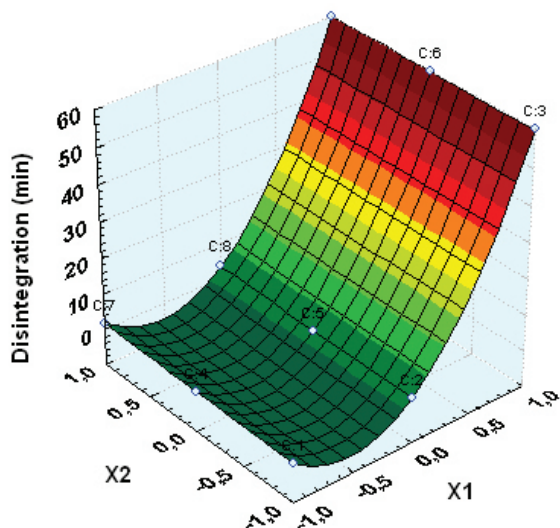
Figure 7: Response surface plot for disintegration times of the tablets as a function of the amount of MS (X1) and mixing time with lubricant (X2). C points show the measured responses.

The *in vitro* dissolution profiles of the tablets are shown in Figure 8. The dissolution specification, Q, for the PDH tablets has been stated in the USP (USP 30) as dissolution not less than 75% of the labeled amount of PDH within 45 min. The dissolved amounts of PDH within 45 min are shown in Table 2. PDH dissolution from the tablets containing high level of MS (F3, F6, and F9) was very slow (37.6%, 41.6%, and 28.9%) while more than 75% of PDH (86.1%-93.1%) dissolved from the other tablets containing low and medium level of MS.

Determination coefficient (R^2 value) obtained for dissolution percent of PDH from the tablets was 0.989.
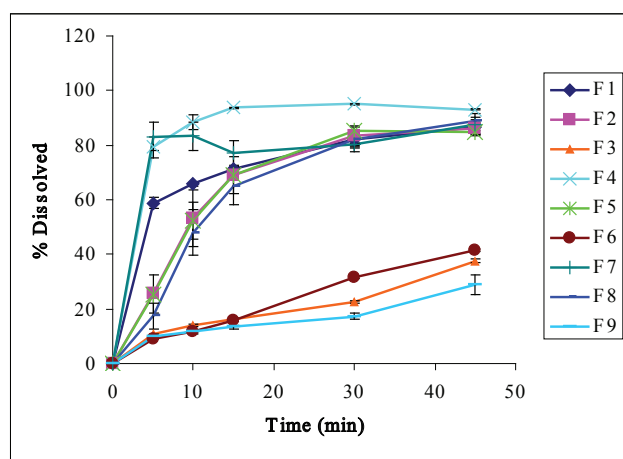

Figure 8: PDH release from the tablets.

The increasing level of MS significantly decreased the percent of PDH dissolved within 45 min ($p<0.001$), and the relationship between the amount of MS and the percent dissolved was quadratic ($p<0.01$) (Table 3, Fig. 9). The surface coverage effect of hydrophobic MS particles over the other tablet constituents resulted in the delayed dissolution of PDH from the tablets. The lubrication time did not significantly affect the percent of PDH dissolved (Table 3, Fig. 9).

CONCLUSION

Factorial design and nonlinear regression analysis of the results adequately described the quantitative effects of MS and the time of lubrication on the properties of powder mixtures composed from Cellactose®80 and PDH and on the quality properties of the prepared tablets. The lubricant amount had a significant effect on all the evaluated properties. Lubrication time affected the angle of repose, the intercept of Heckel equation, and, to a lesser extent, the Py values of the powder mixtures. The optimum properties were observed at 2% MS concentration and for 6 min of lubrication time although the effect of time depended on the concentration of MS. Such studies should be performed for formulation development and the scale-up process of tablet dosage forms since any change in time and level of lubricant may exert detrimental effects on the tableting process and product quality.
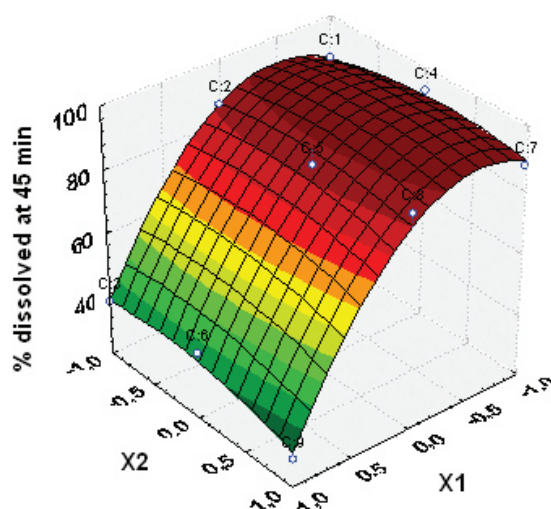

Figure 9: Response surface plot for percent dissolution of PDH from the tablets within 45 min as a function of the amount of MS (X1) and mixing time with lubricant (X2). C points show the measured responses.

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