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A Multivariate Strategy for Tablet Manufacturing Optimization

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SUMMARY. The objective of this work was to develop a multivariate strategy to optimize tablet manufacturing employing mephenesin as model drug. The process variables for granulation step were binders and lubricants types, while the mixture variables included the proportions of binders and lubricants. To reduce the experimentation and tablet characterization in the compression step, a principal component analysis was performed. Tabletting process was studied according to a three level factorial design. The factors were the scores in first principal component of granulation variables and hardness of the tablets. The properties of tablets were mainly influenced for the scores of granules. The optimum formulation, achieved using the desirability function, was the formulation with PVP K 90 as binder (4.25 %) and talc as lubricant (1.25 %). The multivariate strategy provides an effective tool for tablet manufacturing optimization when the high experimentation costs are prohibitive or the granulation process is influenced by many factors.

INTRODUCTION

Approaches to investigate the manufacturing and processing of pharmaceutical formulations have gained more attention within recent years. Statistical modelling and experimental designs are essential tools for the development and understanding of complicated products and processes [1]. Pharmaceutical technology usually employs both methods [2].

By utilizing design of experimental studies, the effects of critical material and process parameters on critical quality attributes can be understood. This is also encouraged by some guidelines [3,4]. Mixture designs [5], full factorial and fractional factorial designs [6,7] or surface response methodology [8] have been most frequently used with this utility. Recently crossed experimental designs [9,10], multivariate designs [11] and multivariate strategies [12] have been increasingly utilized. They are examples in which statistical modelling and experimental designs have been used to determine optimal values of process variables, suitable excipient types and proportions. The use of multivariate data analysis may be enable detection of a cause and effect relationship among variables, thus relating the association of variables with physical, chemical or biological phenomena. The dimensionality of the process data can be also reduced using multivariate techniques. Principal component analysis (PCA) is an effective tool for analyzing the process [13].

PCA is a popular data analysis method in pharmaceutical research. It has been used to detect hydrate formation [14,15] and different phases during wet granulations [16]. Tablets compressed

KEY WORDS: Crossed experimental design, Mephenesin, Multivariate strategy, Principal component analysis, Tablet manufacturing.

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with either as single punch or rotary tablet press were classified with PCA according to their tablet hardness [17]. Other applications in pharmaceutical technology include particle characterization [18] and optimization of manufacture of solid dosage form [19]. Process monitoring has been performed using methods basing on PCA [13,20-22]. Lindberg & Lundstedt [23] have reviewed applications of multivariate analysis in pharmaceutical development work.

Nevertheless, as many variables can affect pharmaceutical processes and formulations, finding optimal variable values could be expensive and time consuming, even employing statistical strategies. Therefore, it is necessary to efficiently combine statistical and technological knowledge to reduce the number of variables and experiments.

Previously, we reported a crossed experimental design using hardness as the only process variable as an efficient strategy to quickly determine the optimal design process for tablet manufacturing [9]. This approach is recommended when experimental work to study the tablet manufacturing process is defined by few granulation variables o factors or when an exact knowledge about the process is desired. This methodology could be costly inappropriate in complex solid pharmaceutical forms. The principal purpose of this work was to apply a multivariate strategy as a tool to optimize tablet manufacturing when granulation step is defined by many critical variables or the cost for accurate statistical modeling of whole process is prohibitive. Mephenesin, a centrally acting muscle relaxant drug [24], was used as model drug.

MATERIALS AND METHODS

Materials

The following active pharmaceutical ingredient and excipients were used: mephenesin (Unilab, India), polyvinylpyrrolidone (PVP) Kollidon 90 (Basf, Germany), povidone (KOLLIDON KVA-64, Basf, Germany), hydroxypropylmethylcellulose (HPMC, Methocel® K4M, Blanver, Brazil), microcrystalline cellulose PH-101 (Blanver, Brazil), dibasic calcium phosphate (Encompress) (Budenhein, Germany), magnesium stearate (Ajax, Australia), talc (Merck, Germany), colloidal silicon dioxide (Aerosil 200) (Wacker, Germany). All other chemicals and solvents were of analytical reagent grade.

Granules preparation

First, mephenesin was milled in a micromill (Culatti, Italy) and sieved through a 1.5 mm sieve. Then the drug was weighed and mixed with constant amounts of microcrystalline cellulose PH-101 and Encompress (Table 1) as fillers. The total amount of the mixture was kept constant, and the relative amounts of the different excipients varied according to the crossed experimental design (Table 2). Wet massing and drying of mephenesin granules was performed using a fluidized bed drier Glatt® model GPCG (Germany). The wet masses were dried for 15 min at 60 °C, and then blended with the lubricants before tabletting.

The influence of the binder and lubricant types and percentages on the granule adherence was studied by a crossed experimental design (Table 2). Process variables were binder and lubricant types whereas mixtures variables were binder and lubricant percentages. Simultaneously, 37 mixtures of the crossed experimental design without lubricant were employed to study the rest of granule properties. The effect of the binder amount was considered as a ratio of the binder mass and the sum of drug, microcrystalline cellulose and Encompress masses, it was defined as *MR*.

Granules properties

The mean granule size was determined by applying a shaking sieve with a set of sieves of the following apertures; 1250, 800, 710, 630, 500, 250 and 125 μm. For the determination of bulk and tap densities, 40 g of the sample was poured in a 100 mL tared graduated cylinder.

Function	Formulation ingredients			Ranges or values (%)	
	Types			Low	High
Binder	PVP	KVA-64	HPMC	3.50	5.00
Lubricant	magnesium stearate	talc	Aerosil	0.50	2.00
Drug	mephenesin			71.43	
Filler	microcrystalline cellulose PH-101			constant	
Filler	Encompress			constant	

Table 1. Tablet composition, types and percentage ranges of the binder and the lubricant for the crossed experimental design.

Sample	Binder (%)	Lubricant (%)	Binder type	Lubricant type	Sample	Binder (%)	Lubricant (%)	Binder type	Lubricant type
1	5.00	0.50	PVP	talc	20	4.25	1.25	KVA64	Aerosil
2	4.25	1.25	HPMC	Mg stear.	21	4.25	1.25	KVA64	talc
3	3.50	2.00	HPMC	Mg stear.	22	3.50	2.00	PVP	talc
4	4.25	1.25	KVA64	Mg stear.	23	4.25	1.25	HPMC	talc
5	5.00	0.50	PVP	Mg stear.	24	3.50	2.00	PVP	Mg stear.
6	3.50	2.00	KVA64	Mg stear.	25	4.25	1.25	PVP	talc
7	5.00	0.50	KVA64	Aerosil	26	3.50	2.00	PVP	Aerosil
8	4.25	1.25	PVP	Aerosil	27	4.25	1.25	HPMC	Aerosil
9	5.00	0.50	KVA64	talc	28	4.62	0.88	PVP	talc
10	5.00	0.50	HPMC	Aerosil	29	4.62	0.88	KVA64	talc
11	5.00	0.50	KVA64	Mg stear.	30	4.62	0.88	HPMC	talc
12	5.00	0.50	PVP	Aerosil	31	4.62	0.88	PVP	Mg stear.
13	3.50	2.00	HPMC	talc	32	4.62	0.88	KVA64	Mg stear.
14	3.50	2.00	HPMC	Aerosil	33	4.25	1.25	HPMC	Aerosil
15	5.00	0.50	HPMC	Mg stear.	34	5.00	0.50	KVA64	Aerosil
16	3.50	2.00	KVA64	talc	35	5.00	0.50	PVP	Aerosil
17	3.50	2.00	KVA64	Aerosil	36	5.00	0.50	HPMC	Mg stear.
18	5.00	0.50	HPMC	talc	37	3.50	2.00	HPMC	Aerosil
19	4.25	1.25	PVP	Mg stear.					

Table 2. Crossed experimental design for the granulation step. Mg stear: magnesium stearate.

The volume was then read directly from the cylinder and used to calculate the bulk density (Db) according to the mass/volume ratio. For tap density (Dt) the cylinder was tapped 1000 times using a tap density analyzer (Erweka SVM1, Germany). The flow rate was determined according to the fixed-funnel method [25]. The Hausner ratio, indirect measurement of powder and granule flowability, was calculated according to its mathematical definition [26].

The friability of the granules was examined by introducing 20 g of the granules (diameter > 0.25 mm) together with a volume of glass beads (diameter 4mm) similar to the granule volume in a friabilator (Pharma Test, model TTSR–A, Germany) over 5 min at a rotational speed of 20 rpm. Then the glass beads and the granules were taken out from the friabilator and the glass beads were removed by an appropriated sieve. Moisture content of granules was determined using an infrared dryer (Sartorius, Germany). Moisture content of granules was less than 2 %.

The adherence of lubricated granules was determined using the same funnel employed for flow rate determination as the percentage of retained granule mass in the funnel with respect to the initial mass (50 g) after flow.

Preparation of tablets

Tablet manufacturing was performed using a three level factorial design (Table 3) with two factors: the granule scores obtained in the principal component analysis (PCA) of granule properties, and three fixed hardness values: 5.0, 7.0 and 9.0 kgF/Monsanto. Granules were compressed with a single punch tabletting machine (Kilian, model KS, Germany) using concave punch of 12.7 mm in diameter. The mass for each tablet was fitted in 700 mg.

Sample	Granule scores in first principal component	Hardness (KgF/Monsanto)
1	0	9
2	1	5
3	1	7
4	0	7
5	0	5
6	1	9
7	0	7
8	-1	5
9	-1	9
10	0	7
11	0	7
12	0	7
13	-1	7

Table 3. Experimental matrix corresponding to the three level factorial design for compression step.

Tablet properties

The percentages of friability were calculated as the percentage of weight loss of 20 tablets after 100 rotations in a Pharma Test, model TTSR–A (Germany) friabilator. Tablet height was

measured with an Ultra-Micrometer Fowler (USA) sensitive 0-1 inch. The hardness was quantified by using a tablet hardness tester of Monsanto type (Toshiba, India).

The paddle method was used for all the *in vitro* dissolution studies using a PHARMA TEST, model PTW S3C (Germany) dissolutor. The rate of stirring was 75 rpm. The tablets were placed in 900 mL of hydrochloric acid 0.1M, as dissolution medium, for 60 min. Six tablets of each formulation were analyzed. The mean and S.D of the dissolved were calculated. Amounts of the model drug released from tablets were analyzed using a HPLC KNAUER (Germany). All chromatographic runs were performed in a LiChrosorb RP-18 (25 cm x 4.6 mm, 5 µm particle size) column using water and acetonitrile (60/40) as the mobile phase. The parameters employed were: flow rate was 1.0 mL/min, UV detection at 278 nm, column temperature 25 °C, and at injection volume 20 µL.

Statistical analysis

Crossed experimental design for granule adherence, the rest of granule properties and tablets properties were planed and analyzed by Design -Expert Version 6.0.1 (Stat-Ease, Inc., Minneapolis, EUA) software. PCA for granule properties was performed in the SIMCA P version 11.0 (DEMO) software (Umetrics AB, Umeå, Sweden). The linear regression was carried out in Microsoft®Excel 2002.

RESULTS AND DISCUSSION

In the statistical methodology carried out for optimizing tablet manufacturing, the excipients to be used in the tablet formulation, the elaboration method according to drug properties and the facilities available were considered. Subsequently excipients with the same functions and the percentages of critical excipients were combined in a crossed experimental design (Table 2). The purpose of the crossed experimental design in our study case was to determine the influence of excipient type and percentage on the granulation step. The selection of variables and their respective levels for including in this experimental design (first step of the proposed methodology), it is defined considering the previous knowledge about chemical and physical drug properties as well as granulation equipment. Another important aspect to be rigorous in granulation variables and levels definition is the predominant influence of granulation factors on tablet properties [19].

Granule characterization

The effect of considered variables on granule properties is illustrated in Table 4 and the best models for each response variable in Table 4. In preliminary evaluations of mephenesin, model drug, a marked adherence to the metallic surfaces was observed. Then, adherence, an uncommon parameter, was considered as a response variable of the granules. The best model to describe adherence behavior contained only the binder type as significant variable ($p = 0.0048$). The binder that bestows more adherence to the granules was KVA64. PVP and HPMC do not differ in influence on granule adherence. The KVA64 is sometimes used in tablet manufacturing by direct compression. Thus, the adhesive property of KVA64 is greater than PVP and HPMC because it is capable of binding even in dry conditions.

The mean granule size (MGS) depended mainly on the binder type and the influence of the interaction between binder type and binder mass ratio, therefore the contribution of the binder mass ratio differs for different types of binder. The mean granule size increases in proportion with MR using HPMC and KVA64, whereas MGS increases as PVP content decreases. In general granules manufactured with PVP and HPMC had higher values of mean granule sizes than KVA64.

This is observed in specific equations [**1-3**] for each binder:

$MGS = 1158.3 - 10043.6 \cdot MR$ for PVP [**1**]
$MGS = 652.0 + 925.3 \cdot MR$ for HPMC [**2**]
$MGS = 300.6 + 5531 \cdot 1.MR$ for KVA64 [**3**]

Bulk and tap densities also depended principally on the binder type (Table 5). The positive influence on both densities increased in the following order: PVP, KVA64 and HPMC. The bulk density was also affected in a smaller scale by the binder mass ratio however bulk density increased only 0.02 g/cm^3 in the binder mass ratio interval evaluated. Despite the detected statistical influences, bulk and tap densities of all granules are within suitable ranges for both variables [25].

The flow rate was also affected by the binder type (Table 5). The best values of flow rate were observed using HPMC. No significant difference was found between PVP and KVA64, both showed poor flowability (Table 4).

The granule friability was independent of the analyzed factors: the binder type ($p = 0.3624$) and the binder mass ratio ($p= 0.8971$). The val-

Sample	Adherent (%)	Mean granule sizes (µm)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Flow rate (g/cm^2s)	Friability (%)
1	0.0068	516.5	0.44	0.46	5.21	8.21
2	0.0136	699.0	0.51	0.56	17.34	7.76
3	0.0060	770.0	0.50	0.57	18.90	12.32
4	0.0088	556.8	0.46	0.50	0.00	15.14
5	0.0068	662.8	0.41	0.46	0.00	8.67
6	0.0084	489.2	0.45	0.50	0.00	8.96
7	0.0068	716.6	0.51	0.56	0.00	12.17
8	0.0060	741.6	0.44	0.46	0.00	14.83
9	0.0104	600.1	0.46	0.51	0.00	16.70
10	0.0056	687.4	0.48	0.54	16.69	9.25
11	0.0112	610.8	0.49	0.52	11.11	7.59
12	0.0064	611.7	0.45	0.47	0.00	5.44
13	0.0048	699.7	0.48	0.53	17.27	11.82
14	0.0048	709.4	0.46	0.51	0.00	20.77
15	0.0056	666.3	0.50	0.56	16.75	9.36
16	0.0080	489.7	0.43	0.48	0.00	17.62
17	0.0084	514.0	0.46	0.50	0.00	10.69
18	0.0040	660.7	0.48	0.55	17.07	12.08
19	0.0060	710.8	0.41	0.44	0.00	9.78
20	0.0080	646.1	0.48	0.53	7.78	9.99
21	0.0116	533.1	0.42	0.46	0.00	18.70
22	0.0056	791.4	0.41	0.44	0.00	7.47
23	0.0064	769.3	0.46	0.49	16.44	11.74
24	0.0056	699.0	0.42	0.45	0.00	10.11
25	0.0056	689.5	0.45	0.50	10.12	8.54
26	0.0056	859.6	0.41	0.47	0.00	14.73
27	0.0044	656.2	0.50	0.54	17.69	11.81
28	0.0056	649.9	0.42	0.45	0.00	16.53
29	0.0100	448.8	0.44	0.49	0.00	9.69
30	0.0104	702.4	0.49	0.55	14.55	14.29
31	0.0060	677.5	0.43	0.46	0.00	10.03
32	0.0044	610.2	0.40	0.49	4.11	11.18
33	0.0052	677.5	0.53	0.57	17.98	9.21
34	0.0084	466.8	0.46	0.51	0.00	9.53
35	0.0060	705.5	0.43	0.47	0.00	10.07
36	0.0056	772.3	0.50	0.55	18.27	9.64
37	0.0000	551.0	0.48	0.55	7.00	13.00

Table 4. Granule properties belong to crossed and one factor experimental designs. The number of the experiments and excipient proportions is defined in Table 2.

Variable	Best adjusted model	Fisher test for significance of parameters		
		Binder mass ratio (MR)	Binder type (BT)	MR and BT
Mean granule sizes (MGS) (µm)	2 Factor interaction	0.5323	<0.0001	0.0036
Bulk density (BD) (g/cm^3)	Linear	0.0302	<0.0001	-
Tap density (TD) (g/cm^3)	Linear	0.0868	<0.0001	-
Flow rate (FR)	Linear	0.0649	<0.0001	-

Table 5. Best models for granule variables and some statistical parameters. (-): interaction MR and BT not considered in the adjusted model.

ues of granule friability oscillated around 11.5 % for all formulations. In summary, the binder type was the principally parameter for mephenesin granule properties variability. The influence of binder mass ratio, lubricant type, binder and lubricant proportion were not significant.

To reduce the experimental time and cost, during compression and after tablet characterization, a PCA was applied. The multivariate technique is useful to diminish the number of dimensions in big tables [27] like it is generated from a granulation experimental matrix. The tables include the percentage of the considered excipients and all values of granule properties. Wet granulation variables such as operational factors were not considered in this design because dependent variables are more important, such as wet mass density and viscosity, particle size distribution, flowability at the end of the granulation step which can be modulated in specific equipment on pilot or industrial scale. Based on this criterion; the reduction of experimental variables, specifically granulation variables, is possible and as a consequence the total experimental work to develop a new tablet [9].

In addition, the methodology presented does not include any granulation process variables because of the scale-up of granulation processes is a difficult task and the trial and error methods have been suggested [28]. Thus manufacturers can lose time and money determining accurate relationships among granulation process variables and the tablet quality parameters on lab scale. This methodology could be useful for any tablet manufacturing method. In the direct compression method, it is further recommended because the granulation variables do not exist.

Principal component analysis

The practical alternative of this methodology is the PCA to reduce the variable number through the formulation scores in principal components (PC) and to combine them with the hardness employing a three level factorial design. In this work the PCA was used to determine the differences and similarities among granules and the influencing variables.

In order to reduce the associated experimentation with the compression step, some granules generated from the crossed experimental design (Table 4) were previously removed. The criteria taken into consideration for that were high values of adherence and extremely low values of flow rate. Formulations with KVA64 were eliminated due to of the high adherence.

Samples belonging to the crossed experimental design like: 1, 2, 3, 10, 13, 15, 18, 23, 25, 27, 30, 33, 36 and 37 were included in the PCA. The multivariate technique was applied to the data, which contains the granule properties and binder and lubricant percentages. Excipient percentages were taken into consideration despite the lack of influence on granule properties because excipient percentages could affect tablet properties.

One principal component was enough to describe a high percentage (38.45 %) of variability in granule properties and excipient percentages (Fig. 1). In other tablet formulation studies, two or more principal components could be necessary but the experimentation would increase. As it can be seen, sample 1 was isolated from the rest of the samples, because of poor flowability and small mean granule size with respect to other samples considered. Thus, it was removed for subsequent analysis.

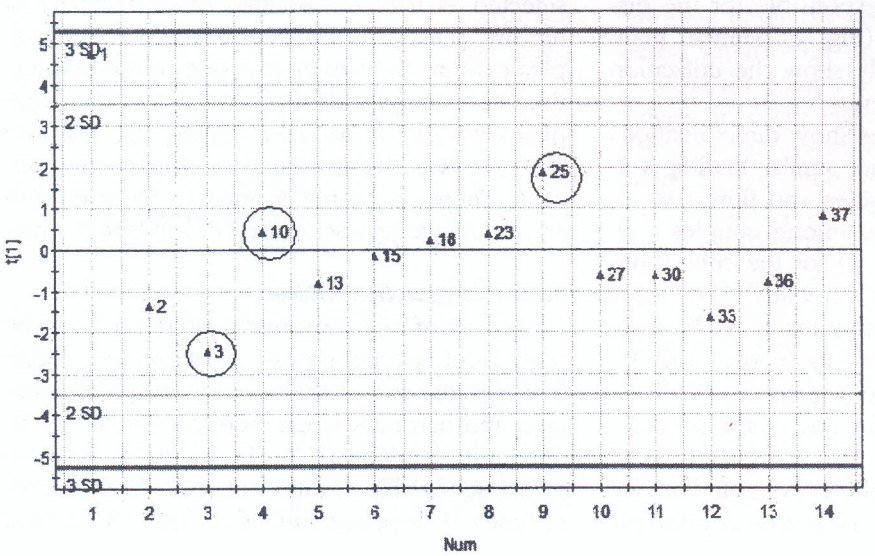

Figure 1. Score plot for PCA applied to granulation step. 3, 10 and 25: selected levels as -1,0 and +1 of the first principal component scores.

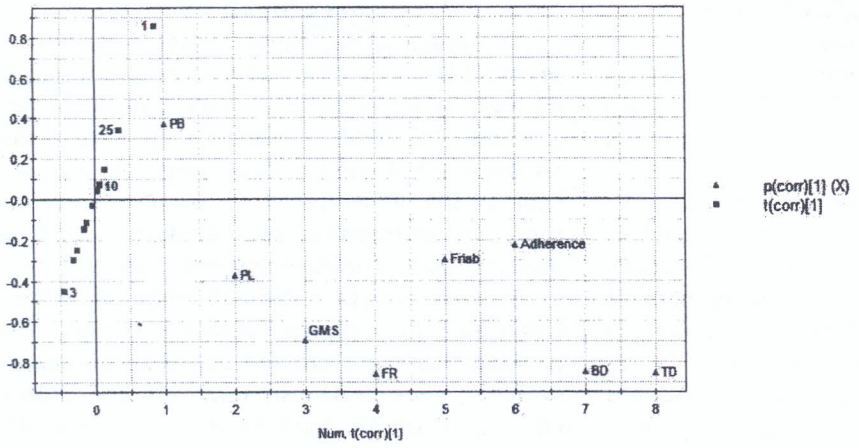

Figure 2. Biplot graph (loading and score) belong to PCA applied to granulation. PB: binder percentage, PL: lubricant percentage, GMS: mean granule size, BD: bulk density, TP: tap density, FR: flow rate, Friab: granule friability.

The reasons to define the similitude or difference among experiments can be found in the biplot graph (loading and score, Fig. 2). This figure allows visualizing with fewer dimensions the data included in Table 4 and Figure 1 facilitating the detection of similarities among granules. The Biplot graphic allowed detecting the variables, which cause the differences among granules.

Samples with positive scores have low flow rates, low granule mean sizes, low bulk and tap density values because loadings of these variables have opposite sign. On the other hand, samples with positive scores have high values of binder percentage because the loading of binder percentage has the same sign as the samples. The granule variables with high loadings are responsible for the variability of data that describe the granules. For instance, adherence and granule friability have almost not significance. Conversely flow rate, bulk and tap densities, granule mean size, lubricant percentages and binder percentages are mainly responsible for the dispersion of granule data (Fig. 2). Hence, main granule variables indirectly show the utilization of different types of binders.

The loading proximities show direct relations among variables. It's mean, similar loading values of bulk and tap densities and flow rate reveal similar Hausner ratios among samples (Fig. 2). All Hauser ratios (Fig. 3) for the considered samples are below the critical value (1.4) which defines granules as cohesive materials [26]. Only the samples 1 and 25 (PVP as binder) and 37, the sample with the lowest percentage of HPMC respectively, differ with the rest of the granules studied (HPMC).

Another advantage of the PCA applied to the granulation step is the use of scores in principal

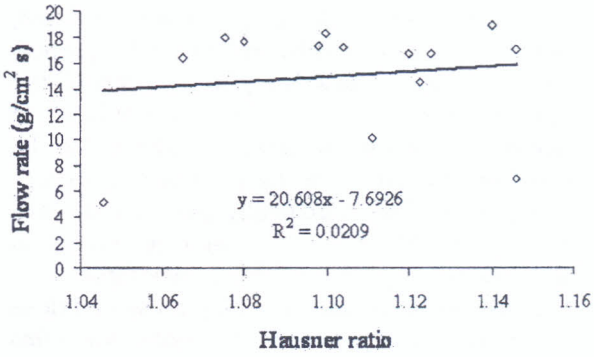

Figure 3. Correlation between flow rate and Hausner ratio for samples considered in PCA.

components as additional variables in the compression step. The granulation scores in an experimental design for the compression step permit studying the tablet manufacturing process as a whole. In parallel, the experimental costs also decrease. The experiments 3, 10 and 25 were selected as levels -1, 0 and +1 respectively of the first principal component score. These samples explore the complete space of the granulation step. Sample 10 was similar to other samples with respect to score values; the selection criterion was the presence of Aerosil as lubricant. Therefore, three lubricants were considered in the compression step experimental plan.

Tablet characterization

Results of tablet properties derived from the three level factorial design are showing in Table 6, where the scores of the first principal component and hardness range were considered as independent variables. The best models for each response variable are illustrated in Table 7. Other types of response surface designs like central

Sample	Friability (%)	Height (mm)	Drug release (%)
1	0.110	5.57	90.39
2	0.006	6.60	93.32
3	0.000	5.68	98.47
4	0.287	5.91	90.9
5	0.413	6.08	94.68
6	0.000	5.58	99.9
7	0.359	5.91	95.8
8	0.287	5.88	88.36
9	0.178	5.63	92.87
10	0.344	5.91	-
11	0.325	5.91	-
12	0.290	5.91	-
13	0.255	5.80	90.25

Table 6. Tablet properties belong to three level factorial design. Only 2 repetitions of the central point for dissolution test were realized.

Properties	Best models in terms of actual factors
Height (mm)	$6.91+0.77 \cdot G-0.15 \cdot H-0.10 \cdot G \cdot H$
Friability (%)	$0.55+0.12 \cdot G-0.04 \cdot H-0.18 \cdot G^2$
Drug release (%)	$93.49+3.37 \cdot G$

Table 7. Best models equations for tablet parameters. H: Hardness (Kgf/monsanto); G: Granule properties (score of the first principal component).

composite and Box-Behnken design could be used for the same purpose. The selection of one type of design depends on experimental costs and modeling accuracy.

For the mephenesin fast release tablet, height, friability and drug release were studied. Other parameters like drug release at different times could be evaluated in extended release tablets. The tablet height was negatively influenced by the granule score on the first principal component, hardness and the interaction between both variables. In other words when HPMC was used as a binder, the tablet height decreases, which is evidence of the better binding capacity of HPMC compared to PVP. Similar and expected behavior was observed when the hardness increased. The tablet friability depends on the score of granule properties and hardness in mode similar to the tablet height which confirms the higher binding capacity of HPMC compared to PVP.

The last analyzed tablet property, drug release, only depends on the scores of granules but the relationship is contrary to tablet height and friability. The PVP allowed better drug release because the binding capacity was lower

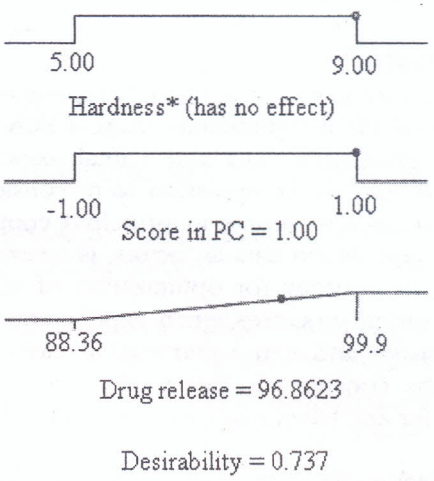

Figure 4. Ramp function graph for mephenesin tablet optimization.

than HPMC. In addition the HPMC could delay the drug release because HPMC is a hydrophilic polymer which has been used in controlled release solid systems [29].

Tablet optimization

When principal components were defined, the scores turn into factors together with the hardness range of the last experimental design to study the compression step. Finally the best parameter values for tablet manufacturing are achieved using the desirability function, a numeric method for multiple optimizations [30]. This method takes into consideration some criteria for different variables in only one mathematical equation. The relative importance among the interest variables is defined employing an importance scale.

Despite the significant statistical influences of the scores in first principal component and hardness range on tablet properties, the only selected variable for optimizing was drug release because the height and friability are in suitable ranges. In other tablet formulation different response variables and criteria (maximum, minimum, target value, etc.) could be included in the desirability function. The solution of desirability function was the highest value of the first principal score for granule properties and any value of hardness range. However it is recommended to use high hardness values to guarantee low values of tablet friability (Fig. 4).

The optimum formulation, achieved using the desirability function, was the formulation with PVP K 90 as binder (4.25 %) and talc as lubricant (1.25 %).

CONCLUSION

The combination of a crossed experimental design to study the granulation step, a PCA applied to granulation data and a final response surface design for compression step, considering hardness and scores in principal components of granulation data as factors, is a suitable multivariate strategy for optimization of tablet manufacturing processes when experimentation is expensive and many granulation variables should be considered. This method could be applied for any tablet manufacturing method.

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