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Graphical Abstract

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ABSTRACT

The SeDeM diagram expert system has been used to study excipients, Captopril and designed formulations for their galenic characterization and to ascertain the critical points of the formula affecting product quality to obtain suitable formulations of Captopril direct compression SR matrix tablets.

The application of the SeDeM diagram expert system enables selecting excipients with in order to optimize the formula in the preformulation and formulation studies.

The methodology is based on the implementation of ICH Q8, establishing the design space of the formula with the use of experiment design, using the parameters of the SeDeM diagram expert system as system responses.

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1. Introduction

The SeDeM Method (Suñé-Negre et al., 2005) is a new galenic method for application in tablet-preformulation and formulation studies. It provides information about the suitability of active ingredients and excipients in powder for direct compression. This information indicates the degree to which the substances can be successfully compressed by means of direct-compression technology. The SeDeM method makes it possible to detect the powder properties that need to be adjusted to facilitate the formulation of the end product for direct compression. The SeDeM method is therefore also a useful tool for studying the reproducibility of the process used to prepare a powder substance and, consequently, for its validation (Pérez-Lozano et al., 2006).

Furthermore, it has been shown to be a suitable tool for preformulation and formulation by characterizing the galenic properties

of excipients in order to define their suitability for direct compression (Aguilar et al., 2009; Suñé-Negre et al., 2008)

The SeDeM diagram expert system is based on the concept of quality by design described in ICH Q8 (EMA, 2004) since it evaluates critical quality attributes that have an impact on the quality of the final product. The SeDeM diagram expert system provides the profile of excipients and active product ingredients (API) in powder form with respect to their suitability for direct compression. This profile indicates whether a powder can successfully be compressed by direct compression technology or whether it needs to be adjusted with appropriate additional excipients. In addition, this SeDeM diagram expert system could be seen as an innovative quality by design (ICH Q8) tool, since it evaluates factors that are not studied in the traditional drug formulation method and provides information about which properties can be improved. Thus, this tool helps the formulator to design robust processes which can influence the quality of the final product when it is marketed.

Captopril is an angiotensine-converting enzyme inhibitor that has been widely used for the treatment of hypertension and congestive heart failure. Captopril acts orally and the dosage used for the treatment of congestive heart failure ranges from 50 to 150 mg daily. After oral ingestion of a single dose the maximum hemodynamic effect is observed after 45–90 min. The drug is freely water

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Table 1

Parameters and equations used in SeDeM methodology.

Incidence	Parameter	Symbol	Unit	Equation
Dimension	Bulk density	Da	g/ml	$Da = P/V_a$
	Tapped density	Dc	g/ml	$Dc = P/V_c$
Compressibility	Inter-particle porosity	Ie	–	$Ie = Dc - Da/Dc \times Da$
	Carr index	IC	%	$IC = (Dc - Da/Dc) \times 100$
Flowability/powder flow	Cohesion index ^a	Icd	N	Experimental
	Hausner ratio	IH	–	$IH = Dc/Da$
	Angle of repose	(α)	°	$Tg\alpha = h/r$
	Powder flow	t''	s	Experimental
Lubricity/stability	Loss on drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/dosage	Particles < 50 μ m	% PF	%	Experimental
	Homogeneity index ^b	(I θ)	–	Eq. (1)

^a Hardness (N) of the tablets obtained with the product in question, alone or blended with lubricants if highly abrasive.^b Determines particle size. In accordance with the percentages of the different particle-size fractions by applying Eq. (1).

soluble and has elimination half-life after an oral dose of 1.7 h. It is stable at pH 1.2, and as the pH increases, the drug becomes unstable and undergoes a degradation reaction. Captopril has been the drug of choice in hypertension management. However, after a single oral dosage of the drug, the antihypertensive action is only effective for 6–8 h. Development of a controlled delivery system for Captopril

• Homogeneity index (I θ)

These parameters are determined by means of the new SeDeM diagram method, based on known equations (Pérez-Lozano et al., 2006; Suñé-Negre et al., 2005, 2011a, 2011b) and duly validated and reproducible experimental tests, as shown in Table 1.

Eq. (1) named in Table 1 is

$$I\theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \dots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}} \quad (1)$$

where

I θ : Relative homogeneity index. Particle-size homogeneity in the range of the fractions under study.

F_m : Percentage of particles in the majority range.

F_{m-1} : Percentage of particles in the range immediately below the majority range; F_{m+1} : Percentage of particles in the range immediately above the majority range.

n : Order number of the fraction under study, within a series, with respect to the majority fraction.

d_m : Mean diameter of the particles in the majority fraction.

d_{m-1} : Mean diameter of the particles in the fraction of the range immediately below the majority range.

d_{m+1} : Mean diameter of the particles in the fraction of the range immediately above the majority range.

Once the values have been obtained following the specific methods, certain limits are set based on the study of the chosen parameters and the values described in the handbook of pharmaceutical excipients (Rowe et al., 2009) (see Table 2). The next step is to convert the numeric limits for each SeDeM Diagram parameter to radius values r , in accordance with Table 2 (Aguilar et al., 2009, 2012; Pérez-Lozano et al., 2006; Suñé-Negre et al., 2005, 2008, 2011a,b).

When all radius values are 10, the SeDeM Diagram takes the form of a circumscribed regular polygon, drawn by connecting the radius values with linear segments. The results obtained from the earlier parameter calculations and conversions are represented by the radius. The figure formed indicates the characteristics of the product and of each of the parameters that determine whether or not the product is suitable for direct compression. In this case, the SeDeM Diagram is made up of 12 parameters, which would form an irregular 12-sided polygon.

To determine whether or not the product is acceptable for direct compression in numerical form, the following indexes are calculated based on the SeDeM Diagram as:

$$\text{Parameter index (IP)} = \frac{\text{No. } p \geq 5}{\text{No. Pt}} \quad (2)$$

is difficult because of in vivo and in vitro instability. The drug also undergoes dose dumping and burst phenomenon (being freely water soluble) when formulated as a controlled or sustained release formulation (Jiménez-Martínez et al., 2008).

The concept of the ICH Q8 guideline is based on defining a design space. The aim of this paper is to establish a design space that enables knowing the system using the SeDeM diagram expert system as a critical attribute of product quality.

In another article it will explain the design of experiments with the aim of establishing the design space in the dissolution test as the product's most important critical attribute. In this paper we use the same variables but taking as answers the variables of the SeDeM diagram expert system, with the final goal of understanding the behavior of the system from a pharmacotechnical viewpoint.

2. Product characterization using the SeDeM method

As established in earlier studies (Pérez-Lozano et al., 2006; Suñé-Negre et al., 2005) the SeDeM Method is based on the experimental study and quantitative determination of the characterization parameters of powdered substances that provide the necessary information about a substance's appropriateness for obtaining tablets using direct-compression technology.

The parameters considered are the following:

- Bulk density (Da)
- Tapped density (Dc)
- Inter-particle porosity (Ie)
- Carr index (IC)
- Cohesion index (Icd)
- Hausner ratio (IH)
- Angle of repose (α)
- Powder flow (t'')
- Loss on drying (% HR)
- Hygroscopicity (%H)
- Particle size (%Pf)

Table 2Conversion of limits for each parameter into radius values (r).

INCIDENCE	Parameter	Limit value	Radius (r)	Factor applied to v
Dimension	Bulk density	0–1 g/ml	0–10	10 v
	Tapped density	0–1 g/ml	0–10	10 v
Compressibility	Inter-particle porosity	0–1.2	0–10	10 v /1.2
	Carr index	0–50 (%)	0–10	v /5
	Cohesion index	0–200 (N)	0–10	v /20
Flow ability/powder flow	Hausner ratio	1–3	10–0	5(3– v) ^a
	Angle of repose	50–0 (°)	0–10	10–(v /5)
	Powder flow	20–0 (s)	0–10	10–(v /2)
Lubricity/stability	Loss on drying	0–10 (%)	10–0	10– v
	Hygroscopicity	20–0 (%)	0–10	10–(v /2)
Lubricity/dosage	Particles <50 μ m	50–0 (%)	0–10	10–(v /5)
	Homogeneity index	0–2 $\times$ 10 ^{–2}	0–10	500 v

^a Same equation than (30–10 v)/2, but simplified.

No. $p \geq 5$: Indicates the number of parameters whose value is equal to or higher than 5. No. Pt: Indicates the total number of parameters studied.

The acceptability limit would correspond to: $IP \geq 5$

Parameter profile index (IPP) $IPP = \text{mean } r \geq 5$ of all parameters

Mean $r = \text{mean}$ value of the parameters calculated.

The acceptability limit would correspond to:

$IPP = \text{mean } r \geq 5$

Good compression index (IGC) is calculated as follows:

$$\text{Good compression index (IGC)} \quad IGC = IPP \times f \quad (3)$$

where f is the reliability factor and is calculated as follows:

$$f = \frac{\text{Polygon area}}{\text{Circle area}} \quad (4)$$

Circle area

The acceptability limit will be calculated by:

$$IGC = IPP \times f > 5. \quad (5)$$

3. Materials and methods

3.1. Materials

The active substance under study is Captopril (Farmahispania, Spain).

The excipients that have been used for the study SeDeM were microcrystalline cellulose (Avicel® PH101, FMC Biopolymer (Norway)), barium sulfate (Panreac, Spain), ascorbic acid (Fagron, Spain), ethylcellulose (Ethylcellulose N100®, Aqualon, (USA)), and hydroxypropylmethylcellulose (HPMC K15 M Premium®, Colorcon, Inc. (USA)).

Other ingredients used were talc (Fagron, Spain), magnesium stearate (Fagron, Spain), and colloidal silicon dioxide (Aerosil®, Fagron, (Spain)).

3.2. Methods

3.2.1. Preparation of the different formulations

A formulation is presented for obtaining sustained release matrix tablets which can be obtained by direct compression. Given the characteristics of Captopril, it is decided to opt for a tablet consisting of ascorbic acid as the antioxidant which produces an acid pH in the gastrointestinal system to minimize the oxidation of Captopril, barium sulfate to give density to the tablet (Clarke et al., 1995) so that it is retained in the stomach, a combination of HPMC K15M Premium® and Ethylcellulose N100® to modulate the release of Captopril (Chattaraj and Das, 1996; Hjartstam and

Hjertberg, 1998; Ju et al., 2006; Katikaneni et al., 1995; Lin and Lin, 1995, 1996; Siepmann and Peppas, 2001; Upadrashta et al., 1993), Avicel® PH101 to obtain a good cohesion, and magnesium stearate, talc and Aerosil® to enhance the lubricity and flow properties of the formulation.

The manufacturing process of the formulations is as follows: the raw materials are weighed individually into polyethylene bags. Then the following raw materials are mixed in a polythene bag: Captopril, ascorbic acid, talc, ethylcellulose N100®, HPMC K15M Premium®, barium sulfate and 70% of the Avicel® PH101. Subsequently the product is mixed manually for 2 min, it is sieved in a 0.8 mm sieve, it is transferred to a suitable container, and mixed for 8 min at 20 rpm in the Glatt biconical mixer. This intermediate product is called mixture A.

In a plastic bag, 30% of the Avicel® PH101, Aerosil® and the magnesium stearate are mixed by hand for 2 min. The product is sieved in a 0.6 mm sieve and is incorporated to mixture A. Finally the product is mixed at 20 rpm for 3 min in the biconical Glatt drum. The different formulations are shown in Table 3.

The experimental design used is the design of mixtures (Refs. 1 to 7), wherein the variables are the concentration of Ethylcellulose N100® and of HPMC K15M Premium®, setting the other components of the formula at 70% (w/w), with 30% (w/w) being the maximum concentration for each of the variables.

3.2.2. Tablets preparation

The blends were compressed in a Bonals® (Cornellà de LL, Spain) continuous eccentric press, provided with 19 mm $\times$ 10 mm punches.

3.2.3. Tablets characterization

In the characterization of the tablets the methods applied were resistance to crushing of tablets and Friability.

4. Results and discussions

4.1. SeDeM diagram results for the API and excipients

Fig. 1 shows the SeDeM diagram expert system of Captopril and different excipients in the formula, and Table 4 shows the radius obtained for each of the parameters studied.

Captopril has bulk and tapped density values that enable direct compression technology as it represents 10% (w/w) in the formula: however, it presents poor flow and compressibility values, and so the use of excipients presenting a good compressibility, such as Avicel® PH101, Ethylcellulose N100® and HPMC K15M Premium®, is critical. Avicel® PH101 is the excipient of the formula that has the best compressibility due to its plastic behavior and its ability

Table 3

Composition of the different formulations (Refs. 1–7).

Raw materials	Percentage (%)						
	Ref. 1	Ref. 2	Ref. 3	Ref. 4	Ref. 5	Ref. 6	Ref. 7
Ethylcellulose N100®	30	25	20	15	10	5	0
HPMC K15 M Premium®	0	5	10	15	20	25	30
Captopril	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4
Aerosil®	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Avicel® PH101	25	25	25	25	25	25	25
Ascorbic acid	20	20	20	20	20	20	20
Barium sulfate	10	10	10	10	10	10	10
Total	100	100	100	100	100	100	100

Fig. 1. SeDeM diagram for the raw materials.**Table 4**

Individual radius parameters, mean incidence values and parametric index for excipients and captopril.

Parameter/Incidence	HPMC K15 M Premium®	Ethylcellulose N100®	Captopril	Barium sulfate	Ascorbic acid	Avicel® PH101
Bulk density	3.24	3.32	4.30	9.95	5.75	3.12
Tapped density	4.59	3.76	6.04	10.00	6.65	4.16
Dimension	3.92	3.54	5.17	9.98	6.20	3.64
Inter-particle Porosity	7.57	2.93	5.58	1.92	1.96	6.68
Carr index	5.88	2.34	5.76	4.59	2.71	5.00
Cohesion index	7.05	9.11	0.00	0.41	0.00	10.00
Compressibility	6.83	4.79	3.78	2.30	1.56	7.23
Hausner Ratio	7.92	9.34	7.98	8.52	9.22	8.34
Angle of repose	3.23	3.78	2.96	3.91	3.09	3.62
Powder flow	0.00	7.00	0.00	8.25	0.00	0.00
Flowability/powder flow	3.71	6.71	3.65	6.89	4.10	3.98
Loss on drying	5.45	8.62	9.56	9.96	10.00	4.81
Hygroscopicity	7.24	9.63	9.85	9.94	9.92	9.42
Lubricity/Stability	6.35	9.12	9.70	9.95	9.96	7.12
Particles <50 µm	0.00	9.18	0.00	7.59	5.63	0.00
Homogeneity index	4.85	1.15	7.05	6.20	6.35	8.65
Lubricity/dosage	2.43	5.17	3.53	6.89	5.99	4.33
Good compression index	4.52	5.57	4.69	6.44	4.86	5.06

to generate hydrogen bridge bonds. Ethylcellulose N100[®] is more compressible than HPMC K15M[®] as it has a higher capacity of plastic deformation, although chemically it is less susceptible to make hydrogen bridge bonds and, by having a larger particle size, it presents less cohesive Van der Waals forces.

The SeDeM diagram expert system predicts the galenic behavior of the formulations from the characteristics of the excipients. In this case, the radius values of the fine particles and flow of Avicel[®] PH101, HPMC K15M Premium[®] and Captopril exhibit very poor values, and so it was decided to incorporate 0.5% (w/w) of Aerosil in the formulations to optimize the flow of the fine particles. During compression of Captopril and ascorbic acid, adhesion on punches is observed, and thus a need was seen to incorporate an antiadherent in the formula such as talc at a concentration of 4% (w/w) and 0.5% (w/w) of magnesium stearate as a lubricant.

4.2. SeDeM diagram results for the formulations

Fig. 2 shows the SeDeM diagram expert system of the different formulations, and in Table 5 the radius for each of the parameters under study.

Table 6 shows the results of friability and resistance of crushing of the tablets of each reference. The values of both the friability as the resistance of crushing are similar in all formulations, indicating that there are no differences between the tablets in relation to these pharmacotechnical parameters when variation exists in the proportion of Ethylcellulose N100[®] with HPMC K15M[®].

4.2.1. Dimension

There are no differences in the apparent and tapped density between the different formulations (Table 5). The radius of the dimension parameter of HPMC K15M[®] is 3.92 while that of the Ethylcellulose N100[®] is 3.54, so it is logical that as the percentage of HPMC K15M[®] in the formula increases, no differences between the apparent and tapped density are observed.

4.2.2. Compressibility

When the percentage of HPMC K15M[®] in the formula increases, the compressibility parameter and the radius values of the carr index, also increase. The cohesion index radii remain constant from formula 2–7 with values of 10. The cohesion index is higher as the percentage of HPMC K15M[®] increases. That is because the HPMC K15M[®] has a particle size of <50 microns greater than the Ethylcellulose N100[®]. By decreasing particle size, the cohesive forces of the formula are higher due to the increase in Van der Waals forces and the increased contact surface area between the particles. Furthermore, the HPMC K15M[®] has a higher percentage of water thereby increasing the capillary forces between the particles. The HPMC K15M[®] is more polar than the Ethylcellulose N100[®], and so more hydrogen bridge bonds will be established with the other components of the formula, since being mainly polar components there will be more interaction between them.

However, ethylcellulose N100[®] when compressed alone has better compressibility compared with HPMC K15M[®]. This means that the physicochemical properties of the HPMC K15M[®] are more conducive to the compressibility of the formula by providing moisture that favors capillary forces between the particles and particle size, by increasing the contact surfaces and, consequently, the particle bonds giving rise to tablets with greater hardness.

4.2.3. Flowability/powder flow

By increasing the percentage of HPMC K15M[®], the flowability/powder flow parameter decreases, obtaining a radius value of 6.96 for formulation 1 and a radius value of 3.90 for formulation 7. This is because the HPMC K15M[®] has a 51% of fine particles <50 μm

compared to 4% of the Ethylcellulose N100[®], and so when increasing HPMC K15M[®] there are more Van der Waals interparticle forces associated with particles of less than 50 μm , resulting in a greater cohesion of the product thus decreasing the radius values of the Hausner ratio parameters, angle of repose, and powder flow. The flow behavior of formulation 1 is mass flow, while when increasing the percentage of HPMC K15M[®], the flow behavior changes to core flow.

Whereas all excipients have poor radius values in the flow parameter except ethylcellulose N100[®] and barium sulfate as shown in Table 4, the incorporation of 0.5% Aerosil[®] was considered of great importance in the preformulation stage to achieve correct powder flow for the manufacture of direct compression tablets, as shown in Table 5 in the radius values ≥ 5 obtained in the Flowability/powder flow parameter in formulations 1–4.

4.2.4. Lubricity/stability

The HPMC K15M[®] has a higher percentage of humidity than the ethylcellulose N100[®], besides being more hygroscopic, and hence increasing the percentage of HPMC K15M[®] also increases the percentage of humidity and hygroscopicity of the formula. All formulations present radius values of ≥ 5 in the lubricity/stability parameter. However, when the percentage of HPMC K15M[®] increases it is more likely that Captopril will oxidize resulting in degradation products, because the formulation is more hygroscopic and contains more moisture (Table 5).

4.2.5. Lubricity/dosage

When the percentage of HPMC K15M[®] is increased, the percentage of particles <50 μm increases, obtaining radius values of 0 in formulations 6 and 7, and of 2.15 in formulation 1. The radius values in the dosage/lubricity parameter vary between 1 and 2 (Table 5).

Formulation 7 is the one that has a more narrow distribution of particle size, and is therefore the formulation that has a higher radius value in the homogeneity index parameter.

The high percentage of fine particles is the major cause of the poor flow of formulations 4, 5, 6 and 7 (Table 5).

4.2.6. Good compression index

The IGC values obtained for each formulation designed (Ref. 1 to Ref. 7) were processed statistically using Statgraphics Centurion XVI software. The results have been adjusted to a simple linear regression model considering the good compression index as dependent variable and the formulations as independent variable resulting in an $r^2 = 0.9532$, the results of which are shown in Table 7.

Since the p -value in the ANOVA table is less than 0.05, there is a statistically significant relationship between good compression index and Formulations with a confidence level of 95.0%. The R -squared statistic indicates that the adjusted model explains 95.3232% of the variability in good compression index. The correlation coefficient is equal to -0.976336 , indicating a relatively strong relationship between variables. Standard error of the estimate indicates that the standard deviation of residuals is 0.077127. The mean absolute error (MAE) of 0.0591837 is the average value of the residual. The Durbin-Watson (DW) statistic examines the residuals to determine if there is any significant correlation. Since the p -value is greater than 0.05, there is no indication of serial autocorrelation in the residuals with a confidence level of 95.0%.

Fig. 3 shows the values of the good compression index, adjusting to a linear equation to describe the relationship between the good compression index and formulations.

In order to find the linear regression that best adjusts to the results obtained, we have considered a total of 27 models, and the one that best adjusts is the squared Y square root X model, giving

Fig. 2. SeDeM diagram for the different formulations.

Table 5

Radius parameters, mean incidence values and parametric index for the different formulations.

Parameter/Incidence	Formulations						
	1	2	3	4	5	6	7
Bulk density	4.48	4.42	4.64	4.42	4.28	4.15	4.32
Tapped density	6.15	5.59	5.85	5.87	5.93	5.83	5.96
Dimension	5.32	5.01	5.25	5.15	5.11	4.99	5.14
Inter-particle Porosity	5.05	3.95	3.72	4.66	5.42	5.78	5.31
Carr index	5.43	4.19	4.14	4.94	5.57	5.76	5.50
Cohesion index	9.03	10.00	10.00	10.00	10.00	10.00	10.00
Compressibility	6.50	6.05	5.95	6.53	6.99	7.18	6.94
Hausner ratio	8.14	8.68	8.70	8.36	8.07	7.98	8.10
Angle of repose	4.24	3.88	3.34	3.89	3.71	3.53	3.59
Powder flow	8.50	7.67	6.50	4.67	0.00	0.00	0.00
Flowability/powder flow	6.96	6.74	6.18	5.64	3.93	3.83	3.90
Loss on drying	9.00	8.69	8.48	8.09	7.61	7.70	7.51
Hygroscopicity	9.69	9.75	9.72	9.67	9.64	9.45	8.57
Lubricity/stability	9.34	9.22	9.10	8.88	8.62	8.58	8.04
Particles <50 µm	2.15	1.82	1.59	1.34	0.92	0.00	0.00
Homogeneity index	1.20	1.40	1.45	1.50	2.45	2.50	3.45
Lubricity/dosage	1.67	1.61	1.52	1.42	1.68	1.25	1.73
Good compression index	5.80	5.56	5.40	5.35	5.04	4.97	4.94

Table 6

Friability and rupture strength values obtained in the different formulations.

	Formulations						
	1	2	3	4	5	6	7
Friability (%)	0.39	0.39	0.32	0.24	0.32	0.33	0.35
Rupture strength (Newtons)	172 ± 16	169 ± 20	174 ± 25	169 ± 62	161 ± 58	1774 ± 30	195 ± 25

Table 7

Results of adjusted to simple linear regression model of the IGC.

Coefficients					
	Least squares	Standard	t-Statistic		
Parameter	Estimates	Error		p-Value	
Intercept	5.88286	0.0651842	90.2497	0.0000	
Slope	−0.147143	0.0145756	−10.0951	0.0002	
Analysis of variance					
Source	Sum of squares	Df	Mean square	F-statistic	p-Value
Model	0.606229	1	0.606229	101.91	0.0002
Residual	0.0297429	5	0.00594857		
Total (corr.)	0.635971	6			

Correlation coefficient = −0.976336.

R-squared = 95.3232%.

R-squared (adjusted for d.f.) = 94.3879%.

Standard error of EST. = 0.077127.

Mean absolute error = 0.0591837.

Durbin–Watson statistic = 2.16591 (p = 0.3682).

Lag 1 residual autocorrelation = −0.280088.

The equation of the adjusted model is as follows:

Good compression index = 5.88286 − 0.147143 × Formulations.

Fig. 3. Good compression index (simple linear model).

a correlation coefficient of 0.9852 and an $r^2 = 0.9707$ the results of which are shown in Table 8.

Since the p -value in the ANOVA table is less than 0.05, there is a statistically significant relationship between good compression index and formulations with a confidence level of 95.0%. The R -squared statistic indicates that the adjusted model explains 97.0704% of the variability in good compression index after being transformed to a logarithmic scale to linearize the model. The correlation coefficient is equal to −0.985243, indicating a relatively strong relationship between variables. Standard error of the estimate indicates that the standard deviation of residuals is 0.651761. The mean absolute error (MAE) of 0.440439 is the average value of the residual. The Durbin–Watson (DW) statistic examines the

residuals to determine if there is any significant correlation. Since the p -value is greater than 0.05, there is no indication of serial autocorrelation in the residuals with a confidence level of 95.0%.

Fig. 4 shows the values of the good compression index adjusting the equation with the squared Y square root X model to describe the relationship between the good compression index and formulations.

The squared Y square root X model is the one which gives the highest value of R -Square at 97.0704%, that is 1.7471% higher than the linear model.

Formulation 1 is the one with the best good compression index with a radius value of 5.80, while formula 7 has a radius value of 4.94.

There is an almost linear relationship between the different formulations in the good compression index parameter. Increasing the percentage of HPMC K15M[®] causes an increase in the percentage

Table 8Results of adjusted to squared Y square root X regression model of the IGC.

Coefficients					
	Least squares	Standard	t-Statistic		
Parameter	Estimates	Error			p-Value
Intercept	39.3994	0.91026	43.2837		0.0000
Slope	−5.85815	0.45513	−12.8714		0.0001
Analysis of variance					
Source	Sum of squares	Df	Mean square	F-statistic	p-Value
Model	70.3763	1	70.3763	165.67	0.0001
Residual	2.12396	5	0.424793		
Total (corr.)	72.5003	6			

Correlation coefficient = −0.985243.

R-squared = 97.0704%.

R-squared (adjusted for d.f.) = 96.4845%.

Standard error of EST. = 0.651761.

Mean absolute error = 0.440439.

Durbin–Watson statistic = 2.62428 (p = 0.6542).

Lag 1 residual autocorrelation = −0.374093.

The equation of the adjusted model is as follows:

Good compression index = $\sqrt{39.3994 - 5.85815 \times \sqrt{\text{Formulations}}}$.

Fig. 4. Good compression index (Y-square-X square root model).

of fine particles which hinders the flow of the powder, in addition to increasing the humidity and the hygroscopicity of the formula, thereby increasing the percentage of HPMC K15M[®] in the formula, the radius value of the good compression index decreases linearly as shown in Figs. 3 and 4.

Accordingly, the greater the percentage of ethylcellulose N100[®] there is in the formulation and the lower that of HPMC K15M[®], the powder mixture will have better characteristics for direct compression.

5. Conclusions

1. The SeDeM Diagram is a useful tool for the galenic characterization of excipients and drugs with respect to their suitability for direct compression.
2. The SeDeM Diagram is a useful tool for the design of experiments, using the values of the radius of the formulations in the Good compression index parameter as the critical quality attribute for the study of the system.
3. Formulation 1 is the best formulation for direct compression of Captopril, with a radius value of 5.80 in the good compression index parameter.
4. There is an almost linear relationship in the radii of good compression index according to the percentage of ethylcellulose N100[®] and HPMC K15M[®] among the 7 formulations in the linear model and in the Y-square X-square root model.
5. The SeDeM Diagram is a useful tool to observe the behavior of the system, if it is linear, or if there are any interactions between the factors.

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