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*Full Length Research Paper*

# Optimization of a novel tablets formulation using D-optimal mixture design

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**This study involved the obtaining of a new tablet formulation of *Tamarindus indica* L., using a D-optimal mixture design. Tablets were obtained by wet granulation. Compressibility, angle of repose, flowability, particle size and humidity were the responses for the granules evaluation, while hardness, disintegration time and friability were responses for the tablets. The desirability function was applied for tablets optimization. All responses were adjusted to statistical models. Polyvinylpyrrolidone is the excipient that more affects all responses. The D-optimal design allowed selecting the optimal proportions of the excipients: lactose monohydrate 36.54%, microcrystalline cellulose 30.00% and polyvinylpyrrolidone 6.93%.**

**Key words:** Mixture design, tablets, tamarind, soft extract, desirability.

## INTRODUCTION

*Tamarindus indica* L. or tamarind, as commonly known, is a medium-sized tree, which belongs to the Caesalpinaceae family. The leaves composition of this plant include proteins, fatty acids, carbohydrates, tannins, flavonoids, essential oils, volatile compounds and some micro elements like calcium, magnesium, iron, phosphor, copper, sulphur, sodium and potassium. Tamarind leaves are rich in flavonoids as orientine, isoorientine, vitexine, and isovitexine. Polyphenols like apigenine, ferulic acid and cafeic, luteoline, rutine and vicenine are present too (Dehesa et al., 2006). Vitamin A and C are also present (El-Siddig et al., 2006). Tamarind is a medicinal plant that has been used for centuries in Cuba. It is the most useful plant for liver disorders treatment. Their leaves have hepatoprotective activity, associated with the presence of polihydroxylated compounds; with majority being polyphenols and flavonoids (Jouyex et al., 1995).

The extracts of the leaves of this plant have protective activity against the arteriosclerosis induced by a hypercholesterolemic diet. A clinical study, suggests that the extracts of tamarind leaves improves levels of total cholesterol and reduces the diastolic pressure (Martinelo et al., 2006; Iftekhar et al., 2006). The leaves of this plant has a broad spectrum of antimicrobial activity, because of they are potential source of new classes of antibiotics that could be useful for infectious diseases (Dougary,

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2006; Escalona et al., 2010a). The aqueous extract of tamarind leaves has hepatoprotective activity against acute intoxication induced by acetaminophen, showing a liver regenerative effect (Pimple et al., 2007; Mahesh et al., 2010; Meher and Das, 2013). The tamarind soft extract is a brownish viscose syrup, with natural odor of fresh fruit. This one contains not less than 63 and not more than 67% of total solids. Soft extract contain 6.75% of polyphenols expressed as tannic acid. Tablets are the most manufactured pharmaceutical form around the world and probable the most investigated ones.

However, the development of a new formulation of tablets is a very complex work that depends on both formulation factors and manufacturing process. The complete knowledge of the factors affecting the development process of pharmaceutical tablets is very important for the development of a new formulation. Once these factors are identified, they could be mathematically modelled and allowed to predict the behaviour of most important properties of the product.

The development of any pharmaceutical form necessitate the complete study of different levels of excipients used in various formulations, in order to identify the exact proportion of what maximizes quality and stability of the final product.

The aim of this work was to obtain a new tablet formulation, starting from the soft extract of the leaves of *T. indica* L, by using a D-optimal mixture design.

## MATERIALS AND METHODS

### Soft extract

Firstly, fluid extract was prepared by percolation (Escalona et al., 2010). Posteriorly soft extract is obtained by concentration in a vacuum evaporation system (KIKA WERKE GMBH & Co. Germany) at 42±2°C, until reduce the volume from 4 to 1 ml.

### Excipients

The microcrystalline cellulose (Microcell MC-101, Blanver, Brazil), and lactose monohydrate (Contero Excipient, New Zealand) are the most used excipients in the formulation of tablets and capsules (Kashif et al., 2014, Rani and Begum, 2014). The poly-vinylpyrrolidone (Kolidón 25, Basf, Germany) is a binder used for formulating tablets because, binder contributes to a better tablet disintegration (Lachman et al., 1981; Dineshmohan et al., 2014). The colloidal silicon dioxide (Aerosil® V-200, Degusa, Belgium) was selected because it provides good flowability to powders and granules, and for providing protection against excess humidity (Lachman et al., 1981; Gibson, 2006). The croscarmellose sodium (AcDiSol, Blanver, Brazil) is very useful as tablet disintegrant, and the magnesium stearate (Derive SA, Germany) is one of the most lubricants used in the manufacture of tablets (Lachman et al., 1981).

### Experimental design

The excipients proportion restrictions used for tablets formulation are listed in Table 1. The mixtures of active ingredient and excipient were made according to the 14-run D-optimal mixture design. This kind of design is particularly useful in a restricted region because of maximization of the volume of each ingredient in a k-dimensional space. In this way, you can use only the interest excipients, keeping constant the quantities of the rest of the formulation ingredients (Gabrielson et al., 2002). The total amount of the mixture was held constant. The relative amounts of the different excipient varied according to the mixture design (Table 2).

### Granules and tablets preparation

Wet granulation method, using absolute alcohol as solvent was used to prepare granules and tablets. The mixture of excipients was made, in each case, in the proportions described in Table 2. Drying was done in an oven Nova Ethics (Brazil), at 42°C for 1 h. The granules were mixed with the rest of the excipients using a turbula mixer. Tablets of 600 mg with the equivalent to 20% of soft extract, as total solids were prepared. The compression was made in an eccentric tablet machine (Manesty, UK), using flat-faced bevelled punches, 12.7mm on diameter, at a compression force of 80 MPa.

### Physicomechanical properties of the granules

#### *Compressibility index*

For bulk ($D_b$) and tapped ($D_t$) densitiesevaluation, an appropriate amount of granules were placed in a 100 ml graduated cylinder. The volume reading directly from the cylinder was used to calculate the bulk density according to the mass/volume ratio. For tapped density, the cylinder was tapped 1000 times using a tap density analyser (Erweka SVM1, Germany). Compressibility index (CI) was calculated using the following expression:

$$CI = ((D_t - D_b)/D_t))*100$$

#### *Flow rate*

Flow ability is the capability of a mass powder or granules to flow through a hopper. Granules flow rate was measured by pouring a mass (m) of granules through a glass funnel (wall of 45°) having a round orifice of 8.0 mm (d). The funnel's outlet was separated 100 mm respect to a horizontal surface. Flow rate was calculated using the equation:

$$Fr = m/0.785.d^2.t$$

Where *m* is the granules mass expressed in grams, *t* is the time that mass of granules takes to flow through the funnel in seconds; *d* is the diameter of the orifice of funnel in cm (Iraizoz et al., 1992).

#### *Angle of repose*

Angle of repose was evaluated by discharging a mass of granules through a glass funnel of internal diameter 8 mm that is hold at constant distance from the horizontal surface. The height (h) of the heap formed and the radius (r) of the cone base were measured (USP, 2012).The angle of repose ($A_r$) was calculated using the following equation:

$$A_r = \tan^{-1}(h/r)$$

#### *Particle size characterization*

In all cases, the particle size was performed by applying a shaking siever with a set of sieves; 800, 630, 450, 250, 125 µm apertures.

**Table 1.** Excipients proportion restrictions.

| Excipients | Levels | |
|---|---|---|
| | Low (%) | High (%) |
| Lactose monohydrate | 31.50 | 40.00 |
| Microcrystalline cellulose | 30.00 | 35.00 |
| Polyvinylpyrrolidone | 3.50 | 7.00 |

**Table 2.** D-optimal mixture design for evaluating granules and tablet formulations.

| Run | LM (%) | MCC (%) | PVP (%) | Partial (%) LM +MCC+PVP | CSD (%) | CCNa (%) | MS (%) | TSE (%) | Total (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 34.50 | 33.75 | 5.25 | 73.50 | 20.00 | 1.50 | 3.5 | 1.50 | 100.00 |
| 2 | 35.75 | 32.50 | 5.25 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 3 | 36.50 | 30.00 | 7.00 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 4 | 40.00 | 30.00 | 3.50 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 5 | 31.50 | 35.00 | 7.00 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 6 | 35.00 | 35.00 | 3.50 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 7 | 31.50 | 35.00 | 7.00 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 8 | 37.50 | 32.50 | 3.50 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 9 | 34.00 | 32.50 | 7.00 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 10 | 35.00 | 35.00 | 3.50 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 11 | 36.50 | 30.00 | 7.00 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 12 | 37.88 | 31.25 | 4.38 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 13 | 33.25 | 35.00 | 5.25 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |
| 14 | 40.00 | 30.00 | 3.50 | 73.50 | 1.50 | 3.50 | 1.50 | 20.00 | 100.00 |

MCC, microcrystalline cellulose; LM, lactose monohydrate; PVP, polyvinylpyrrolidone; CSD, colloidal silicon dioxide; CCNa, sodium croscarmellose; MS, magnesium stearate; TSE, tamarind soft extract.

Particle size distribution was verified.

***Residual humidity***

The residual humidity was performed by the gravimetric method, using a gravimetric balance (Sartorius, SA 325. Germany) (USP, 2012). Measures were made intriplicate.

**Technological properties of tablets**

***Hardness***

Tablets hardness was evaluated using a Erwekastrength tester (Offenbach, Germany). The mean value of 10 determinations was reported (USP, 2012).

***Disintegration time***

Disintegration time was measured according to the British Pharmacopoeia (BP, 2010) in a disintegration tester (PTZ1; Pharmatest GmbH, Hinesburg, Germany). Deionised water at 37±2°C was used as immersion medium. For each formulation, six randomly selected tablets were tested. All measurements were made in triplicate.

***Friability***

Tablets friability was measured as the percentage of weight loss of 20 tablets tumbled in a friabilator (Pharma Test, model TTSR-A (Germany). After 4 min of rotation at 25 rpm, the dust of tablets was removed, and the percentage of weight loss was calculated (Gibson, 2006; USP, 2012).

**Data analysis**

All responses for granules and tablets characterization were treated using Design Expert software (Version 6.0.1, Stat-Ease, Inc. Minneapolis, USA). The best-fitted mathematical models for each response were selected. To select the model that best describes the variability of response depending on the factors used (quantities of excipients), the following criteria were taken into account; the highest adjusted R-squared value ($R^2$) and the predicted R-squared ($Q^2$). For the selection of the model was also considered the different minor between $R^2$ and $Q^2$, the minor value of the sum of squares of the predicted error (PRESS) and the test of lack of fit without statistical significance ($p > 0.05$). The number of experimental points (14) was enough to adjust the response until special cubic model (Gabrielson et al., 2002).

## RESULTS AND DISCUSSION

### Characterization of granules

A D-optimal mixture design was carried out to evaluate the granules behaviour as a function of selected excipient proportion. Table 3 shows the results of the experiments

**Table 3.** Physicomechanical properties of the granules. The shown data represent triplicates ± SD.

| Run | Compressibility index (%) | Angle of repose (º) | Flow rate (g/cm².s) | Residual humidity (%) | Particle size(µm) |
|---|---|---|---|---|---|
| 1 | 23.22±1.28 | 29.90±1.69 | 11.90±0.82 | 2.20±0.12 | 216.33±7.22 |
| 2 | 21.12±1.33 | 28.89±0.32 | 12.20±1.14 | 1.99±0.14 | 210.3±16.34 |
| 3 | 15.34±1.02 | 24.65±0.96 | 13.02±0.25 | 2.70±0.21 | 212.32±19.14 |
| 4 | 19.01±1.55 | 30.90±0.79 | 9.20±1.20 | 2.00±0.20 | 215.14±19.87 |
| 5 | 16.26±0.94 | 27.36±1.68 | 12.21±0.61 | 2.80±0.33 | 199.23±15.14 |
| 6 | 21.98±0.74 | 32.13±0.87 | 7.36±0.96 | 1.85±0.16 | 200.12±13.25 |
| 7 | 17.25±0.85 | 27.12±0.97 | 12.68±0.35 | 2.64±0.47 | 209.67±21.10 |
| 8 | 23.05±2.29 | 31.21±0.98 | 8.25±0.17 | 2.10±0.27 | 209.45±22.32 |
| 9 | 18.23±0.96 | 25.52±2.36 | 12.73±0.55 | 2.50±0.29 | 222.23±13.45 |
| 10 | 19.12±1.48 | 31.58±2.29 | 7.90±0.88 | 2.10±0.25 | 232.17±19.63 |
| 11 | 14.55±0.84 | 24.65±2.08 | 13.03±0.99 | 2.35±0.31 | 218.92±13.43 |
| 12 | 22.25±1.49 | 30.26±1.56 | 10.54±1.33 | 2.37±0.12 | 245.22±12.47 |
| 13 | 23.65±2.36 | 30.25±1.88 | 10.65±0.47 | 1.80±0.08 | 227.43±19.96 |
| 14 | 23.50±3.24 | 30.33±1.24 | 9.60±0.47 | 2.40±0.33 | 231.36±23.12 |

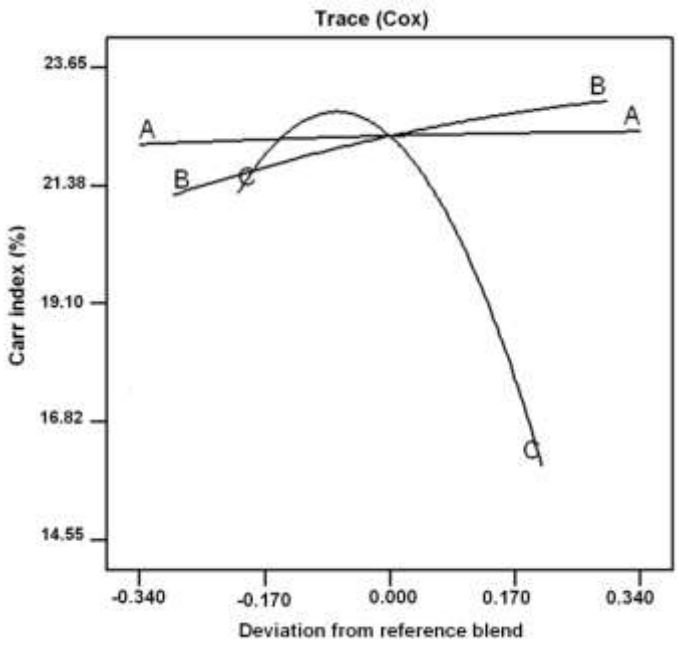


**Figure 1.** Trace **(**Cox) graph for Compressibility index. A: Lactose monohydrate. B: Microcrystalline cellulose C: Polyvinylpyrrolidone. Reference blend: A:38.25%; B: 30.50%; C: 5.75%

according to D-optimal mixture design for granules characterization. The compressibility index has been proposed as an indirect measure of bulk density, particle size and shape, surface area, moisture content, and cohesiveness of materials because all of these properties can influence on it (USP, 2012). Values ranged of 14.55 to 23.65% were obtained. These values show acceptable good flow properties according to literature (USP, 2012).

The particle size obtaining in all run are showed in Table 3. Particle size distributions in all cases were normal (Data not reported). Normality in particle size distribution of powders and granules, generally allows them to flow and compress well. In all cases, granules humidity was minor than 3%, value reported as good according to the study of Lachman (1981). No relationship of these responses (particle size and humidity) with the excipients proportion variability was observed. Polyvinylpyrrolidone (PVP) was the excipient that makes the greatest variability in the formulation compressibility index (Figure 1). High amounts of this excipientin formulations, improve the compressibility of the granules. Lactose monohydrate and microcrystalline cellulose showed little influence on this property. Compressibility was good when the amount of PVP in the formulation was around 7.0% and microcrystalline cellulose was around 30.00% (Runs 3 and 11). The normal distribution of particle size and appropriate residual moisture in powders and granules improve the compressibility and fluidity of these powders (Rahmanzadeh et al., 2014). Table 4 presents the models adjusted for each response and the statistics considered as selection criteria. The variability of the compressibility index data was adjusted to a quadratic model (Table 5). This model showed the highest values of $R^2$ and $Q^2$. The lack of fit test was not significant ($p > 0.05$) and had the lowest value of predicted residual sum of squares of errors (PRESS).

The ability to flow by the granules using the angle of repose and the flow rate (Figure 2A and 2B, respectively) were evaluated. The best flow ability takes place when the amount of PVP in the formulations was high. Lactose monohydrate had no significant effect on the variability of the flow properties. The lower angle of repose and the higher flow rate occurs when the amount of microcrystalline cellulose in the formulation is low (30.00%). For the angle of repose and the flow rate, the data were fitted to quadratic models (Table 4). In both cases, high values of $R^2$ and $Q^2$ and a minimum difference between them were observed. PRESS value in each case was low among the possible models obtained.

**Table 4**. Statistics for fitted mathematical models obtained to each response on the granules formulations.

| Response | $R^2$ | $Q^2$ | PRESS | $P_{(Anova)}$ | $p_{(Lack\ of\ fit)}$ |
|---|---|---|---|---|---|
| **Compressibility index** | | | | | |
| Linear | 0.4624 | 0.2515 | 99.68 | 0.0131 | 0.0095 |
| Quadratic | 0.7200 | 0.5023 | 66.29 | 0.0429 | 0.7067 |
| Special cubic | 0.7000 | 0.3408 | 87.80 | 0.5160 | 0.0332 |
| **Angle of repose** | | | | | |
| Linear | 0.9597 | 0.9451 | 4.76 | 0.0001 | 0.0466 |
| Quadratic | 0.9883 | 0.9800 | 1.73 | 0.0041 | 0.5827 |
| Special cubic | 0.9872 | 0.8964 | 8.99 | 0.2953 | 0.0468 |
| **Flow rate** | | | | | |
| Linear | 0.8757 | 0.8489 | 8.03 | 0.0001 | 0.1257 |
| Quadratic | 0.9706 | 0.9511 | 3.22 | 0.0028 | 0.2419 |
| Special cubic | 0.9794 | N/A | N/A | 0.7891 | 0.0738 |

$R^2$, determination coefficient; $p_{Lack\ of\ fit}$; p-value of Lack of fit test; $p_{(Anova)}$, p value of Anovatest; $Q^2$, Goodness of prediction; PRESS, Predicted Residual Sum of Squares of errors.

**Table 5**. Mathematical model selected for each response of granules formulation, expressed as real components, with the coefficients statistical probability (α=0.05).

| Factor | Compressibility index | | Angle of repose | | Flow rate | |
|---|---|---|---|---|---|---|
| | Coefficient | p-value | Coefficient | p-value | Coefficient | p-value |
| LM | 0.222 | <0.0001 | 0.435 | <0.0001 | 0.185 | < 0.0001 |
| MCC | -0.339 | <0.0001 | 0.405 | <0.0001 | -0.408 | < 0.0001 |
| PVP | -78.267 | <0.0001 | -18.197 | <0.0001 | -26.042 | < 0.0001 |
| LM*PVP | 1.151 | 0.0101 | 0.231 | 0.0034 | 0.402 | 0.0018 |
| MCC*PVP | 1.292 | 0.0075 | 0.309 | 0.0010 | 0.468 | 0.0004 |

LM, Lactose monohydrate;MCC, Microcrystalline cellulose;PVP, Polyvinylpyrrolidone

In both cases, lack of fittest was not significant (p-value>0.05). Table 4 shows the values of the coefficients of each of the factors and the observed interactions between these factors, for both properties. PVP interacts with lactose monohydrate and microcrystalline cellulose. Both interactions improve the fluidity of the granules. The lower angle of repose and the higher flow rate were observed in runs 3 and 11. These runs had the same composition, lactosemonohydrate (36.50%); micro-crystalline cellulose (30.00%) and 7.00% of PVP.

## Characterization of the tablets

Table 6 shows the results for D-optimalmixture design for tablets preparation. The models adjusted for each response for tablets are shown in Table 7. In the same way, Table 8 shows the selected fitted model for each property with the corresponding statistic. The hardness showed a linear behavior related to the excipients proportions (p< 0.05). The test of lack of fit was not significant. There was not found any statistical significance for all other considered model (Table 7). The adjusted model showed excellent values of $R^2$ and $Q^2$. This model was selected because, in spite of that, the $R^2$ and $Q^2$ are lower than the other models; the difference between them was minimal (0.0253). This fact implies that the fraction of variability explained for linear model is very close to the fraction that can be predicted by itself. The last is expressed as a minor PRESS value of this model . Experimental runs 3 and 11 showed higher hardness (Table 6). PVP showed greater influence on the tablet hardness, than the rest of the excipients (Figure 3A; Table 8). With increasing the content of PVP in the formulation, the tablet hardness increase. The highest hardness was found in the formulation containing greater amount of PVP, the lowest percentage of microcrystalline cellulose and around the average of the addition of lactose

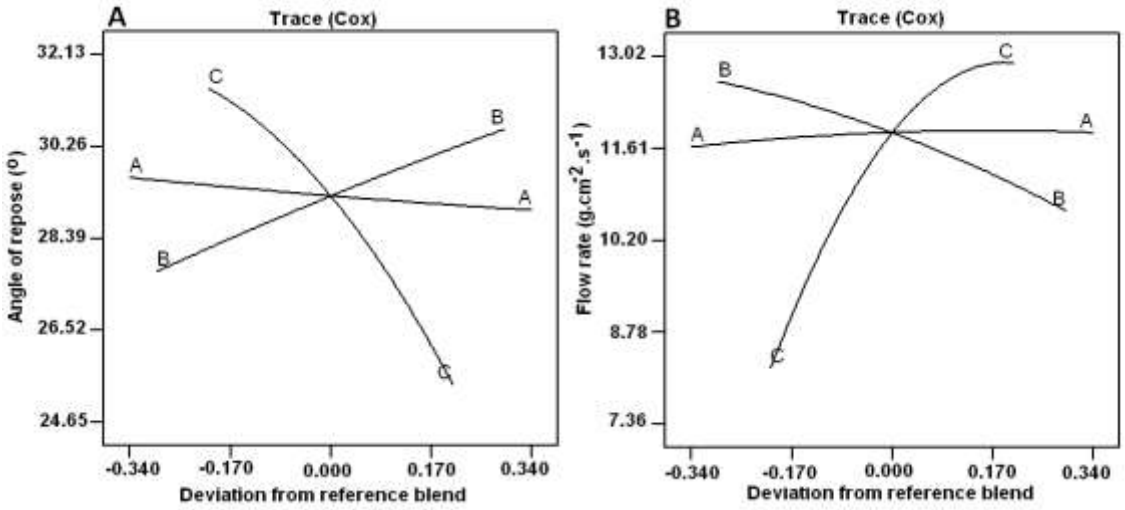


**Figure 2.** Trace **(**Cox) graph for angle of repose (A) and flow rate (B). A: Latose monohydrate. B: Microcrystalline cellulose C: Polyvinylpyrrolidone. Reference blend: A:38.25%; B: 30.50%; C: 5.75%.

**Table 6.** Experimental matrix obtained in the D-optimal mixture design for tablet formulation with the standard deviation (n=3).

| Run | Hardness(kg/f) | Disintegration time (min) | Friability(%) |
|---|---|---|---|
| 1 | 5.76±0.26 | 13.50±1.14 | 1.30±0.04 |
| 2 | 5.76±0.35 | 12.50±1.10 | 1.29±0.07 |
| 3 | 5.96±0.28 | 12.00±0.51 | 0.62±0.10 |
| 4 | 5.56±0.05 | 15.00±0.26 | 1.37±0.08 |
| 5 | 5.81±0.12 | 12.50±1.3 | 0.90±0.08 |
| 6 | 5.18±0.14 | 19.00±2.28 | 1.40±0.20 |
| 7 | 5.81±0.21 | 12.50±0.37 | 0.84±0.11 |
| 8 | 5.45±0.27 | 16.00±1.39 | 1.39±0.23 |
| 9 | 5.86±0.04 | 12.00±0.56 | 0.67±0.14 |
| 10 | 5.25±0.33 | 19.00±3.26 | 1.39±0.08 |
| 11 | 6.07±0.13 | 10.00±0.55 | 0.64±0.10 |
| 12 | 5.56±0.11 | 14.00±0.27 | 1.33±0.07 |
| 13 | 5.61±0.17 | 14.00±0.29 | 1.32±0.00 |
| 14 | 5.56±0.31 | 15.00±0.41 | 1.35±0.09 |

monohydrate (Figure 3B).

Disintegration time is a measure of how well the tablets are broken up when they are in contact with the body fluids. For uncoated tablets a time not more than 15 min is recommended (USP, 2012). As is shown in Table 7, the best-adjusted model for this property was quadratic. The statistical significance of the Anova test ($p<0.05$), the higher values of $R^2$ and $Q^2$, and the lower PRESS compared with the other considered models, demonstrated that the quadratic model is the better predictor of the disintegration time variability. As the quantity of PVP augment on formulation, a lower disintegration time was reached (Figure 4A). Lactose monohydrate showed a similar behavior (Figure 4A). As literature report, lactose monohydrate produces soft tablets that disintegrate very well (Lieberman et al., 1981). It was observed that there was a statistical significance for interactions between lactose monohydrate-PVP and microcrystalline cellulose-PVP ($p<0.05$).

Both interactions tend to reduce the disintegration time. The lowest disintegration time was reached with the proportions lactose monohydrate 36.50%, microcrystalline cellulose 30.00% and PVP 7% (Figure 4B). Figure 5A presents a trace graph showing the influence of the excipients on the friability of the tablets. Lactose monohydrate showed little influence on this property. When the percentage of microcrystalline

**Table 7.** Statistics for all possible model obtained to each response on tablets formulation.

| Property | Adj-$R^2$ | $Q^2$ | PRESS | P (Anova) | P (Lack of fit) |
|---|---|---|---|---|---|
| **Hardness** | | | | | |
| Linear | 0.9090 | 0.8837 | 0.09 | 0.0001 | 0.0919 |
| Quadratic | 0.9367 | 0.8959 | 0.10 | 0.1242 | 0.1890 |
| Special cubic | 0.9280 | 0.5754 | 0.36 | 0.8725 | 0.0970 |
| **Disintegration time** | | | | | |
| Linear | 0.8330 | 0.7643 | 20.49 | 0.0001 | 0.1572 |
| Quadratic | 0.9441 | 0.8792 | 10.50 | 0.0077 | 0.7437 |
| Special cubic | 0.9398 | 0.8362 | 14.24 | 0.5318 | 0.6778 |
| **Friability** | | | | | |
| Linear | 0.8330 | 0.7643 | 0.20 | 0.0001 | 0.0020 |
| Quadratic | 0.9441 | 0.8792 | 0.03 | 0.0001 | 0.1918 |
| Special cubic | 0.9398 | 0.8362 | 0.05 | 0.0882 | 0.3013 |

Adj-$R^2$, adjusted R-squared; $Q^2$predicted R-squared;PRESS, Predicted Residual Sum of Squares. (α= 0.05).

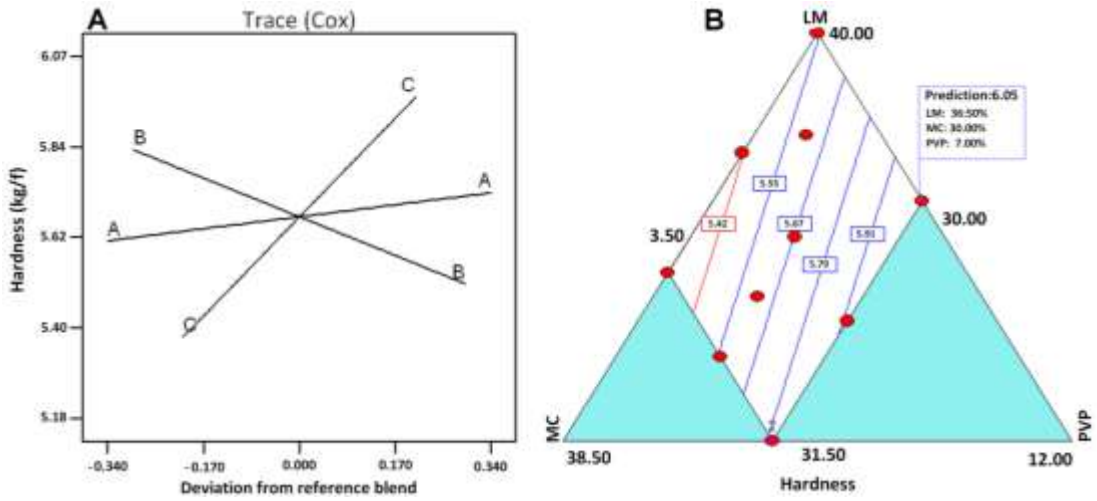


**Figure 3.** Trace **(**Cox) graph (A) and contour (B) for tablet hardness. A, latose monohydrate; B, microcrystalline cellulose; C, polyvinylpyrrolidone. Reference blend: A:38.25%; B: 30.50%; C: 5.75%.

cellulose increased in the formulation, tablet friability was increased accordingly, this probably was due to a decrease in tablet hardness. Conversely, when the percentage of PVP was increased, the hardness increased and lower friability values were observed (Figure 5A and 5B).

To describe the behavior of tablets, friability a quadratic model was selected (Table 7). This model showed the highest values of $R^2$ and $Q^2$ and the lowest value of PRESS. On the other hand, Anova test were significant ($p < 0.05$) and the lack of fittest was not significant ($p > 0.05$). Table 8 shows the positive influence of PVP and microcrystalline cellulose for tables' friability (negative).

## Tablets optimization

For the optimization of this oral dosage form, a numerical method based on desirability function was used. This method takes into account various criteria for different response in only one mathematical equation. The relative important of the response are expressed as a scale from 1 to 5, with 5 being the most important. The conditions to optimize the tamarind tablet formulation were; minimized is integration time (importance of 5); maximize hardness (importance of 4) and minimize tablets friability (importance of 4). The higher importance of disintegration time is obvious.

Figure 6 shows the ramp graph of the optimized tablets

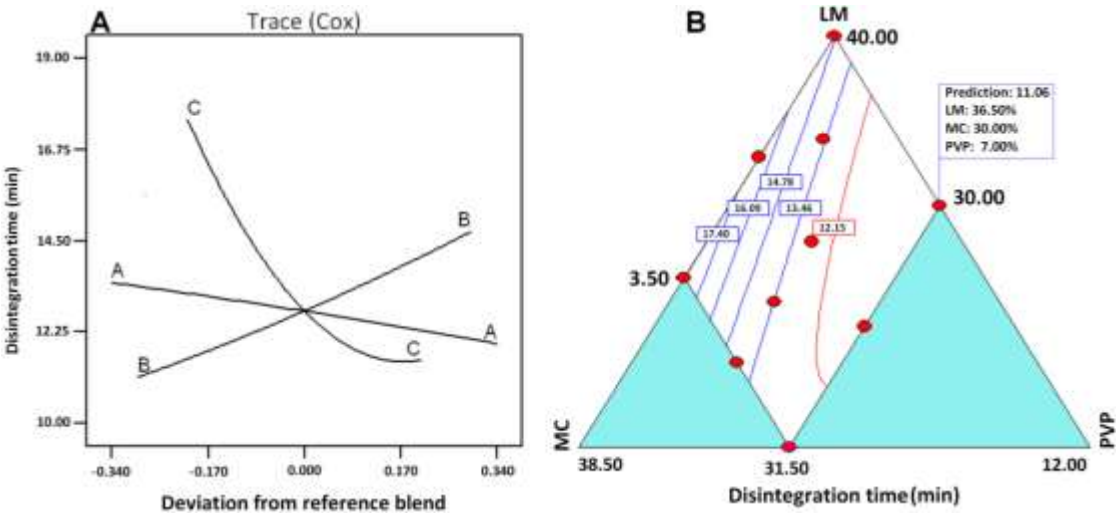


**Figure 4.**Trace **(**Cox) graph (A) and contour (B) for disintegration time. **A,** latose monohydrate; B, microcrystalline cellulose; C, polyvinylpyrrolidone. Reference blend: A:38.25%; B: 30.50%; C: 5.75%.

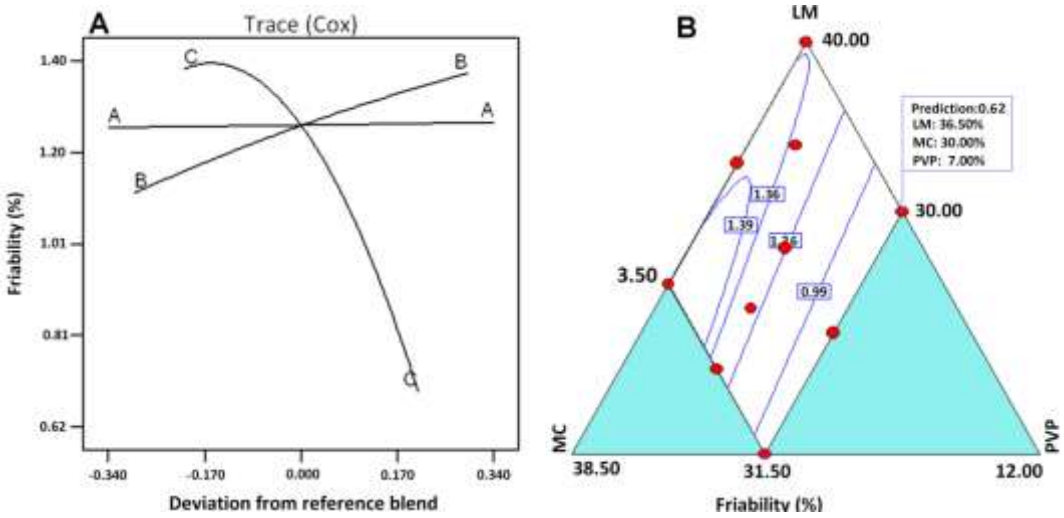


**Figure 5.** Trace (Cox) graphs (A) and of contour (B) for tablet friability. A, latose monohydrate; B, microcrystalline cellulose; C, polyvinylpyrrolidone. Reference blend: A:38.25%; B: 30.50%; C: 5.75%.

**Table 8.** Adjusted mathematical model selected for each response on tablets formulation, expressed as real components, with the coefficients statistical probability.

| Factor | Hardness | | Disintegration time | | Friability | |
|---|---|---|---|---|---|---|
| | Coefficient | p-value | Coefficient | p-value | Coefficient | p-value |
| LM | 0.088 | <0.0001 | -0.096 | <0.0001 | 0.020 | < 0.0001 |
| MCC | 0.041 | <0.0001 | 1.174 | <0.0001 | -0.014 | < 0.0001 |
| PVP | 0.233 | <0.0001 | 34.779 | <0.0001 | -4.803 | < 0.0001 |
| LM*PVP | - | - | -0.504 | 0.0026 | 0.068 | < 0.0001 |
| MCC*PVP | - | - | -0.644 | 0.0008 | 0.079 | < 0.0001 |

LM: Lactose monohydrate, MCC: Microcrystalline cellulose, PVP: polyvinylpyrrolidone. (α=0.05)

formulation. The proportions that guarantees the minimum disintegration time with an adequate hardness

**Table 9.** Observed and predicted properties used for the optimization process (n= 5).

| Properties | Predicted | Observed | t-test | p-value |
|---|---|---|---|---|
| Disintegration time (min) | 11.04 | 9.50±1.00 | -3.8891 | 0.0001 |
| Hardness (kg/F) | 6.04 | 6.15±0.45 | -0.7778 | 0.4376 |
| Friability (%) | 0.63 | 0.67±0.08 | 0.3987 | 0.6905 |

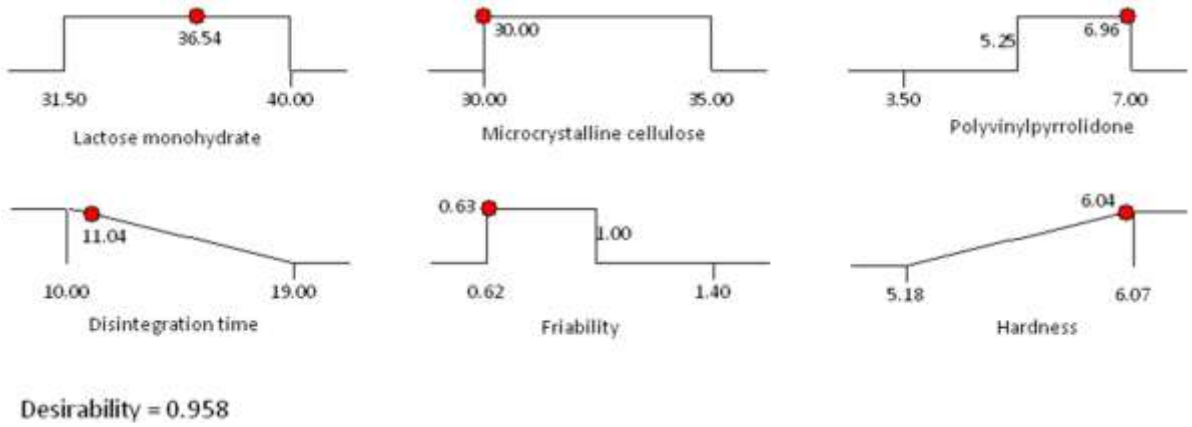


**Figure 6.** Ramp graph for the tablet optimal formulation. Red points indicate the amount of the ingredient optimized by the software. The slope indicates the direction where the response is improved.

and tablets friability was lactose monohydrate 36.54%; microcrystalline cellulose 30.00%, PVP 6.96%. A t-test was made to compare the observed tablets properties with the predicted values for the optimization model. There were no statistical different between observed and predicted values for hardness and friability (p-value>0.05; Table 9). The observed tablet disintegration time was statistically different to the predicted. Nonetheless, the observed disintegration time was less than the predicted for the optimization model. The obtained results demonstrate that the D-optimal mixture design can be properly used for the optimization of the Tamarind extract tablets. The rest of the technological properties for this tablet formulation were satisfactory (USP, 2012).

The D-optimal mixture design allowed the obtaining of optimal proportions of the excipients for the tablets formulation. PVP was the excipient that showed more influence on the tablets properties. The obtained tablets showed good technological properties. The proportions of the optimal mixture; expressed as percentage was lactose monohydrate 36.54%; microcrystalline cellulose 30.00% and PVP 6.96 %.

## Abbreviations

**MCC,** microcrystalline cellulose; **Ar,** angle of repose; **LM,** lactose monohydrate; **Fr,** flow rate; **PVP,** polyvinyl-pyrrolidone; **RH,** residualhumidity; **CSD,** colloidal silicon dioxide; **PS,** particle size; **CCNa,** sodium croscarmellose; **MS,** magnesium stearate; **TSE,** tamarind soft extract; **CI,** compressibility index; **Dt,** tapped density; **Db,** bulk density;

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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