# Cubic Spline and Characterization of Metronidazole to Determine the Changes in the Solid Solution

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*Abstract*— Studies in pharmaceutical systems are used to improve the physicochemical properties of drugs, one of them are solid dispersions requiring a carrier to achieve that purpose. Polyethylene glycol 6000 (PEG6000) is used as a carrier, because it has a high hydrophilicity and is used in the pharmaceutical industry as an excipient and active. In this work the PEG6000 merges with metronidazole for the formation of three solid dispersions, the antiparasitic drug is insoluble in water, creating problems of bioavailability in the body. Solid solutions were prepared with a ratio of 1:0.25, 1:0.50, 1:0.75 metronidazole: PEG6000. The study of bioactivity of the solid solutions was performed by Differential Scanning Calorimetry (DSC) and X-ray diffraction (XRD), showing that part of metronidazole is retained in the volume (structure) of PEG6000 and some joins the surface. The data analyzed were for the absorbance of each sample that were applied a cubic interpolation to determine differences between the dispersions.

*Keywords*— Metronidazole, data matrix, polyethylene glycol, drugs, polymer solid dispersions.

## I. Introduction

Studies in pharmaceutical systems [1] where altering the properties of the drugs when they have problems with solubility, gastric irrigation or even fraction of the dose administered to the patient (bioavailability).

In the most common mentioned are: drug encapsulation, use of porous matrices and the development of solid dispersions [2], where chemical dealing polymeric substances such as cyclodextrins, hydroxymethylcellulose (HPMC) and cellulose derivatives (urea, albumin) and polyethylene glycols (PEGs) in the pharmaceutical industry have many uses [3].

Because of the variation which presents the molecular weight of these polymers are used as excipients, such as low molecular weight PEGs (400-200), used in liquid formulations, eye drops, presentations and fillings parenteral gelatin capsules, as bases in the manufacture of ointments and suppositories or as active ingredients in the manufacture of ophthalmic demulcent. 3350 PEGs are used in laxatives and those with molecular weights greater than 20000 Daltons are used in organ preservation [4].

Metronidazole is an imidazole-derived drug whose therapeutic effect and is effective against trichomonas parasite, but it has a poor water solubility of 1000 mg/100 mL of water [5]. Therefore, in this research are to improve the water solubility and dissolution rate of metronidazole using PEG6000 as a carrier using the technique of solid dispersions by varying the concentration of PEG6000 with respect to metronidazole, getting three solid dispersions: Metronidazole (1)-(0.25) PEG6000 (M-PEG6000:1-0.25), metronidazole (1)-(0.50) PEG6000 (M-PEG6000:1-0.50) and metronidazole (1)-(0.75) PEG6000 (M-PEG6000:1-0.75) which as mentioned are the study samples. Then apply a cubic interpolation to each of the samples only for the absorbance of each of the solid dispersions of metronidazole and obtain values that are not tabulated.

## II. Research Frameworks

There are four tables of data for the absorbance of the solid dispersion of metronidazole whose general form is shown in table I:

Table I. General data table.

| | | | |
|---|---|---|---|
| $X_1$ | $X_2$ | ..... | $X_n$ |
| $Y_1$ | $Y_2$ | ..... | $Y_n$ |

The table above describes a relationship between a magnitude of X and one Y depends on X. Then the problem is to obtain values of Y for X values that not appear on the table. One way to solve the problems to build a function f that passes through

the points (Xi, Yi) with i = 1, 2 ..., n and then align Y for S(x), another words, "interpolate" the data (Xi, Yi), which are obtained using cubic spline according to [6] is the best method of interpolation.

Are the $n+1$ data:

| $x$ | $x_0$ | $x_1$ | $\cdots$ | $x_n$ |
|---|---|---|---|---|
| $y$ | $y_0$ | $y_1$ | $\cdots$ | $y_n$ |

A interpolating cubic spline of these data is a function $s(x)$ defined as follows (1):

$$s(x) = \begin{cases} s_0(x) & si \quad x \in [x_0, x_1] \\ s_1(x) & si \quad x \in [x_1, x_2] \\ \vdots & \\ s_{n-1}(x) & si \quad x \in [x_{n-1}, x_n] \end{cases} \quad (1)$$

Where each $s_i(x)$ is a cubic polynomial; $s_i(x_i) = y_i$, for all $i = 0,1,\ldots,n$ and such that $s(x)$ have first and second continuous derivative $[x_0, x_n]$.

The following explains in detail what a cubic spline is and the concept of interpolation. The phenomena of nature are seen with some regularity and it is a cause of study the way in which they occur, allowing inferences about the behavior of a phenomenon in situations that are not measured directly. In mathematical and experimental models this behavior can be measured with an interpolation and polynomial approach.
The analysis performed by the absorbance data obtained, this will be done by interpolation, which consist to find a figure within a range in which extreme values are known. The general problem of interpolation is when you have a function which is only known by a number of points in the same (Table II) and when you want to find the value of a halfway point of the function, a function whose graph passes through these points is necessary to estimate the desired values. The interpolation used for this work was the cubic spline [6].

Suppose you have n +1 points:

$$P_k(x_k, y_k), where\ y_k = f(x_k), k = 0,1,..,n$$

In which you want to interpolate the function f. It is not necessary that the abscissas are equally spaced, but they are ordered, ie:

$$x_0 < x_1 < x_2 < ... < x_n$$

What matters is to find a cubic polynomials $q_k(x)$ to interpolate the function f in the subinterval

$$[x_k, x_{k+1}],\ k = 0,1,\ldots,n-1$$

The cubic function is called in $[x_0, x_n]$ if there are cubic polynomials such that $q_0(x), q_1(x), \ldots, q_{n-1}(x)$ :

$$s(x) = q_k(x)\ en\ [x_k, x_{k+1}],\ to\ k = 0,1,...,n-1$$

To interpolate s (x) at the points $P_0$, $P_1$, ..., $P_n$, $q_k$ (x) have to check according to (2).

$$\begin{aligned} q_k(x_k) &= y_k \\ q_k(x_{k+1}) &= y_{k+1}, k = 0,1,...n-1 \end{aligned} \quad (2)$$

{

At this point it is supposed 2n conditions. Polynomials qk (x) have the same slope and the same socket on the nodes that join them as shown in (3).

$$\begin{aligned} q'_{k-1}(x_k) &= q'_k(x_k) \\ q''_{k-1}(x_k) &= q''_k(x_k), k = 1,...n-1 \end{aligned} \quad (3)$$

{

The fulfilled conditions are now 2 (n-1). It is necessary to check the conditions (2) and (3) and it ensures that *s (x)* has its first and second continuous derivatives on $[x_0, x_n]$, in this case we say that s (x) is a cubic spline to $P_0$ , $P_1$, ..., $P_n$.
If s (x) is cubic in the $[x_0, x_n]$ interval, its second derivative s"(x) is linear in the same range and interpolates the points ($x_k$, s"($x_k$)) and ($x_{k+1}$, s"($x_{k+1}$)) in $[x_k, x_{k+1}]$. So, $q_k$ (x) is a polynomial of degree one which interpolates at ($x_k$, s"($x_k$)) and ($x_{k+1}$, s"($x_{k+1}$)) [6]:

$$q_k(x) = s''(x_k)\frac{x - x_{k+1}}{x_k - x_{k+1}} + s''(x_{k+1})\frac{x - x_{k+1}}{x_{k+1} - x_k},$$
$$k = 0,1,...,n-1.$$

Denoting $h_k = x_{k+1} - x_k, k = 0,1,...,n-1$
y $\sigma_k = s''(x_k), k = 0,1,...,n$ we have (4):

$$q''_k(x) = \frac{\sigma_k}{h_k}(x_{k+1} - x) + \frac{\sigma_k + 1}{h_k}(x - x_k), \quad (4)$$
$$k = 0,1,...,n-1$$

Integrating to obtain the second derivative (5) is obtained

$$q_0(x) = \frac{\sigma_k}{h_k}\frac{(x_{k+1}-x)^3}{6} + \frac{\sigma_{k+1}}{h_k}\frac{(x-x_k)^3}{6} + C_k + D_{k^x} \quad (5)$$

The linear term is written as

$$C_k + D_k x = A_k(x-x_k) + B_k(x_{k+1}-1)$$

$A_k$ y $B_k$ are arbitrary constants, then we obtain (6):

$$q_k(x) = \frac{\sigma_k}{h_k}\frac{(x_{k+1}-x)^3}{6} + \frac{\sigma_{k+1}}{h_k}\frac{(x-x_k)^3}{6} + A_k(x-x_k) + B_k(x_{k+1}-x) \quad (6)$$

Applying in (6) the conditions of (2) we have (7.8):

$$y_k = \frac{\sigma_k}{h_k}\frac{h_k^3}{6} + \frac{\sigma_{k+1}}{h_k}0 + A_k 0 + B_k h_k = \frac{\sigma_k}{6}h_k^2 + B_k h_k \quad (7)$$

$$y_{k\square 1} = \frac{\sigma_{k\square 1}}{h_k}h_k^3 \square A_k h_k = \frac{\sigma_{k\square 1}}{6}h_k^2 \square A_k h_k \quad (8)$$

Applying the equation Ak and Bk and substituting in (6) we have (9):

$$q_k(x) = \frac{\sigma_k}{6}\left[\frac{(x_{k+1}-x)^3}{h_k} - h_k(x_{k+1}-x)\right] + \frac{\sigma_{k+1}}{6}\left[\frac{(x-x_k)^3}{h_k} - h_k(x-x_k)\right] + y_k\left[\frac{(x_{k+1}-x)^3}{h_k}\right] + y_{k+1}\left[(x_{k+1}-x)\right], k = 0,1,\ldots,n-1 \quad (9)$$

This is the equation of the spline $q_k$ (x).

We need to know the values of $\sigma_1, \sigma_1, \ldots, \sigma_n$, (n +1 unknowns) to which it is used (3); deriving in (9) we have (10,11).

$$q'_k(x) = \frac{\sigma_k}{6}\left[\frac{-3(x_{k+1}-x)^2}{h_k} - h_k\right] + \frac{\sigma_{k+1}}{6}\left[\frac{(x-x_k)}{h_k} - h_k\right] + \frac{y_{k+1}-y_k}{h_k}$$

Therefore,

$$q'_k(x) = \frac{\sigma_k}{6}(-2h_k) + \frac{\sigma_{k+1}}{6}(-h_k) + \frac{y_{k+1}-y_k}{h_k} \quad (10)$$

$$q'_k(x_{k+1}) = \frac{\sigma_k}{6}(h_k) + \frac{\sigma_{k+1}}{6}(2h_k) + \frac{y_{k+1}-y_k}{h_k} \quad (11)$$

Replacing k by k-1 in (11) to obtain $q'_{k-1}$ ($x_k$) and equating to (10) we obtained (12):

$$h_{k-1}\sigma_{k-1} + 2(h_{k-1}+h_k)\sigma_k + h_k\sigma_{k+1} = 6(f[x_k,x_{k+1}] - [x_{k-1},x_k]), \quad where k = 1,2..,n-1 \quad (12)$$

The cubic splines are used to compare the curves obtained for each sample of the absorbance of the solid dispersion of metronidazole, and later to determine differences between them using the area under the curve of each spline and to conclude whether the differences are significant for that experiment [6, 7].

## III. Experiment

Three metronidazole solid dispersions were obtained and PEG6000 varying the concentration of PEG6000 compared to metronidazole in the following way: for each gram of metronidazole was added in a platinum crucible 0.25, 0.50 and 0.75 g of PEG6000 (in different events), the homogeneous solid mixture melts at 85 º C for 5 minutes and then allowed to cool to room temperature. Fluxes are ground in an agate mortar until a fine powder of M-PEG6000 solid dispersions: 1-0.25, M-PEG6000: 1-0.50 and M-PEG6000: 1-0.75, which were derived from data arrays for the numerical analysis including commercial metronidazole ([8], [9], [10]).

The analysis of X-ray diffraction applied to the three solid dispersions: AR metronidazole, metronidazole PEG6000 and commercial are shown in Figure 1. All the diffractograms show a crystallization of monoclinic type with a space group of P21/c, spectroscopic data of a = 16.1178, b = 7.5473, c = 13.4161 Å, V = 1520.3 Å, b = 111.3210 Å and Z = 4, (6), showing bands of intense diffractions at 2θ features 12.5º and 14.1º, for samples of metronidazole (analytical grade) and commercial type, respectively. In the M-PEG6000 solid dispersions :1-0 50 and M-PEG6000 :1-0 75 The bands only for the PEG6000 diffraction at 19.4 ° and 23.1 ° in (2). Which indicates that metronidazole may be occluded in the bulk of PEG6000 and not on the surface of it, because no bands of diffraction characteristics of metronidazole in the solid dispersions are observed. This follows because the homogeneous solid mixtures that melt at 85 ° C, lower than the melting point has metronidazole, so it is still in solid dispersions, as confirmed by DSC studies.

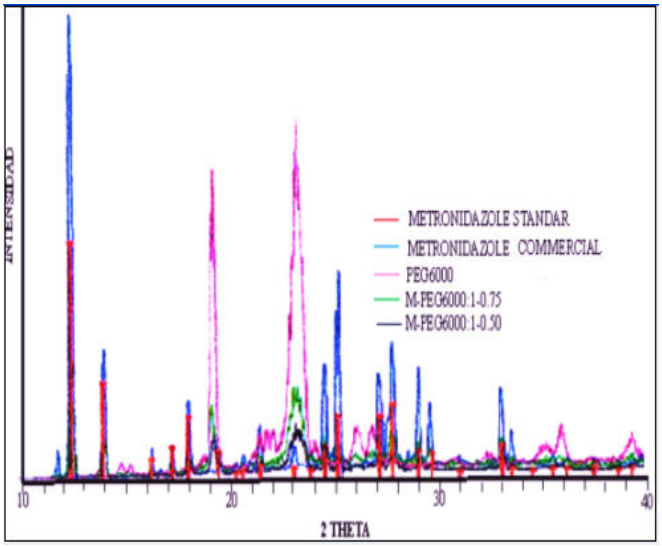



Fig 1. XRD of pure metronidazole, commercial and Solid dispersions M-PEG6000:1-0.50 y M-PEG6000:1-0.75

The thermograms of metronidazole, PEG6000 and solid dispersions are shown in Figure 2. Metronidazole has a single endothermic peak, whose melting point is 96.29 ° C and a melting enthalpy of 38.9 J/g. The PEG6000 shows an endothermic peak at 62,015 ° C, with an enthalpy of fusion of 239.9 J/g. The thermograms of M-PEG6000 solid dispersions:1-0 50 and M-PEG6000 :1-0.75 show endothermic peaks with a melting point of 57.46 °C and 58.64 ° respectively, corresponding to the polymer without registering the thermal effects due to the drug. This is attributed to the liquid state where there is a miscibility between both compounds and has been able to form a eutectic mixture.

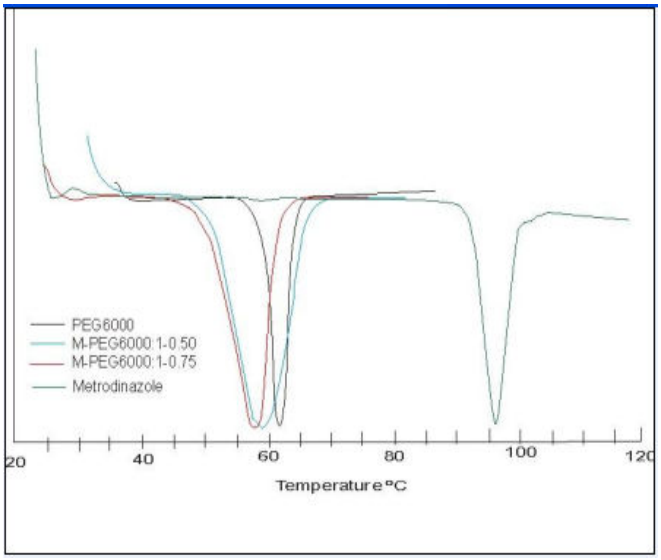



**Figura 2.** DSC thermograms of pure metronidazole, PEG6000 and M-PEG6000 solid dispersions :1-0 50 and M-PEG6000 :1-0 75

## IV. Development

Figure 3 shows the graph of the dissolution profile of metronidazole commercial and solid dispersions. The dissolution profile of solid dispersions compared with commercial tablets and the results were between 48 and 90% drug release over the business from the standpoint of physical chemistry. It should be mentioned that the force of compression used, gives the appropriate hardness to ensure dissolution of the drug. The results of Figure 3, indicate that the solid dispersion dissolution rate was better was the M-PEG6000:1-0.50 followed by M-PEG6000 dispersions: 1-0.25, M-PEG6000:1-0.75 and much more the commercial tablets of metronidazole.

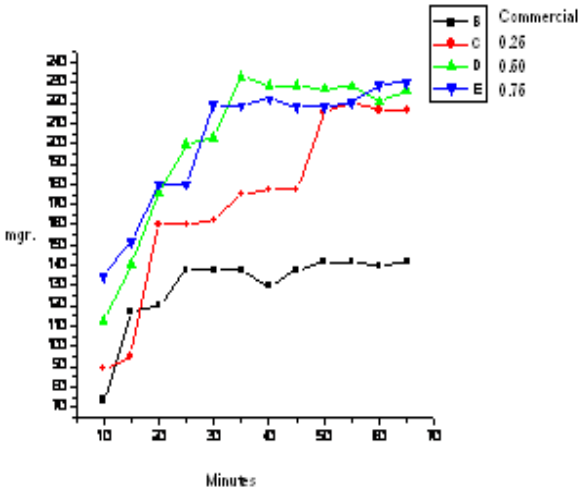



Figure 3. Graphic release of metronidazole, compared with solid dispersions commercial metronidazole.

## V. Findings

The first phase consisted of calculating the absorbance values for each stage of solid dispersion in 1:0.50, 1:0.75 and 1:0.25.

Table II shows the data table used for each sample.

Table II data matrix of each sample

| Minutes | Absorbance of the solid dispersion 1:0.50 | Absorbance of the solid dispersion 1:0.75 |
|---|---|---|
| 10 | 0.4645 | 0.5539 |
| 11 | 0.4885 | 0.6028 |
| 12 | 0.547 | 0.6132 |
| 13 | 0.6084 | 0.6725 |
| 14 | 0.5798 | 0.6545 |
| 15 | 0.5784 | 0.6249 |
| 20 | 0.7248 | 0.7415 |

| | | |
|---|---|---|
| 21 | 0.7676 | 0.7376 |
| 22 | 0.7037 | 0.7472 |
| 23 | 0.7482 | 0.7952 |
| 24 | 0.7822 | 0.8851 |
| 25 | 0.7112 | 0.741 |
| 30 | 0.7256 | 0.9029 |
| 31 | 0.7449 | 0.7329 |
| 32 | 0.8227 | 0.776 |
| 33 | 0.8432 | 0.7232 |
| 34 | 0.8529 | 0.7013 |
| 35 | 0.9592 | 0.9021 |
| 40 | 0.8299 | 0.9147 |
| 41 | 1.01 | 0.752 |
| 42 | 0.8245 | 0.7138 |
| 43 | 0.8838 | 0.8333 |
| 44 | 0.8707 | 0.7584 |
| 45 | 0.8687 | 0.8987 |
| 50 | 0.9359 | 0.8989 |
| 51 | 0.9381 | 0.7993 |
| 52 | 0.8799 | 0.7582 |

Table II data matrix of each sample

| Minutes | Absorbance of the solid dispersion 1:0.25 | Absorbance of the solid dispersion of commercial metronidazole |
|---|---|---|
| 10 | 0.3067 | 0.3067 |
| 11 | 0.4779 | 0.4779 |
| 12 | 0.2819 | 0.2819 |
| 13 | 0.2618 | 0.2618 |
| 14 | 0.5172 | 0.5172 |
| 15 | 0.3928 | 0.3928 |
| 20 | 0.6597 | 0.6597 |
| 21 | 0.6838 | 0.6838 |
| 22 | 0.5895 | 0.5895 |
| 23 | 0.3931 | 0.3931 |
| 24 | 0.7094 | 0.7094 |
| 25 | 0.541 | 0.541 |
| 30 | 0.6564 | 0.6564 |
| 31 | 0.6978 | 0.6978 |
| 32 | 0.543 | 0.543 |
| 33 | 0.7688 | 0.7688 |
| 34 | 0.5798 | 0.5798 |
| 35 | 0.7218 | 0.7218 |
| 40 | 0.6936 | 0.6936 |
| 41 | 0.6927 | 0.6927 |
| 42 | 0.6154 | 0.6154 |
| 43 | 0.7442 | 0.7442 |
| 44 | 0.6948 | 0.6948 |
| 45 | 0.5987 | 0.5987 |
| 50 | 0.8884 | 0.8884 |
| 51 | 0.8156 | 0.8156 |
| 52 | 0.6433 | 0.6433 |
| 53 | 0.7512 | 0.7512 |
| 54 | 0.7072 | 0.7072 |
| 55 | 0.7585 | 0.7585 |
| 60 | 0.7808 | 0.7808 |
| 61 | 0.8933 | 0.8933 |
| 62 | 0.7386 | 0.7386 |
| 63 | 0.7724 | 0.7724 |
| 64 | 0.7902 | 0.7902 |
| 65 | 0.7668 | 0.7668 |

The following program calculates the cubic spline for the absorbance of each solid dispersion of metronidazole, which was programmed using MATLAB, which only shows the calculation of cubic spline for the sample of solid dispersion of metronidazole to 1:0.50, since it is the same process used for the other stages, where only change of the sample data.

```
Y =[0.4645, 4648 … 0.8705,0.7768];

X =[10 11 12 13 14 15 20 21 22 23 24 25 30
31 32 33 34 35 40 41 42 43 44 45 50 51 52
53 54 55 60 61 62 63 64 65];

Absorbance of the solid dispersion of
metronidazole is plotted to a 1:0.50

Plot(x,y,'r')

Spline function is calculated
pp = spline(x,y);

100 values not tabulated are evaluated

z =linspace(10,65,100);

Spline function is evaluated with these
values

sval= ppval(pp,z)

Spline function is plotted with these
values
plot(z,sval,'b')

The area of the spline is calculated and
the absorbance of solid dispersion

areaI = trapz(x,y)
areaII = trapz(z,sval).
```

Where:

x is the data for the X axis
Z is the vector with values not tabulated, (100).
Y are the values for Y axis
pp are the values of the Spline values not tabulated
sval are the values of the spline function
areaI = area under the curve of the sample
áreaII = area under the curve of the Spline.

The above process was applied to each sample to the absorbency of the solid dispersion of metronidazole. Once obtained the splines of each sample, we calculated the area under the curve of each spline, using the method of trapezoids for which we used the "trapz [11], whose results are shown in Table III. In the next chart you can see the calculations of the area under the curve of both: the specimen obtained with the spline. With the data the percentage relative error was calculated which was committed to determine differences that may have these areas of the splines.

Table III. Area under the curve of the Spline and the simple

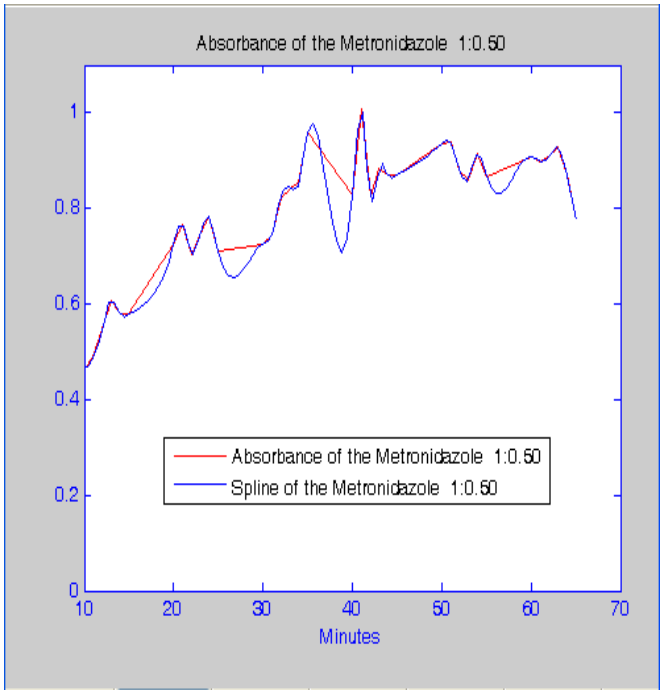
| Área under the curve of the Spline and the sample | Absorbance of the solid dispersion of metronidazole to 1:0.50 | Absorbance of the solid dispersion of metronidazole to 1:0.75 |
|---|---|---|
| Sample | 44.2274 | 44.2960 |
| Spline | 43.5136 | 46.2670 |
| Área under the curve of the Spline and the sample | Absorbance of the solid dispersion of metronidazole to 1:0.25 | Absorbance of the solid dispersion of commercial metronidazole |
| Sample | 35.9748 | 28.4382 |
| Spline | 34.7758 | 27.8670 |

It is notorious that the differences between the areas of the Spline and samples is not significant, the differences are not large, but it is also significant that the areas are different for the samples and the Spline, so we can say that in form are different. To determine the relative error percentage of the samples and the Spline function takes the area of the sample and is subtracted Spline area divided by the sample area multiplied by 100. Table IV shows these errors, where the smallest is observed in solution was 1:0.50 solid, so you can say it is the sample with a softer Spline denoting a higher dissolution rate with respect to the other samples.

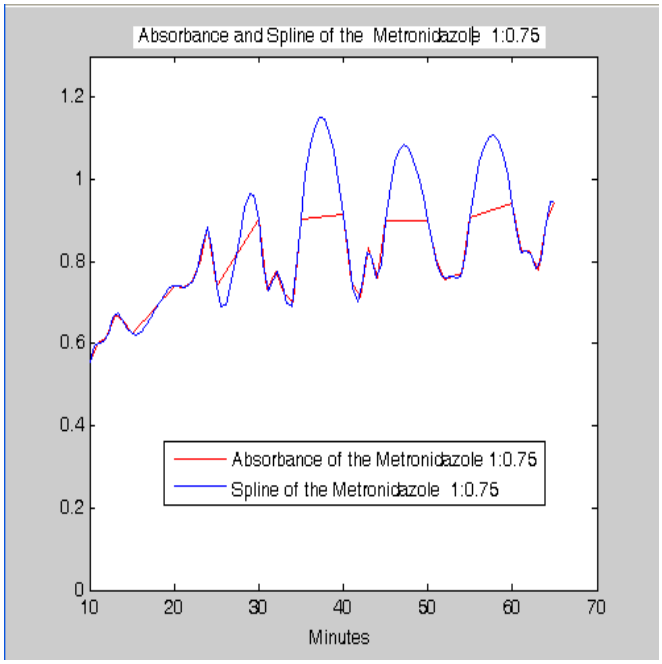
Table IV. Relative percentage errors

| Errors | Percentage relative error of the solid dispersion of metronidazole to 1:0.50 | Percentage relative error of the solid dispersion of metronidazole to 1:0.75 | Percentage relative error of the solid dispersion of metronidazole to 1:0.25 | Percentage relative error of the solid dispersion of commercial metronidazole |
|---|---|---|---|---|
| | 1.6139% | 4,4496% | 3.3328% | 2.0085% |

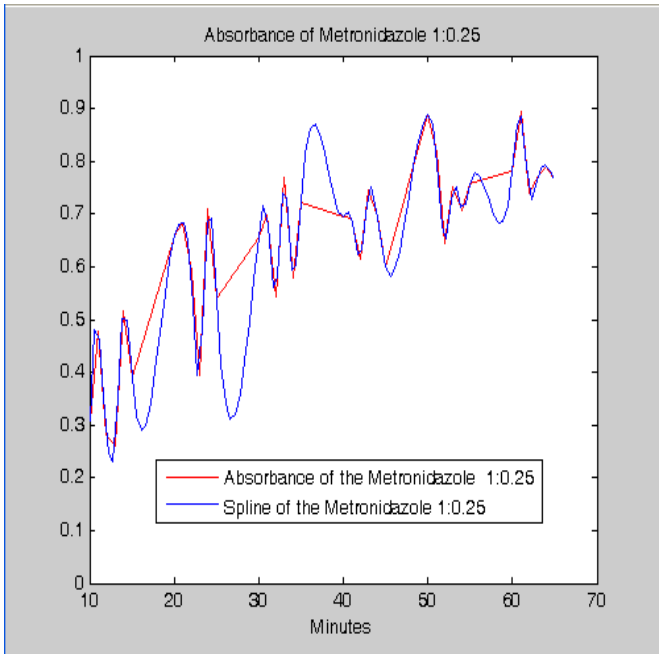
Below are graphically Splines while the absorbance of the solid dispersion of metronidazole taking as range of 10 to 65 minutes predicted points were not assessed in the samples (100 points) (Graph I, II, III and IV) is well known that the differences between the spline and the samples obtained are significant. Comparing the graphs and noting those that have fewer peaks, ie, they are softer; undoubtedly Figure 1 is the one that stands out and then the graph IV.




*Graph I Spline and absorbance for the simple to 1:0.50*

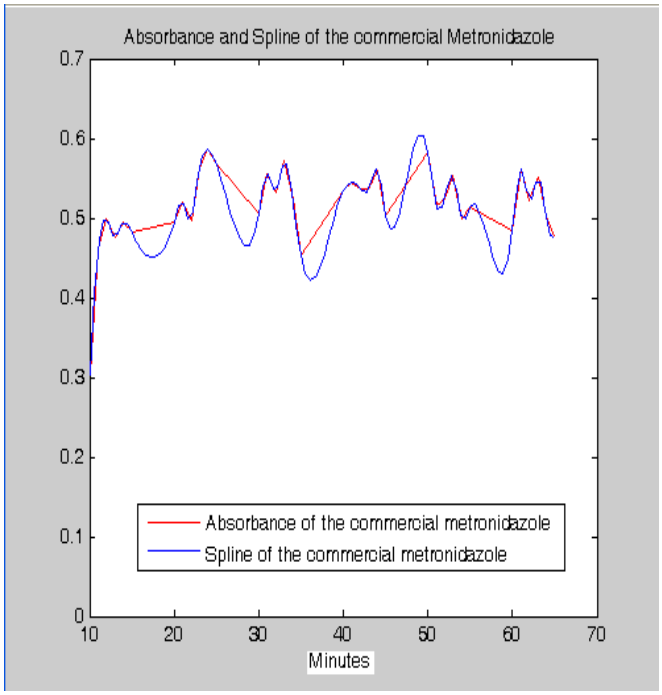



*Graph II Spline y Absorbance for the simple to 1:0.75*



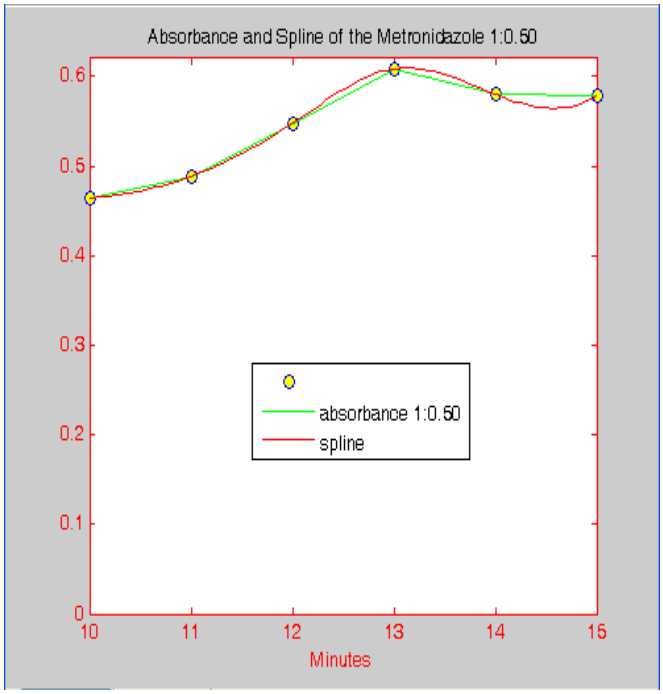

*Graph III Spline and absorbance for the simple to 1:0.25.*

It is also well known that the graph III and IV are those with more peaks. To highlight this claim we proceeded to take a sub-interval of 10 to 15 minutes in order to enlarge the chart and notice more differences between the sample and the Spline absorbance obtained for each of the solid dispersion of metronidazole and also evaluate the interval 100 values are tabulated and can make predictions that allow us to see the dissolution behavior in more detail.

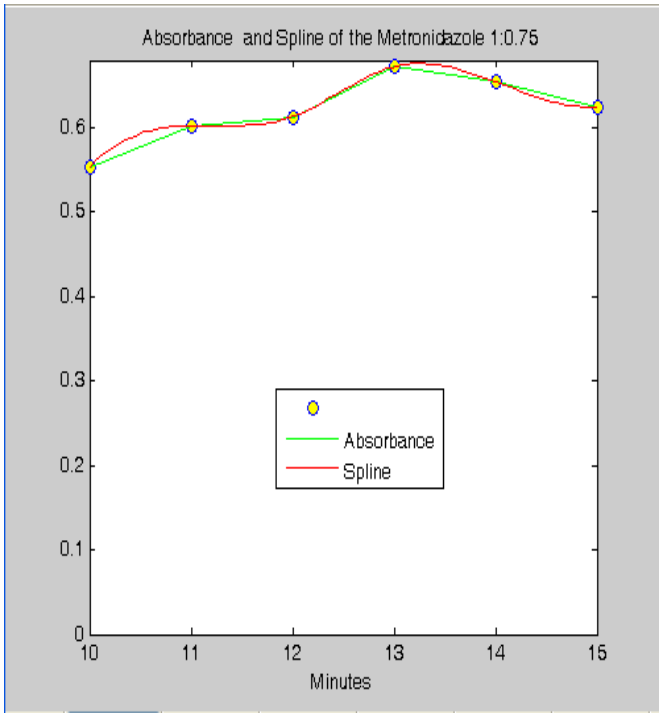



*Graph IV Spline and absorbance for the trade show*

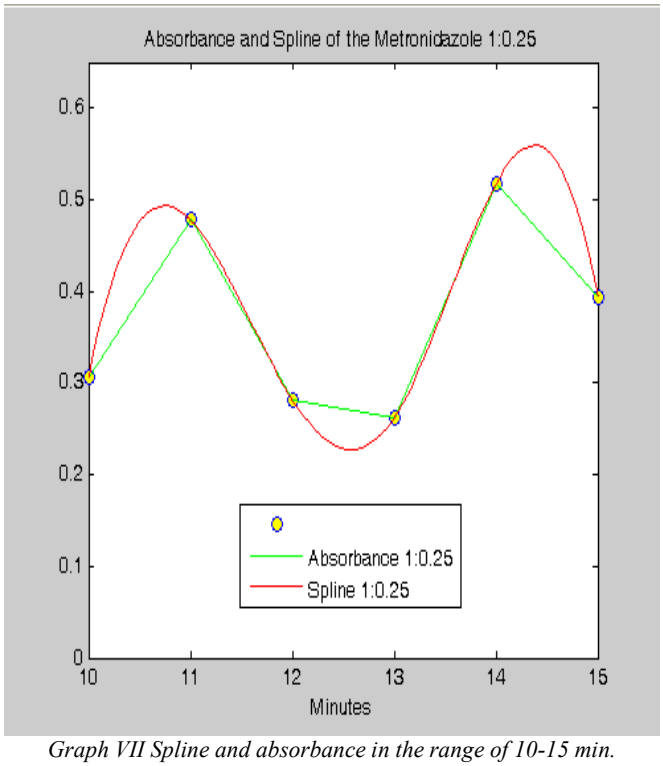
The graphs V, VI, VII and VIII clearly show the differences between the spline function and samples absorbance of the solid dispersion of metronidazole.



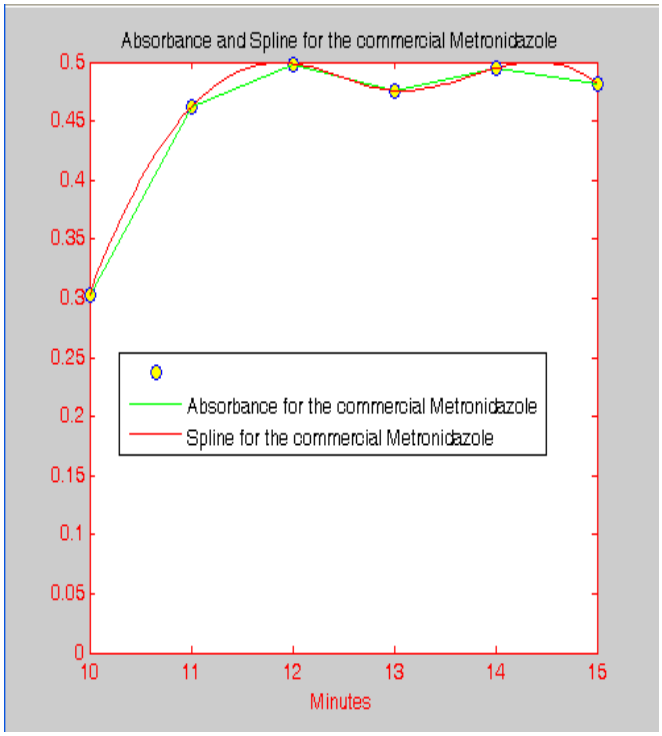

*Graph V Spline and absorbance in the range of 10-15 min.*




*Graph VI Spline and absorbance in the range of 10-15 min*




*Graph VII Spline and absorbance in the range of 10-15 min.*




*Graph VIII Spline and absorbance for the simple in an interval of 10-15 min.*

We can say that the graphics are significantly different even though it is the same variable that measures the absorbance, but undoubtedly the best performance is shown in graph I, which refers to the solid solution of metronidazole to 1:0.50, as which is softer and therefore conclude that it is the one that has better dissolution rate, a situation that coincides with the physicochemical analysis performed.

## VI. Conclusions

Cubic interpolation allow the segmentation of the samples of the experiment to improve the dissolution of metronidazole, consisting of three stages, allowing both numerically and graphically demonstrate that there are changes in the dissolution of metronidazole, where it is evident that the best solution was the solid dispersion of metronidazole against metronidazole 1:0.50 commercial. As the differences between the samples and were not very perceptible Spline will take a 10 .. 15 minutes in order to better visualize the differences in Spline and samples, and the behavior of the same, where we observed that in graphs V, VI, VII and VIII of the splines were different with respect to the spline obtained in each sample, the above is corroborated by calculating the area under the curve of each spline where the areas were different back then the error was calculated relative percentage of each sample where the largest errors were identified in the disposition of metronidazole to 1:0.75 solid. So we can conclude that there were changes in the solid solution of metronidazole.

The results are satisfactory and continue working on this technique for future analysis, as do cubic interpolation not

only to a column of data but for more variables to enrich the analysis.

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