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## **A NEW DESIGN OF *SILYBUM MARIANUM* TABLETS BY DIRECT COMPRESSION**

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**ABSTRACT:** In the present paper we described a new design of herbal medicine tablets by direct compression using the ethanolic extract of *Silybum marianum* (L.) Gaertn. *S. marianum* extract is used in popular medicine as hepatoprotective herbal medicine. The alcoholic extract was obtained from seeds by soxhlet. Five pharmaceutical formulations were prepared using the extract as active principle, Aeroperl® 300 Pharma, as carrier and different diluents (CombiLac®, MicroceLac® 100, StarLac®, Cellactose® 80 and FlowLac® 90). The micromeritic properties were determined for all the physical mixtures. The results of angle of repose, compressibility and Hausner ratio indicated that the all powder mixtures had excellent flow properties and compressibility. In addition, the tablets properties and quality parameters were evaluated (weight variation, hardness, friability, disintegration test, drug content and dissolution test). One formulation (F5: herbal ethanolic extract 20 %, Aeroperl® 20 %, FlowLac® 90 57 %, Glycolate starch 2 % and magnesium stearate 1 %) showed excellent rheological properties and the best biopharmaceutical parameters in concordance with the pharmacopoeial specifications. Thus, taking into account the poor solubility of silymarin in water, this novel design could be easily applied to others poorly soluble drugs or herbal extract in order to improve its bioavailability.

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**KEYWORDS:** Herbal medicine, *Silybum marianum*, direct compression, rheology, dissolution test.

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### **1. INTRODUCTION**

Tablets are the most common solid dosage forms used by humans. Their principal advantages include: ease of manufacturing, convenience of dosing and major stability compared to liquid and

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semisolid pharmaceutical forms [1], [2]. Tablets are conventionally prepared by wet granulation, dry granulation and direct compression [3]. The wet granulation present disadvantages such as: more number of processing steps, high cost and stability problems for moisture and heat sensitive drugs. Dry granulation technique requires the use of special equipment's for pre-compression [4]. In contrast, direct compression has the advantage of requiring a smaller number of production steps [5], [6]. This method can be applied to thermosensitive and moisture-sensitive drugs [7]. Also direct compression produces tablets with faster dissolution times due to primary drug particles are released when disintegration takes place [8]. In this method, fewer excipients are needed and they have to be able to compensate for poor flow and compression properties, which are often inherent to the active principle [9]. In this sense Aeroperl® 300 Pharma is an excellent pharmaceutical absorbent for direct compression. This hydrophilic fumed silica is used as carrier in solid dosage forms, allowing: the incorporation of fluid extracts as well as the improving dissolution of poorly soluble active principles [9], [10]. The active principles from natural sources may be incorporated into the pores by the immersion or impregnation method. In immersion method, the mesoporous material is immersed in organic solution of the fluid extracts followed by stirring or ultrasound to reach a complete absorption and then solvent is eliminated [11], [12]. On the other hand, *Silybum marianum* (L.) Gaertn., “cardo mariano”, is employed in popular medicine as hepatoprotective [13], [14]. The main active ingredients of this extract are five flavolignans: silybin (A and B), isosilybin (A and B), silychristin (A and B), silydianin and taxifolin. To this set of compounds are called silymarin [15], [16]. In the Argentinean market, silymarin is present under the form of tablets obtained by wet granulation (Laragon 150, Roemmers). Herbal medicine tablets commonly contain a high dose of dried plant extract. Therefore, the amount of excipients that can be incorporated in order to obtain reasonable size tablets is usually insufficient to improve the flow and compactability properties of dried plant extracts. In these sense, the uniformity, reproducibility and stability requirements of herbal medicine products represents a challenge in the searching for novel formulations [17]. In addition, low bioavailability of active ingredients is associated with poor solubility. This is an increasing problem in the development of solid pharmaceutical formulation [18], [19]. By taking into consideration all these aspects, in the present work we report a new design to obtain herbal medicine tablets by direct compression. The fluid extract of *S. marianum* was used as active ingredient and Aeroperl® 300 Pharma as carrier.

## 2. MATERIALS AND METHODS

Silymarin, organic solvents, chemicals and reagents of analytical grade were purchased from Sigma-Aldrich. The direct compression excipients investigated in this study included: Aeroperl® 300 Pharma, CombiLac®, MicroceLac® 100, StarLac®, Cellactose® 80 and FlowLac® 90 (Meggler Pharma, Evonik, Wasserburg, Germany). They were donated by Etilfarma. Glycollate starch and magnesium stearate were purchased from Droguería Saporiti S.A.C.I.F.I.A. The quantitative analysis

of silymarin was performed in UV-vis Spectrophotometer (Beckman, DU-640, Minnesota, United States). Scanning electron microscopy images were obtained using a SEM (LEO, 1450 VP, ZEISS, United States). Mini-press mono-punch eccentric machine (Mono-punch excentric, SC model, Buenos Aires, Argentina), Dual Drum Friability Tester (Electrolab, EF-2, Electrolab, India) and Tablet Hardness Tester (DRS Pharmatron, Tablet Tester 8M, DRS, Switzerland) were employed.

### **Vegetal Material**

The seeds of *Sylibum marianum* were commercially obtained in an herbalist's shop in the city of San Luis and identified as genuine by microscopic techniques in the herbarium of the Universidad Nacional de San Luis.

### **Preparation of *S. marianum* extract**

Three exhaustive solid-liquid extractions using a soxhlet type apparatus were performed using 25.0 g portions of the ground seeds. Precisely weighed sample was transferred to a paper thimble. The loaded thimble was inserted into a 400-mL soxhlet extractor. Extractions were performed in the two-step process. In the first step of the procedure, the plant material was defatted for 2 h using 250 mL of n-hexane. In the second, silymarin was extracted for 5 h with 250 mL of ethyl acetate according to Argentine pharmacopoeia [20]. The same procedure was carried out, using ethanol as extraction solvent instead of ethyl acetate.

### **Solid Residue assay (SR)**

The SR content of fluid extract was determined by evaporation of the organic solvent under reduced pressure, and then dried in an oven (40 °C) to constant weight. (Ethyl acetate SR= 9.11 mg/mL; Ethanolic SR= 22.03 mg/mL).

### **Quantitative determination of silymarin in organic extracts**

The quantitative analysis of silymarin was performed by UV-vis spectrophotometric method [21]. A 100 mg of silymarin standard were accurately weight and transfer into 100 mL volumetric flask, dissolve in methanol and make up the volume with methanol and mix well. Total 5 volumetric flasks of 100 mL were taken and marked with 1 to 5. Then 0.3, 0.4, 0.5, 0.6 and 0.7 mL of standard were transferred to volumetric flasks through pipette and make up the volume with methanol and mix well. The  $\lambda_{max}$  of silymarin was measured at 287 nm. From the calibration curve concentration of silymarin was determinate as 19.84 mg/mL and 7.05 mg/mL in ethanolic and ethyl acetate extracts, respectively.

### **Preparation of LSE (Loaded silica extract) and evaluation of powder blend**

The dispersion of the ethanolic extract of *S. marianum* was prepared by a technique involving the use of the previously degassed alcoholic extract obtained, followed by its adsorption on the surface of Aeroperl® 300 Pharma used as carrier. Predetermined weighed amounts of fumed silica were dispersed in a measured volume of the liquid extract to be processed. The solvent was gradually evaporated at room temperature with constant stirring. When the mixture turned semisolid in

consistency, the final solvent evaporation was performed in an oven (40°C) to constant weight. The powder obtained was screened through mesh N° 40.

### **Density and compressibility assays**

To determine the density of the mixture of LSE and excipients, the powder was gently poured into 10 cm<sup>3</sup> graduate cylinder to a total volume of 10 cm<sup>3</sup>. The bulk density (DB) was calculated as the ratio between weight (g) and volume (cm<sup>3</sup>). To determine the tap density (DT) the cylinder was tapped over 1.0 inch vertical drop, at 1s interval, until no measurable change in volume was noticed. The compressibility of the powder was evaluated using the Hausner Ratio (HR) [22], [23]:  
HR= [tap density/ bulk density]

### **Angle of repose**

The dynamic for mixture of powder was determined by the funnel method as described in the literature [22].

### **Tablet compaction**

The LSE and excipients, except magnesium stearate, were blended for 12 min by tumbling, thus the corresponding amount of magnesium stearate was added and blended for another 4 min. The proposed formulas were compressed using a Mini-press mono-punch eccentric machine, with a punch set of 7.0 mm in diameter during four minutes (automatic and continuous operation tablet, production 50 tablets per minute, motor single-phase 3/4 HP, maximum compression force 1.8 Tn). Tests of uniformity of weight, hardness, disintegration and friability were performed, according to the techniques resulting from the collection of various pharmacopoeias. The weight of each tablet was 130 mg. Tablet hardness was measured on recently prepared tablets with an SCOUT hardness tester.

### **Tablets weight variation**

The tablets weight variation test was carried out according to USP [24]. Twenty tablets were weighed individually. The results were expressed as mean value of 20 determinations.

### **Tablet friability**

Ten tablets were selected at random; their surfaces were cleaned to remove adhering dust, weighed and placed in the Friabilator USP, Electrolab Dual Drum Friability Tester (Model: EF-2). They were then allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted and weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss. The replicate determinations of each formulation were averaged. The test was performed by triplicate. The percent friability was calculated as follow:

% Friability= [initial weight- final weight]/ initial weight x 100.

### **Tablet hardness**

The hardness of tablets was determined using Pharmatron, Dr. Schleuniger, tablet tester 8M, and the average hardness of 20 determinations in Kg/cm<sup>2</sup> was determined.

***In vitro* disintegration test**

The disintegration test was following the method established by the USP [24]. The tablet disintegration test apparatus (Electrolab disintegration tester DT2L) was used to determine the disintegration time for all formulations. Six tablets were placed individually in each tube of disintegration test apparatus. The phosphate medium was maintained at a temperature of  $37 \pm 2^\circ\text{C}$  and the time was noted for the entire tablet to disintegrate completely.

***In vitro* dissolution test**

The USP dissolution test apparatus (Hanson Research SR8PLUS) type II was used for the study [24] (seven tablets and standard for each formulation). First, 900 mL of the phosphate buffer pH 7.5 with 2% of sodium lauryl sulfate was taken in a vessel, and the temperature was maintained at  $37 \pm 0.5^\circ\text{C}$ . The speed of the paddle was fixed at 100 rpm. Dissolution samples were withdrawn at 5 minutes intervals, and drug content was determined by measuring the absorbance at 287 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The test was performed by triplicate. Laragon 150 (Roemmers) was used as positive control.

**Statistical analysis**

All results were expressed as mean values  $\pm$  standard deviation (SD). The determined dissolution data was subjected to statistical analysis using a computer program, Graphpad INSTAT<sup>tm</sup> Copyright 1990-1993 (Version 2.04, Ralf Stahlman, Purdue University, USA, 931897S) for a one-way analysis of variance (ANOVA).  $P < 0.05$  was considered as evidence of a significant difference.

**3. RESULTS AND DISCUSSION**

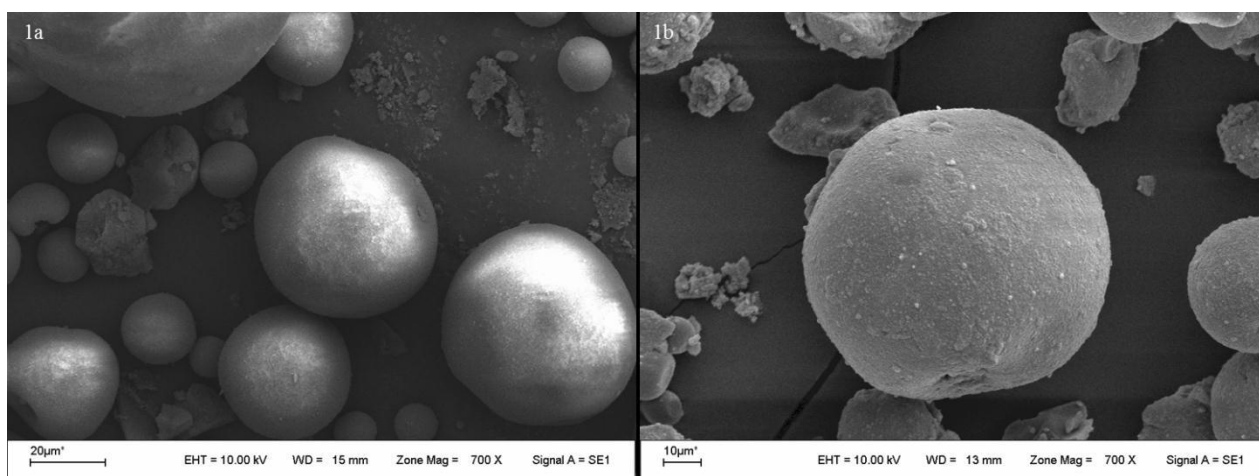
In the present work we design, develop and evaluate tablets by direct compression using the ethanolic extract of *S. marianum* as active ingredient. Ethanolic and ethyl acetate extracts were prepared. Better solid residue was obtained when ethanol was used as extraction solvent. The concentration of silymarin was determined by UV-visible (19.84 mg/mL and 7.05 mg/mL in ethanolic and ethyl acetate extracts).

The design of an appropriate formulation for direct compression depends on the properties of the active ingredient but essentially on the mechanical properties of the excipients. In general, excipients have to flow well, be good binders and they have to correct any mechanically unfavorable properties that active ingredients may have [25], [26]. The compositions of the prepared formulations are shown in Table 1. All of them contained 20 % by weight of *S. marianum* extract and 20 % of Aeroperl<sup>®</sup> as carrier.

**Table 1: Composition of tablets**

Formulation	F1	F2	F3	F4	F5
<i>S. marianum</i> ethanolic extract	20 %	20 %	20 %	20 %	20 %
Aeroperl® 300 Pharma	20 %	20 %	20 %	20 %	20 %
CombiLac®	57 %	-----	-----	-----	-----
MicroceLac® 100	-----	57 %	-----	-----	-----
StarLac®	-----	-----	57 %	-----	-----
Cellactose® 80	-----	-----	-----	57 %	-----
FlowLac® 90	-----	-----	-----	-----	57 %
Glycolate starch	2 %	2 %	2 %	2 %	2 %
Magnesium stearate	1 %	1 %	1 %	1 %	1 %

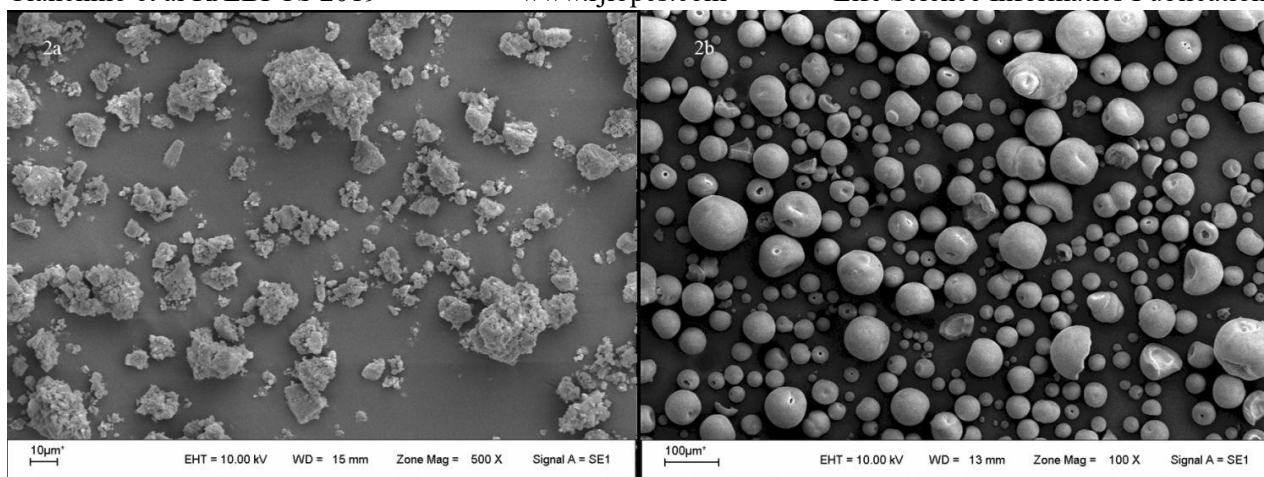
Aeroperl® allows the incorporation of fluid extracts into solid dosage forms improves the dissolution of poorly soluble active and optimizes the rheology properties [11]. In Figure 1 are shows the scanning electron microscopy images of Aeroperl® (Fig. 1a) and Aeroperl® with fluid extract (Fig. 1b).



**Figure 1. Scanning electron microscopy images of Aeroperl® (1a) and Aeroperl® with *S. marianum* extract (1b)**

We can observe smooth spherical particles of Aeroperl® and rough spherical particles of Aeroperl® with fluid extract (Fig. 1b). An excellent distribution of fluid extract was observed in Figure 1b. Rough spherical particles would bring about more favorable flow ability [27], [28].

Figure 2 shows the poor distribution of *S. marianum* extract in Aerosil® compared with Aeroperl®. Clear areas were observed in Fig. 2a.



**Figure 2: Scanning electron microscopy images of Aerofil® with *S. marianum* extract (2a) and Aeroperl® with *S. marianum* extract (2b)**

In addition, five lactose excipients of pharmaceutical degree, frequently used in direct compression, were employed as diluents: CombiLac®, MicroceLac® 100, StarLac®, Cellactose® 80 and FlowLac® 90. These kind of co-processed excipients provide a better tableting performance [29], [30], [31]. On the other hand, Table 2 shows the micromeritic properties for all the physical mixtures of *S. marianum*. The powders of all formulations flowed very well, given that the respective angles of repose between 7° and 13° were less than 25°. Also, in all formulas they were observed good volumetric reduction profiles that are related with the degree of packaging, which results in a very good compressibility. The experimental values were excellent. These values indicated that all powder mixtures had excellent flow properties, good packing ability and met the official requirements.

**Table 2: Micromeritic parameters of physical mixtures containing *S. marianum* ethanolic extract**

Formulation	F1*	F2*	F3*	F4*	F5*
Bulk density (g/cm <sup>3</sup> )	0.51± 0.002	0.54± 0.003	0.56± 0.005	0.48± 0.03	0.59± 0.001
Tapped density (g/cm <sup>3</sup> )	0.59± 0.005	0.62± 0.004	0.65± 0.012	0.55± 0.003	0.67± 0.013
Compressibility (%)	13.12± 0.005	14.39± 0.54	14.13± 0.55	12.01± 0.06	12.05± 0.005
Hausner ratio	1.15± 0.005	1.16± 0.005	1.16± 0.015	1.14± 0.01	1.14± 0.02
Angle of repose (θ)	7.43± 0.4	10.23± 1.2	10.15± 1.27	13± 0.98	8.7± 0.45

\*The values represent the mean of four determinations ± standard deviation.

The tablets were obtained by direct compression using a mono-punch eccentric machine with 7 mm-diameter punches. The experimental results of the tests performed on these tablets are shown in Table 3.

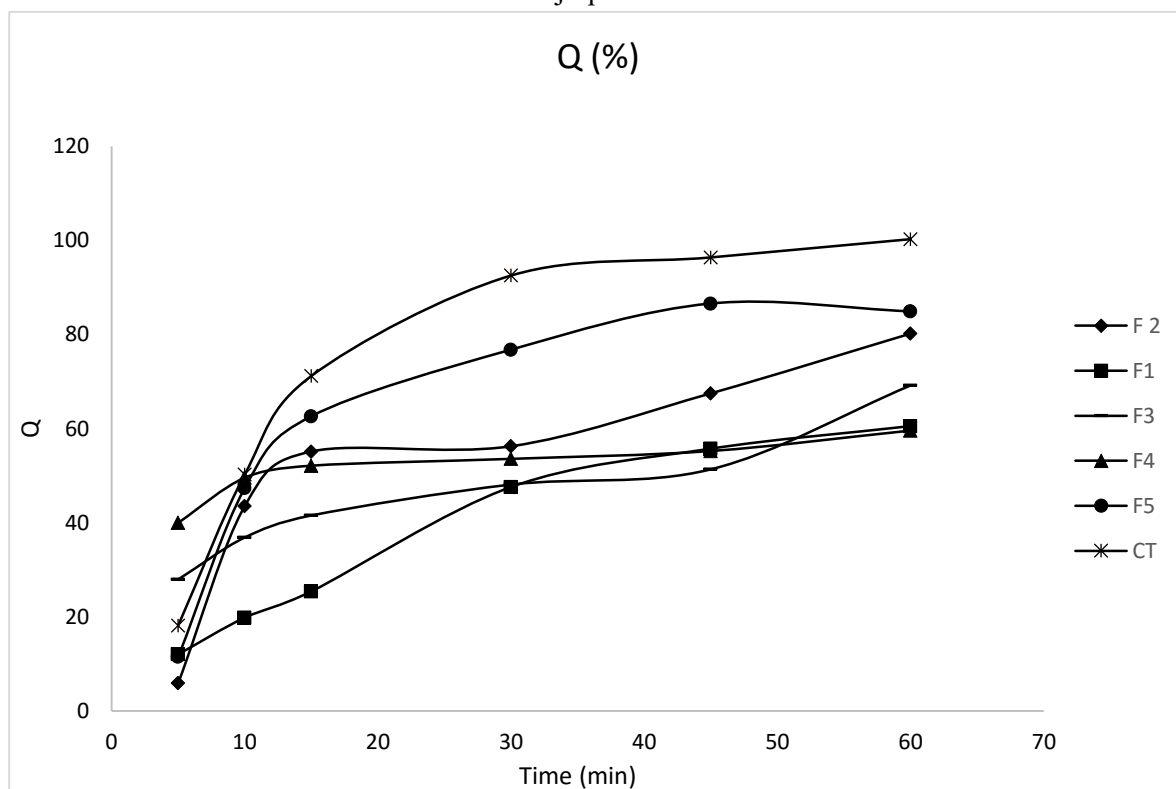
**Table 3: Results of tests performed on *S. marianum* tablets**

Formulation	F1 (n=20)*	F2 (n=20)*	F3 (n=20)*	F4 (n=20)*	F 5(n=20)*
Weight variation (mg)	130.8± 1.35	129.7± 1.05	130.2± 0.63	114.5± 1.36	134.2± 0.61
Friability (%)	0.97± 0.03	0.92± 0.015	0.57± 0.017	1.05± 0.03	0.82± 0.03
Disintegration time (min)	9.3± 0.03	19.4± 0.15	9.02± 0.03	9.01± 0.04	8.05± 0.03
Hardness (Kg/cm <sup>2</sup> )	3.80± 0.15	4.40± 0.11	2.60± 0.25	1.60± 0.23	3.70± 0.17
Drug content (mg/tablet)	12.75± 0.15	20.1± 0.07	15.98± 0.28	12.41± 0.16	21.84± 0.04

\*The values represent the mean of four determinations ± standard deviation.

The batches of tablets produced for F1, F2, F3 and F5 were acceptable, given that its variation in weight was less than 10 %, as established by the USP 34. This allows an appropriate analysis of the trials galenics applied to the tablets, which relate to their integrity until they reach patient and its good disintegration for the release of the active ingredient. Friability, disintegration time and hardness tests give idea of the mechanical strength of the tablets, related to possible deterioration during transportation, packaging and handling. As soon as to friability, only formulations F1, F2, F3 and F5 had a loss weighing less than 1 %, which would determine a higher resistance to abrasion. Formulation F2 had longer disintegration time than the others formulations, which would be related to that this formulation had greater hardness and a lower value of friability. The formula F5 was the one that presented the fastest disintegration. Taking into account the disintegration time, hardness was acceptable for formulations F1, F3, F4 and F5, in concordance with the experimental value obtained. For the formula F4, the variation in weight and hardness, were not in concordance with the official parameters. Moreover, release of the active ingredient from solid dosage forms has been described by various kinetic models, in which the amount of cumulative active ingredient released (Q) is a function of the elapsed test time (t). The quantity of Q is the amount of dissolved active ingredient specified in the individual monograph expressed as a percentage of the labeled content. The in vitro dissolution profiles of all formulation are shows in Figure 3. At 45 minutes Q (%) the experimental values for F1-F5 and positive control were: 55.720 ± 0.023, 67.533 ± 0.088, 51,374 ± 0.102, 55.274 ± 0.014, 86.589 ± 0.003 and 96.430 ± 0.101, respectively (Fig. 3). The dissolution test for tablets described in the USP indicates that no less than 75 % of silymarin content should be dissolved in 45 min. Consequently, only formulation F5 satisfied this official specification like Laragon 150 commercial tablets (CT).





**Figure 3: Dissolution profiles of silymarin from F1-F5 tablets formulation compared to commercial tablets (CT)**

In summary, from the joint analysis of the results, principally the Q value, F5 showed comparatively, the most appropriate parameters of hardness, friability and disintegration time, evidencing their excellent galenic and pharmacokinetic features.

#### 4. CONCLUSION

Using the ethanolic extract of *S. marianum*, a new formulation for direct compression was designed, which showed excellent properties for this purpose together with high mechanical resistance and an excellent disintegration time. The resulting tablets from formulation F5 complies the quality specifications provided by the USA Pharmacopoeia. These properties would be attributed to the manufacture process of FlowLac® 90. Thus, the formulation developed in this study could be easily applied for the manufacture of herbal medicinal tablets by direct compression. Particularly, fluid extracts with actives poorly soluble could be employed, thus ensuring their stability by avoiding heat and humidity factors during the manufacturing process.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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