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Pharmacognosy
Formulation development and evaluation of *Silybum marianum* tablets

Valeria Andrea Cianchino[1], *Laura Silvina Favier*[1,3,4], *Claudia Alicia Ortega*[1], *Cecilia Peralta*[1] & *Diego Alberto Cifuente*[2]

Abstract

In popular medicine *Silybum marianum* is used as a hepatoprotective agent. Silymarin is the major constituent. The present work deals with the formulation and evaluation of *S. marianum* tablets from ethanolic extract by direct compression. The ethanolic extract was obtained from seeds by soxhlet extraction. Two pharmaceutical formulations were prepared using fluid extract as an active principle, and Aeroperl® 300 Pharma as a carrier. In order to improve flow ability and compressibility, co-processed excipients MicroceLac® 100 and FlowLac® 90 were employed. Pre-compression and post-compression parameters were evaluated according to USP 34-NF 29. Besides, silymarin was determined by NMR spectral data. Both formulations showed excellent rheological properties and the best biopharmaceutical parameters were observed in F2 (*S. marianum* ethanolic extract, aeroperl® 300 Pharma, flowLac® 90, glycolate starch and magnesium stearate) in terms of the friability (0.82 %) and the disintegration time (8.05 min).

Key words: direct compression, ethanolic extract, herbal tablets, quality controls, *Silybum marianum*.

Resumen

En medicina popular, *Silybum marianum* se usa como agente hepatoprotector. La silimarina es su componente principal. El presente trabajo trata de la formulación y evaluación de tabletas de *S. marianum* a partir de extracto etanólico por compresión directa. El extracto etanólico se obtuvo de las semillas mediante extracción con soxhlet. Se prepararon dos formulaciones farmacéuticas usando extracto fluido como principio activo y Aeroperl® 300 Pharma como vehículo. Para mejorar la capacidad de flujo y la compresibilidad, se emplearon excipientes coprocesados MicroceLac® 100 y FlowLac® 90. Los parámetros de precompresión y postcompresión se evaluaron de acuerdo con USP 34-NF 29. Además, la silimarina se determinó mediante datos espectrales de RMN. Ambas formulaciones mostraron excelentes propiedades reológicas y los mejores parámetros biofarmacéuticos se observaron en F2 (*S. marianum* ethanolic extract, aeroperl® 300 Pharma, flowLac® 90, glicolado de almidón y estearato de magnesio) en términos de friabilidad (0,82%) y el tiempo de desintegración (8,05 min).

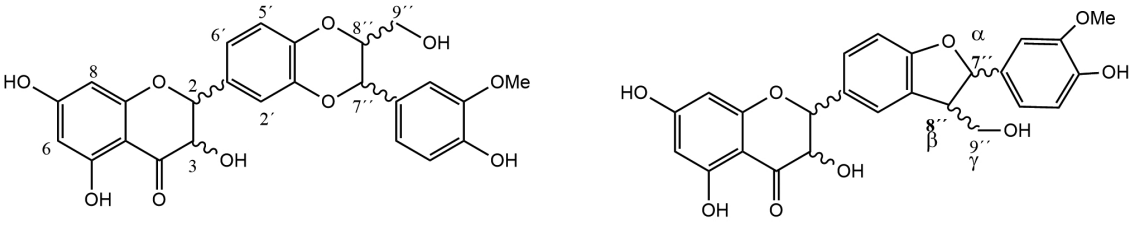
Palabras clave: compresión directa, extracto etanólico, comprimidos herbarios, controles de calidad, *Silybum marianum*.

Introduction

Silybum marianum (L.) Gaertn, "cardo mariano", is employed in popular medicine as a hepatoprotective herbal medicine (Flora *et al.* 1998; Freitag *et al.* 2015; Bouhalit & Kechrid 2018). A set of flavolignans, called silymarin, are the main active ingredients of *S. marianum* extract: silybin A and B (I), isosilybin A and B (I) and silychristin (II) (Fig. 1). Silymarin is poorly soluble in water and it is usually administered in oral forms (Ramírez-Santos *et al.* 2011; Shakeela *et al.* 2014).

The proposed dose of silymarin in the tablets is approximately the dose contained in one cup of tea prepared from 2 g of vegetable drug (Alonso 2004).

[1] Universidad Nacional de San Luis, Área de Tecnología Farmacéutica, Ejercito de los Andes 950, San Luis, Argentina.
[2] Universidad Nacional de San Luis, Área de Química Orgánica, INTEQUI-CONICET, Almirante Brown 1500, San Luis, Argentina.
[3] ORCID: <https://orcid.org/0000-0002-3875-3388>
[4] Author for correspondence: laurasil65@gmail.com



I: silybin A, B, isosilybin A,B

II: silychristin

Figure 1 – Major flavolignans present in silymarin.

In the Argentinean market, silymarin is present under the form of tablets obtained by wet granulation (Laragon 150 commercial tablets, Roemmers (CT)); however, *S. marianum* herbal tablets obtained by dry route and direct compression are not available.

In recent years, the use of herbal medicinal products has increased in importance across the world and novel pharmaceutical formulations are required (WHO 2004). Tablets are the most common solid pharmaceutical dosage formulation used by humans and they are conventionally prepared by wet granulation (WG), dry granulation (DG) and direct compression (DC) (Vila Jato 2001). DC produces tablets with faster dissolution times and requires a smaller number of production steps (Remington 2003). Aeroperl® 300 Pharma is an excellent pharmaceutical absorbent for direct compression. This hydrophilic fumed silica is used as carrier in solid dosage forms since it allows the incorporation of fluid extracts and at the same time it improves dissolution of poorly soluble active principles (Desai 2016; Wei *et al*. 2017).

Direct compression formulations consist of four basic ingredients: a diluent to increase the bulk, a lubricant to improve flow of blend, a disintegrant to improve the biodisponibility and the active ingredient (Singh *et al*. 2004). The excipients have to compensate for poor flow and compression properties, which are often inherent to the active extract (Jivraj *et al.* 2000; Shubhajit & Changquan 2018). In this sense, lactose co-processed excipients improve process ability, performing as diluent and disintegrant agents (Villafuerte Robles 2011; Mamatha *et al.* 2017).

In the present work we report a novel formulation to obtain herbal tablets of *S. marianum* by direct compression using MicroceLac100® (75% alpha-lactose monohydrate and 25% microcrystalline cellulose) and FlowLac90® (spray-dried alpha-lactose monohydrate) as lactose co-processed excipients. Also, starch glycolate was used as a superdisintegrant and magnesium stearate as a lubricant.

In addition, the NMR fingerprint of tablets prepared with silymarin was made.

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, MicroceLac® 100 and FlowLac® 90 (Meggle Pharma, Germany) and were donated by Etilfarma. Glycollate starch and magnesium stearate were purchased from Droguería Saporiti S.A.C.I.F.I.A.

The seeds of *Silybum marianum* were purchased in an herbal shop from the city of San Luis (Argentina) and were identified as genuine by macro and microscopic techniques. The ethanolic extract was obtained by following official methods. The quantitative analysis of silymarin was performed by UV-vis spectrophotometric method (UV-vis Spectrophotometer, Beckman, DU-640) (Gul *et al.* 2015). Concentration of silymarin was determined as 1.96 mg/mL from the calibration curve.

Granulate was obtained by immersing the extract in Aeroperl® used as a carrier, in a 1:1 ratio (Sun *et al.* 2018). The evaporation of the solvent was carried out under reduced pressure and then dried in an oven (40 °C) to constant weight. Two tablet formulations (F1 and F2) were proposed using different diluents (FlowLac 90® and MicroceLac® 100, respectively) (Tab. 1).

The dynamic for each mixture of powder was determined by the funnel method as described in the literature (Lantz & Schwartz 1990). To determine the density of the samples, the powder

Table 1 – Composition of tablets.

Components	Formulations	
	F1	F2
Silybum marianum ethanolic extract (mL/tablet)	26	26
Aeroperl® 300 Pharma (mg/tablet)	26	26
MicroceLac® 100 (mg/tablet)	74.1	-----
FlowLac® 90 (mg/tablet)	-----	74.1
Glycolate starch (mg/tablet)	2.6	2.6
Magnesium stearate (mg/tablet)	1.3	1.3

was gently poured into 10 cm^3 graduate cylinder to a total volume of 10 cm^3. The bulk density (DB) was calculated as the ratio between weight (g) and volume (cm^3). To determine the final tapped density (DT) the cylinder was tapped with 1 inch vertical drop, at 1 second interval, until no measurable change in volume was noticed. The compressibility of the powder was evaluated using the Hausner Ratio (HR) (Schmidt & Rubensdörfer 1994) (Tab. 2).

Table 2 – Densities and flow properties of physical mixtures containing *Silybum marianum* ethanolic extract.

Properties	Formulations	
	F1	F2
Bulk density (g/cm^3)	0.54 ± 0.003	0.59 ± 0.001
Tapped density (g/cm^3)	0.62 ± 0.004	0.67 ± 0.013
Compressibility (%)	14.39 ± 0.54	12.05 ± 0.005
Hausner ratio	1.16 ± 0.005	1.14 ± 0.02
Angle of repose (θ)	10.23 ± 1.2	8.7 ± 0.45

The values represent the mean of three determinations ± standard deviation.

The extract and excipients, except the magnesium stearate, were blended for 10 minutes by tumbling, then the corresponding amount of magnesium stearate was added and blended for five more minutes; and after that, they were compressed by using a mini-press mono-punch eccentric machine, with a punch set of 7.0 mm in diameter during 4 minutes. The weight of each tablet was 130 mg (Fig. 2). Tablet hardness was measured with a Scout hardness tester. The tablets previously weighted were loaded into a friabilator USP (Electrolab Dual Drum Friability Tester EF-2) and the friability was evaluated in accordance with USP 34-NF 29 (USP 2011). Friability (%) = (W1- W2/ W1) x 100. (W1 = weight of tablets before testing and W2 = weight of tablets after testing).

Figure 2 – Prepared tablets from *Silybum marianum* ethanolic extract.

The disintegration test was conducted following the method established by the USP (USP 2011). A 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 the disintegration test apparatus. The phosphate medium was maintained at a temperature of 37 ± 2 ºC and the time was noted for the entire tablet to complete disintegration.

A USP dissolution test apparatus (Hanson Research SR8PLUS) type II was used for the *in vitro* dissolution test. First, 900 mL of the phosphate buffer pH 7.5 with 2% of sodium lauryl sulfate was placed in a vessel, and the temperature was maintained at 37 ± 0.5 ºC. The speed of the paddle was fixed at 100 rpm. Dissolution samples were then withdrawn at 5 minute intervals. Drug concentration was calculated by measuring the absorbance at 287 nm from the standard calibration curve previously obtained using silymarin (Sigma-Aldrich) and expressed as a percentage of the cumulative drug dissolved. The test was performed in triplicate (USP 2011).

The quantitative analysis of silymarin in F1, F2 and in Laragon 150 commercial tablets (CT) was performed by spectrophotometry (Meghreji *et al*. 2010). All determinations were made in triplicate.

Five tablets of F1, F2 and CT were finely powdered. An amount of the powdered tablet equivalent to 50 mg/tablet (F1, F2) and 150 mg/tablet (CT) of silymarin were weighed accurately, and extracted into 3 × 20 ml portions of chloroform with shaking. The residue was filtered using Whatmann No. 42 filter paper. The filtrate was evaporated to dryness under vacuum and the remaining drug was dissolved in methanol and diluted to 100 mL. The final concentration of silymarin was about 0.5 mg/mL (F1, F2) and 1.5 mg/mL (CT). Suitable dilutions were done with methanol before measurements. As a positive control was used CT because it is developed by a leader laboratory.

NMR (^{1}H-, ^{13}C- and ^{13}C ^{1}H HSQC) spectral data of F2, CT and silymarin were obtained in a Bruker Spectra AC-200 (200 MHz, 50 MHz) in Acetone-d_6 (Lee & Liu 2003; Liu & Lee 2012).

All results were expressed as mean values ± standard deviation (SD). The dissolution data was subject to statistical analysis using a computer program, Graphpad INSTAT tm Copyright 1990–1993 (2.04 version, 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.

Results and Discussion

In the present study, the ethanolic extract of *Silybum marianum* was employed as an active ingredient to design, develop and evaluate tablets by direct compression. The fluid extract was obtained by soxhlet extraction and the concentration of silymarin was determined by UV-visible spectrometry (1.96 mg/mL) (Gul *et al.* 2015).

Two appropriate formulations for direct compression were prepared. Their compositions are shown in Table 1. Both formulations have *S. marianum* extract as active ingredient. Because silymarin has poor solubility, Aeroperl® 300 Pharma was used as carrier. The liquid crude extract of the plant was adsorbed by immersing it in granulated colloidal silicon dioxide (Aeroperl® 300 Pharma) in 1:1 relation. In addition, two lactose excipients of pharmaceutical degree, frequently used in direct compression, were employed as diluent agents: MicroceLac® 100 and FlowLac® 90. Both derive from nature and are frequently used as diluent/binder agents in oral dosage. These kinds of co-processed excipients provide a better tableting performance (Lamešić*et al.* 2017; Mužíková *et al*. 2018).

On the other hand, pre-compression and post-compression parameters were evaluated according to official standards. Table 2 shows the densities and flow properties of physical mixtures containing *S. marianum* ethanolic extract. The powders of both formulations flowed very well, given that the corresponding angles of repose between 7º and 13º were less than 25º. The experimental values indicated that both powder mixtures possess good flow properties and good packing ability, and at the same time they meet the official requirements (Lantz & Schwartz 1990).

The tablets were obtained by direct compression using a mono-punch eccentric machine with 7 mm-diameter punches (Fig. 2). The prepared tablets were evaluated for uniformity of weight, hardness, friability and disintegration time. The experimental results obtained are shown in Table 3. Both batches of the manufactured tablets were acceptable according to the US pharmacopeia. The variation in weight was less than 10% (USP 2011). This parameter confirmed the consistency of dosage units during compression. As soon as to

Table 3 – Results of control tests performed on *Silybum marianum* tablet.

Properties	Formulations	
	F1	F2
Weight variation (mg)	129.7 ± 1.05	134.2 ± 0.61
Friability (%)	0.92 ± 0.015	0.82 ± 0.03
Disintegration time (min)	19.4 ± 0.15	8.05 ± 0.03
Hardness (kg/cm^2)	4.40 ± 0.11	3.70 ± 0.17

The values represent the mean of three determinations ± standard deviation.

friability, both formulations had a loss weighing less than 1%, which would determine a higher resistance to abrasion. In relation to the disintegration time, F2 showed the lowest value that would be related with their lower hardness value. Hardness is an important parameter to estimate the disintegration time, since the resistant tablets do not disintegrate in the time required to satisfy the dissolution specifications (Da Silva Solon *et al.* 2010).

The content of silymarin in F1, F2 and CT was shown in Table 4. All the formulations were within the limits set by the USP (2011).

Table 4 – Analysis of silymarin in *S. marianum* tablet formulations (F1, F2) and commercial tablets (CT).

Formulation	Silymarin Nominal quantity (mg)	Silymarin Found (mg) ± SD
F1	50	49.16 ± 0.0059
F2	50	50.47 ± 0.0067
CT	150	150.30 ± 0.0031

Moreover, the cumulative amount of drug released over time was calculated for both formulations. The *in vitro* dissolution profiles are shown in Figure 3. At 45 minutes Q (%) the experimental values were: 96.430 ± 0.101 (CT), 86.589 ± 0.003 (F2) and 67.533 ± 0.088 (F1).

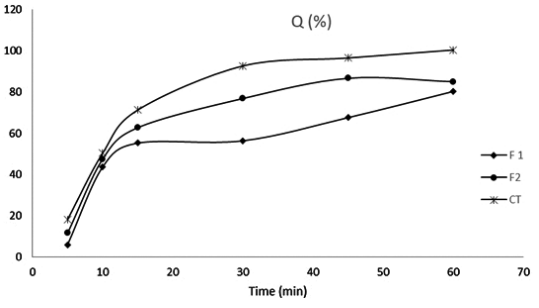


Figure 3 – *In vitro* dissolution profiles test of *S. marianum* tablet formulations (F1, F2) and commercial tablets (CT). profiles test.

The dissolution test for tablets described in the USP indicates that no less than 75% of silymarin content should be dissolved in 45 minutes. Consequently, F2 and CT satisfied this official specification, evidencing their excellent galenic and pharmacokinetic features. Additionally, F2 presented parameters of *in vitro* release closer to CT. These results could be attributed to the absence of microcrystalline cellulose in F2.

Furthermore, mono and bi-dimensional NMR techniques were used to identify silymarin in the manufactured tablets (F2). These data were identified and compared with silymarin from CT and with silymarin Sigma-Aldrich (Kim *et al.* 2003; Bijak 2017). ^{1}H-NMR fingerprint is a useful secondary quality assurance method for the standardization of silymarin. In the ^{1}H-NMR spectrum of F2, in accordance with the information provided by the literature and compared with CT and with silymarin Sigma-Aldrich, the presence of the major constituents was divided into eight

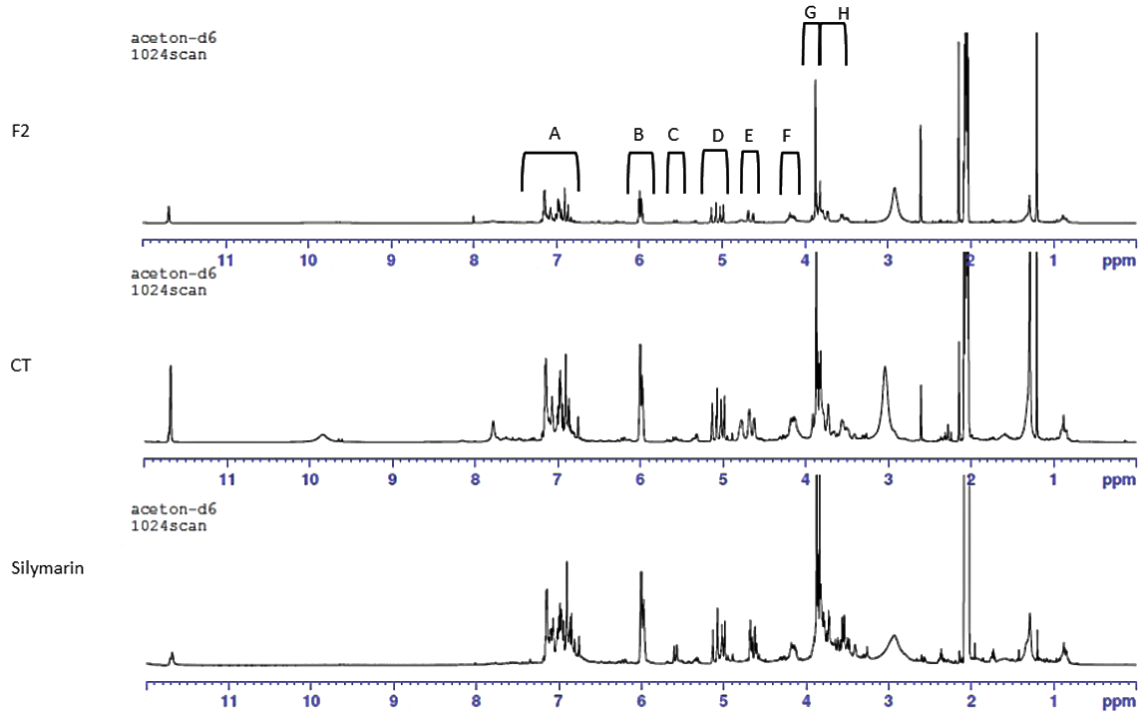


Figure 4 – ^{1}H NMR spectrum of *S. marianum* tablet formulation (F2), commercial tablets (CT) and silymarin).

areas (A-H) (Fig. 4). Each area clearly represented the structural features of flavolignans informed in the literature. The assignment of areas A-H is summarized in Table 5. Among these eight areas, area C represents the unique signal of H-7"of silychristin (II) at 5.61 ppm (*d*, J = 7Hz). Area F only contributed to H-8" of silybin A and B (I), isosilybin A and B (I) at 4.15 ppm as multiplet.

From 2D ^{13}C^{1}H-HSQC twelve regions were determined in the ^{13}C-NMR fingerprint of silymarin of prepared tablets, compared with CT and silymarin Sigma-Aldrich (Fig. 5). The assignment

Table 5 – ^{1}H-NMR fingerprint of silymarin.

Areas	Protons	Assignment
A (δ 6.80~7.20)	H-2', H-5', H-6'	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
B (δ 5.93~6.05)	H-6, H-8	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
C (δ 5.56~5.60)	H-7"	Silychristin (II).
D (δ 4.95~5.15)	H-2	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
	H-7"	Silybin A and B (I), Isosilybin A and B (I).
E (δ 4.60~4.70)	H-3	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
F (δ 4.10~4.25)	H-8"	Silybin A and B (I), Isosilybin A and B (I).
G (δ 3.72~3.90)	OCH_3	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
	H-9"	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
H (δ 3.40~3.70)	H-8"	Silychristin (II).
	H-9"	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).

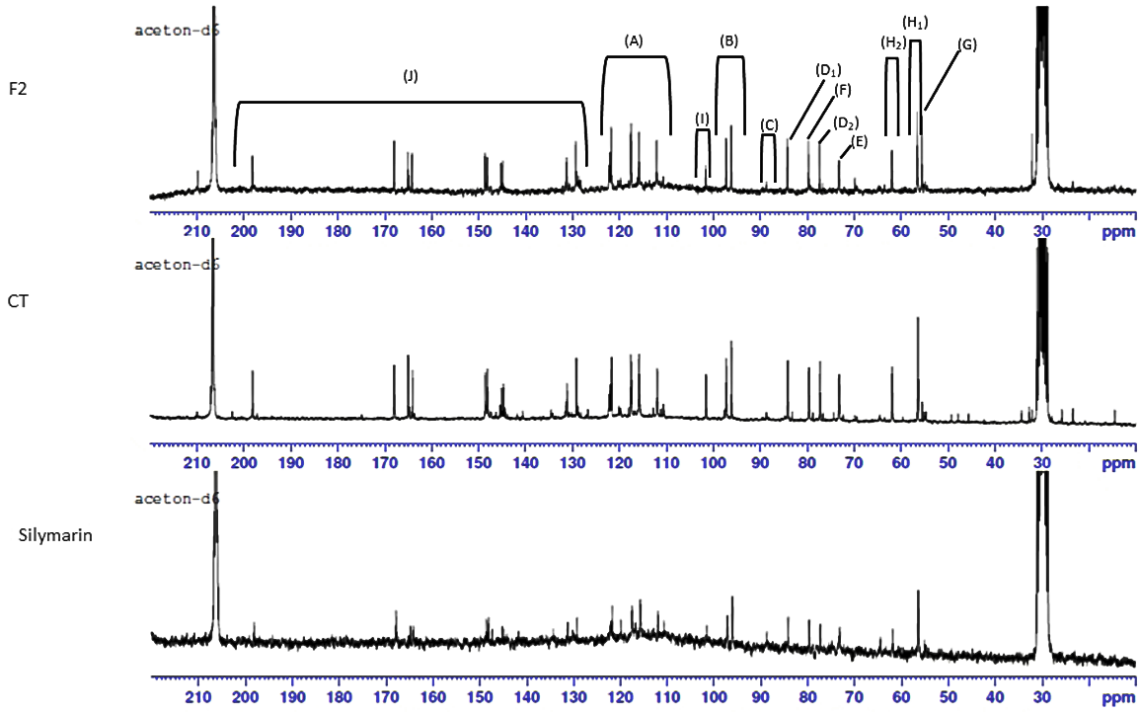


Figure 5 – ^{13}C NMR spectrum of *S. marianum* tablet formulation (F2), commercial tablets (CT) and silymarin.

of areas A-J is shown in Table 6. Among these areas, four were characteristic areas: area C (C-7", d_C 88.67, d) of silychristin (II); area D_2 (C-7', d_C 77.35, d) of silybin A and B (I), isosilybin A and B (I); area F (C-8", d_C 79.73, d) of silybin A and B (I), isosilybin A and B (I) and area H_1 (C-8", d_C56.48, d) of silychristin (II). ^{13}C-NMR fingerprint takes advantage of the fact that samples contain

Table 6 – ^{13}C-NMR fingerprint of silymarin.

Areas	Carbons	Assignment
A (δ 114.05~122.03)	C-2', C-5', C-6'	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
B (δ 96.17~97.24)	C-6, C-8.	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
C (δ 88.67)	C-7"	Silychristin (II).
D_1 (δ 84.20)	C-2	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
D_2 (δ 77.35)	C-7"	Silybin A and B (I), Isosilybin A and B (I).
E (δ 73.25)	C-3	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
F (δ 79.73)	C-8"	Silybin A and B (I), Isosilybin A and B (I).
G (δ 55.58)	OCH3	Silybin A and B (I), Isosilybin A and B (I), Silychristin II).
H_1 (δ 56.48)	C-8"	Silychristin (II).
H_2 (δ 61.95)	C-9"	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
I (δ 101.62)	C-10	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).
J (δ 129.31~198.19)	C-9, C-5, C-7, C-4, C-1', C-3', C-4', C-1", C-3", C-4"	Silybin A and B (I), Isosilybin A and B (I), Silychristin (II).

simplified profiles with minimal signal overlap (Sharmin & Zafar 2017).

In conclusion, the formulation prepared in this study F2 showed excellent technology and quality parameters. This formulation could be used for herbal tablets of fluid extracts with poorly soluble actives, such as silymarin, ensuring their stability by avoiding heat and humidity factors during the manufacturing process.

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