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ORIGINAL RESEARCH PAPER

SILYMARIN FOOD SUPPLEMENTS – ORAL SOLID DOSAGE FORMS

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Abstract: Several tablet formulations containing silymarin were developed, in order to meet the requirements of different markets. Milk thistle - *Silybum marianum* (L.) Gaertn – standardized extracts have proven their positive effect on liver functionality plus other health benefits. Lactose is a widely used excipient for the production of oral solid dosage forms. One important inconvenient of lactose is related to the lactose intolerant potential customers. Cellulose, isomalt and dicalcium phosphate have been selected as alternative possible tablet binders and diluents. Laboratory and pilot batches were studied for each excipient. The pharmacotechnical properties and silybin content of the tablets were measured and recorded in accordance to the European Pharmacopoeia. All pilot batches had results in the desired range of values in order to permit large scale compacting and blistering of the tablets. Currently the formulations containing isomalt and dicalcium phosphate that made the subject of this study are being produced on industrial scale.

Keywords: *cellulose, dicalcium phosphate, isomalt, lactose, milk thistle, silybin, tablet formulation*

INTRODUCTION

Worldwide people are becoming more interested and conscious about their health. The market of food supplements has increased over the years and so has the variety of products in this category [1, 2]. Specific vegetal extracts, minerals, and vitamins have proved their efficiency in sustaining the functions of the main systems of human bodies [3, 4]. One of the organs that contribute essentially to the wellbeing of the organism is the liver. Milk thistle - *Silybum marianum* – standardized extracts have been the subject of several scientific studies that have demonstrated the positive effect of silymarin on liver functionality, regarding the protection against toxic attacks and regeneration [5 - 7].
Lactose is one of the most employed excipients for the production of oral solid dosage forms, especially as tablet binder, tablet and capsule diluent, tablet and capsule filler [8]. One great inconvenient of this excipient is related to the lactose intolerant potential customers.
This study aims to develop formulations for milk thistle tablets, in order to satisfy the requirements of different markets.

MATERIAL AND METHODS

Milk thistle dry extract, refined and standardized - Silymarin, product code 9065110 (Indena, Italy).
The standardized milk thistle extract was analyzed in accordance to the European Pharmacopoeia [9] and all the excipients were of pharmaceutical grade.
Possible interactions between the extract and the excipients were tested by differential scanning calorimetry (DSC); Netzsch calorimeter, model DSC 200F3 Maia.
Laboratory batches (about 500 g): manual homogenization, tableting using a single punch eccentric press.
Pilot batches (about 5 kg): automatic homogenization, tableting using a computer controlled rotary tablet press with interchangeable dies - Fette 102i.
In process-control: height, diameter and hardness tester – Erweka TBH 225 TD, friability tester – Erweka TDR 100, dissolution tester – Erweka TZ 72.
Milk thistle identification and assay: high performance liquid chromatography HPLC – Agilent Technologies 1260 Infinity.

RESULTS AND DISCUSSION

Lactose and three possible substituents were chosen for this study: cellulose, isomalt and dicalcium phosphate. Cellulose is an inert excipient, often used as diluent for oral solid dosage forms [8]. Isomalt provides good pharmacotechnical properties and mild sweetness for the tablets [8]. In comparison with the first two choices, dicalcium phosphate is a relatively new addition to the excipient list.
First of all a lactose containing formulation was developed in order to obtain silybin tablets of 35 mg, 70 mg and 150 mg active ingredients. This was considered the reference formulation. The reference product was a round, biconvex tablet containing *S. marianum* standardized extract equivalent to 35 mg silybin, lactose, starch, pre-gelatinized starch, colloidal silicon dioxide, and magnesium stearate; mean tablet weight

of 140.00 mg. This reference was selected in order to obtain the highest value possible for the ratio tablet number – quantity of raw materials. The reference formulation offered a great advantage for the ongoing development, allowing to dramatically shortening the laboratory batch studies, by starting the tests using directly the previously validated formula. The laboratory batches were quantitatively similar to the reference, the only difference was the nature of the lactose replacing excipient. Possible interactions between the extract containing active ingredients and the excipients were tested by DSC. The stability of the extract was maintained in the presence of the above mentioned substances (Figure 1 - 4).

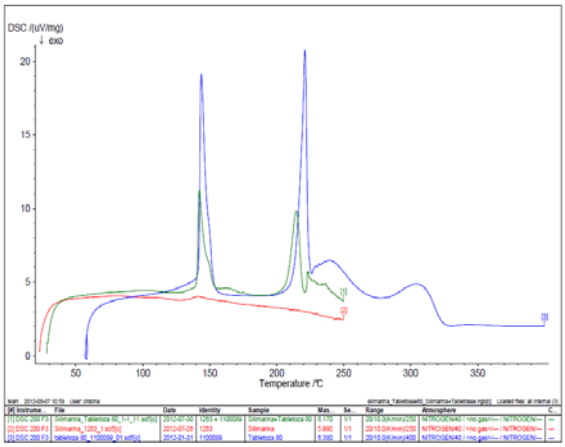

Figure 1. *DSC S. marianum extract-lactose*

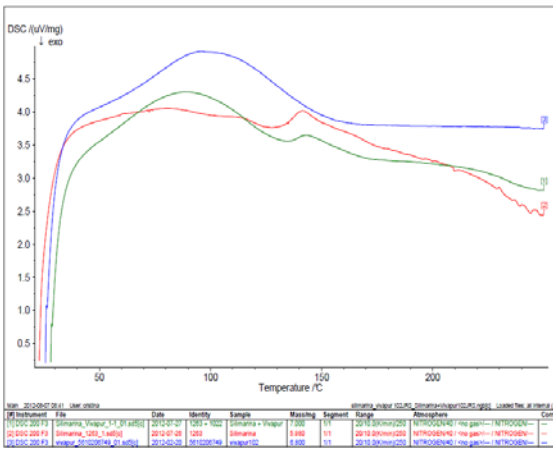

Figure 2. *DSC S. marianum extract-cellulose*

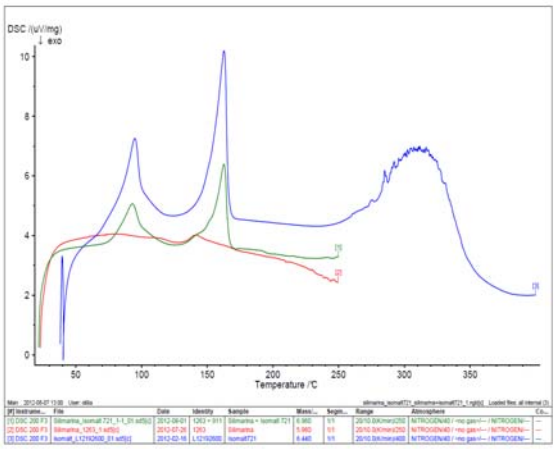

Figure 3. *DSC S. marianum extract-isomalt*

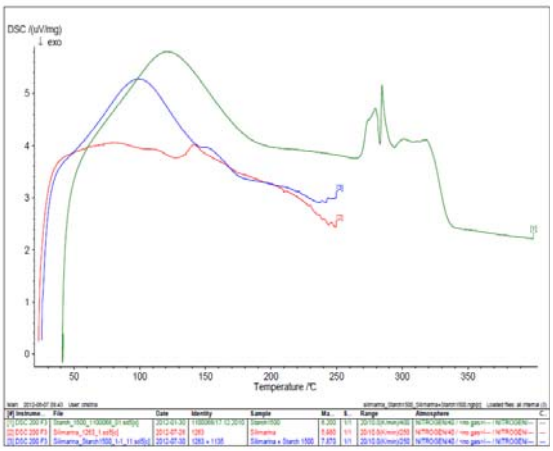

Figure 4. *DSC S. marianum extract-starch*

All the physical-chemical test results of the laboratory batches were compliant to the specification of the bulk product. In order to test the reproducibility of the process and to set a range of values for the machine parameters used for tableting (compression force, pre-compression force), a total of twelve pilot batches were manufactured, three for each excipient: SlbP01LA, SlbP02LA, SlbP03LA – containing lactose, SlbP01CE, SlbP02CE, SlbP03CE – containing cellulose; SlbP01IS, SlbP02IS, SlbP03IS – containing isomalt; SlbP01PH, SlbP02PH, SlbP03PH – containing dicalcium phosphate. The pilot batches had favorable results (Table 1, Figure 5).

Although the cellulose batches comply with the desired specification, the high friability due to the low mechanical resistance may prove problematic for the next step of production - primary packaging, were blisters containing broken tablets are automatically rejected, resulting in low production yields. The gradually variation of the compression force did not solve the problem.

Table 1. *Analysis report of the pilot scale tablet batches odel for drawing a table*

Characteristic, measurement unit	**Admissibility criteria**	**SlbP01LA**	**SlbP01CE**	**SlbP01IS**	**SlbP01PH**
		SlbP02LA	**SlbP02CE**	**SlbP02IS**	**SlbP02PH**
		SlbP03LA	**SlbP03CE**	**SlbP03IS**	**SlbP03PH**
Appearance	Round, intact, biconvex, light brown, pigmented tablet	Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
Average tablet mass, [mg]	140.00 ± 5 % (133.00-147.00)	139.55	139.40	138.92	139.74
		140.30	140.52	139.28	138.36
		139.62	139.25	139.32	139.94
Mass uniformity	Compared to the average mass: Minimum 18/20: M_i ± 7.5% Maximum 2/20: M_i ± 15%	Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
Diameter, [mm]	7.0 ± 0.1 (6.9 – 7.1)	7.0	7.0	7.0	7.0
		7.0	7.0	7.0	7.0
		7.0	7.0	7.0	7.0
Height, [mm]	3.5 ± 0.2 (3.30 – 3.70)	3.5	3.6	3.5	3.5
		3.6	3.6	3.5	3.4
		3.5	3.5	3.5	3.5
Hardness, [N]	30-80	38	32	40	56
		39	33	41	56
		38	30	40	54
Disintegration time, [minutes]	Maximum 15	0 min 41 s	0 min 30 s	1 min 05 s	0 min 58 s
		0 min 45 s	0 min 32 s	1 min 01 s	0 min 56 s
		0 min 42 s	0 min 28 s	1 min 01 s	0 min 58 s
Friability, [%, m/m]	Maximum 1	0.16	0.47	0.18	0.12
		0.17	0.44	0.17	0.13
		0.17	0.42	0.19	0.12
Identification	Retention time for silicristin, silidianin, silibinin A, silibinin B, isosilibinin A, isosilibinin B of the test solution similar to the standard solution.	Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
		Complies	Complies	Complies	Complies
Assay - silybin, [mg]	35.00 ± 5 % (33.25 – 36.75)	34.04	34.42	33.95	35.21
		34.56	34.26	34.02	34.88
		34.22	34.05	34.21	34.68

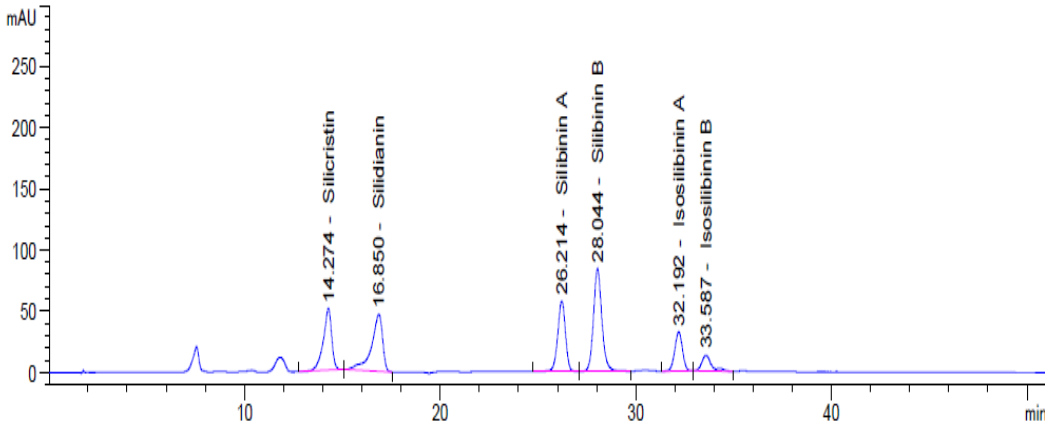

Figure 5. *HPLC – identification and assay of S. marianum extract in oral solid dosage forms*

A possible way to continue the research regarding cellulose and vegetal extracts formulation would be to increase the excipient percentage or to change the commercial sort of cellulose, in order to modify the compressibility of the powders [10].
The isomalt formulation provides all the characteristics for a sustainable production process, in accordance to studies that claim the use of polyols as a present and future trend for the pharmaceutical industry [11, 12]. The consumer benefits of isomalt include a caloric intake reduced to half in comparison to regular sugar and no significant increase of blood glucose or insulin levels [13]. The possibility of replacing sugar with polyols and other sugar-free sweetening ingredients was taken into consideration by health authorities and committees [14].
The dicalcium phosphate formulation had excellent flow properties, good pharmacotechnical characteristics and the production process was reproducible. This excipient is present in numerous new formulations, in order to improve the flow and compressibility of powder mixtures [15, 16].

CONCLUSIONS

Oral solid dosage forms containing milk thistle extracts are widely used in order to support liver functionality and offer several other benefits. Lactose is one of the most employed excipient for tablets, ensuring excellent pharmacotechnical properties. Due to the potential lactose intolerant customers, many markets require lactose free food supplements. Four new formulations for milk thistle extract tablets were created, containing lactose and possible alternatives such as: cellulose, isomalt, and dicalcium phosphate. Currently the formulations containing lactose, isomalt and dicalcium phosphate that made the subject of this study are being produced on industrial scale.

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