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APPLYING A SOLID DISPERSION SYSTEM FOR ENHANCING THE DISSOLUTION OF LIGNANS-ENRICHED FRACTION FROM *SCHISANDRA SPHENANTHERA* EXTRACT

Le Thi Kim Van[1,*], Xa Thi Phuong Thao[1], Nguyen Thi Le[2], Le Bich Nhai[1], Dao Anh Hoang[1], Nguyen Thi Ha Ly[1], Nguyen Minh Khoi[1]

[1]National Institute of Medicinal Materials (NIMM);

[2]Vietnam - Korean Institute of Science And Technology (VKIST)

*Corresponding author: lethikimvannimm@gmail.com

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Summary

Applying a Solid Dispersion System for Enhancing the Dissolution of Lignans-Enriched Fraction from *Schisandra sphenanthera* Extract

This paper aimed to improve the dissolution of biologically active lignans from *Schisandra sphenanthera* (SS) *via* solid dispersion system (SDS) formulation. The lignans-enriched fraction was obtained from an ethylacetate-soluble extraction, is poorly soluble in water. To ameliorate the dissolution of major lignans from this extract, SD formulation was prepared with the combination of Tween 80 and PVP K30 as carriers by using the solvent evaporation method. The optimal formulation containing 1% Tween 80 and 4% PVP K30 showed the release of over 70% of schisandrin (SC) and gomisin B (GB) contents in dissolution profiles after 30 minutes, the dissolution of schisandrin A (SCA) was simultaneously improved in comparison with pure extract in similar condition testing. The combination of hydrophilic polymer and surfactant in the SDS formulation could be effective in enhancing the dissolution of the active lignans from SS. This is a promising strategy to improve the bioavailability of the drug.

Keywords: *Schisandra sphenanthera, Lignans, Solid dispersion, Dissolution, Formulation, Solubilization.*

1. Introduction

Phytochemical investigations of *Schisandra sphenanthera* Rehd. et Wils (SS) have reported a variety of natural constituents including lignans, triterpenes, volatile oils, and polysaccharides [1]. Pharmacological studies have shown SS possessed wide-range bioactivities, such as antitumor, antioxidant, anti-inflammatory, osteoblastic, immune regulation, neuroprotective, kidney protection, hepatoprotective, and antiviral

activities [1]. Major active lignans in SS extract counteracted acetaminophen (APAP)-induced hepatotoxicity by regulating the NRF2-ARE and p53/p21 pathways. Also, Schisandrol B could protect against acetaminophen-induced hepatotoxicity by inhibiting CYP-mediated APAP bioactivation and regulation of p53, p21, CCND1, PCNA, and BCL-2 to promote liver regeneration. In addition, SS could also facilitate liver regeneration after partial hepatectomy in mice [2]. However, the pharmacokinetic analysis for major lignans present in the hexane-soluble extract indicated that these lignans may have low bioavailability. Additionally, because of the poor aqueous solubility of the hexane-soluble extract, it seemed as though it would be rather arduous to develop beverages using the lignan-enriched fraction [3].

There are several formulation strategies for poorly soluble drugs. The commonly employed strategies are crystal modifications, particle size reductions, amorphizations, self-emulsifications, and pH modifications [4]. Several previous approaches have been attempted to enhance the dissolution of lignans from SS extract for preparation. Jin Pei et al researched SS lignans-loaded enteric nanoparticles. This study was prepared and evaluated SS lignans (composed of deoxyschisandrin (DA) and schisantherin A (SA))-loaded enteric nanoparticles produced by a novel toxic solvent-free modified spontaneous emulsification solvent diffusion (SESD) method. An organic SS lignans/Eudragit® S100 solution was injected into an aqueous poloxamer 188 solution under agitation. The nanoparticles were characterized by size distribution, morphology, encapsulation efficiency (EE) and physical stability of the drug, wettability, *in vitro* release, and *in vivo* bioavailability. Nanoparticles with a smooth surface and dense structure were obtained with high EE (EE_{DA} > 90%; EE_{SA} > 85%). The drug was in a noncrystalline state in the matrix and physically stable for 120 days at room temperature. *In vitro* drug release study, the drug dissolution rate from the nanoparticles was significantly enhanced compared to the physical mixture and the pure drug. An almost 2.8-fold increase in oral bioavailability of SA from nanoparticle suspension was observed as compared to the pure drug. The increased relative bioavailability (Fr) of 188.11% indicates a remarkable improvement in the oral absorption of SA [5]. Young Hee Choi et al prepared to improve the dissolution of lignans from lignan-enriched fractions *via* SD formulation with different hydrophilic polymers. Among the tested carriers, poloxamer 407 was most effective in enhancing the release of active lignans from the extract. Compared to the pure extract, poloxamer 407-based SD significantly increased the dissolution of nine active lignans by 1.6 to 300-fold in water. SD also leads to the solidification of sticky extract, providing better flowability and ease of handling [6]. Solid dispersion (SD) formulation with hydrophilic carriers is one of the most widely used approaches to enhancing the dissolution of poorly water-soluble drugs and natural products. For example, poloxamer 407-based SD of valsartan markedly increased the solubility and dissolution of valsartan, resulting in approximately seven-fold enhancement in its oral exposure. Previous studies have also demonstrated that the solubility and dissolution rate of phytochemicals such as curcumin and biochanin A were significantly improved by SD preparation with Solutol HS15. The enhanced drug dissolution from SD & formulation could be the consequence of a combination of several factors, including particle size reduction, change in drug crystallinity, and better wettability of drugs in the presence of hydrophilic carriers [6].

Therefore, this paper aimed to develop an SD formulation that would improve the dissolution of major active lignans from the extract. SD formulations were prepared by using the solvent method and then evaluated the dissolution profiles of three major lignans in SS extract.

2. Materials and methods

Materials

Schisandrin (**SC**) (CAS 1609895; Lot: F00810; purity: 98%), gomisin B reference substance (**GB**) (CAS: 58546-55-7, LOT: PRF10042941, purity: 98 %) and schisandrin A reference substance (**SCA**) (CAS: 61281-38-7; Lot: BP1261, purity: 98%) were purchased from Biopurify Phytochemicals Ltd. Florite R was provided by Tomita Pharmaceutical Co., Ltd, Japan. Magnesium carbonate, Polyvinylpyrrolidone (PVP K30), Tween 80, and *n*-octanol were purchased from China. Acetonitrile (ACN) and ethanol 96% were obtained from Fisher. Double distilled water was provided by the National Institute of Medicinal Materials. All other chemicals were of reagent grade and all solvents were of HPLC grade.

Preparation of the lignans-enriched SS extract

Briefly, SS dried fruits (10 kg) were ground and extracted with ethanol 80% (v/v) two times and the extract solution was evaporated in vacuo, yielding a crude extract. This crude extract was next dissolved in ethyl acetate (EtOAc). The EtOAc soluble fraction was filtered and

evaporated in order to obtain the lignans-enriched SS extract used for the present work. The results were summarized in **Table 1.**

Preformulation study

Linearity: Five standard solutions were prepared by diluting the stock solution with the same solvent. The calibration curve was constructed by plotting the peak area against each concentration. The slope, y-intercept and linearity of the curve were determined by linear regression.

Determination of n-octanol/water partition coefficients of SC, GB, and SCA: The distribution of SC, GB, and SCA between the equal amount of *n*-octanol as oil phase and water were determined by the method in previous literatures [7],[8]. Prior to the study, an equal amount of *n*-octanol and water were mutually saturated in the shaker overnight for at least 12 hours. After the equilibrium had been reached, the two phases (presaturated water with oil phase & presaturated *n*-octanol with water) were separated and stored for further use. An excess amount of lignans-enriched SS extract was dispersed into the mixture of *n*-octanol and water and stirred using an agitation machine with a speed of 200 rpm. After 48 hrs, the two phases were separated by centrifugation (12000 rpm, 10 min). The oil phase was diluted with an appropriate ratio of EtOH. All the samples in oil and aqueous phase were filtered through the PTFE syringe filters (0.45 µm) before HPLC analysis. The experiment was conducted at 25 ± 0.5°C. The apparent partition coefficients (*P*) were calculated using the following equation:

$$\log P = log\left\{\frac{n \times S_o}{S_a}\right\}$$

Whereas n was the diluted ratio, S_o and S_a were the S peaks of markers in the *n*-octanol and water phases, respectively.

Aqueous solubilities of SC, GB and SCA: Solubility studies were performed to determine the equilibrated solubility of **SC, GB** and **SCA** in water at 25 ± 0.5°C. An excess amount of lignans - enriched from SS extract was added into 5 mL of water and the mixture was agitated at 500 rpm for 24 hrs. The sample was centrifuged and the supernatant was filtered in through a 0.22 µm membrane, diluted with EtOH, and analyzed by the HPLC method.

Preparation of solid dispersions

Preparation of SD formulations were prepared by combining hydrophilic polymers and surfactants and then their effectiveness in improving the dissolution of biologically active lignans was evaluated. SDs were prepared by using the solvent method. Briefly, the SDS of SS extract with different ratios of tween 80 and PVP K30 (**Tables 3 and 4)** were dissolved in ethanol. After vigorous mixing, all solvents were removed under a vacuum (Buchi) at 60°C. The obtained SDs were dried with mixture carriers containing Florite R and magnesium carbonate (1:10) and then milled and passed through a sieve of 125 µm. Each batch contained 10 g of lignan-enriched extract.

Assay of lignans content in preparation

The analytical method was validated for system suitability, specificity, calibration curve, accuracy, precision, detection limit, and quantitation limit following the current ICH guidelines in the previous paper [9]. The 0.2-gram powder was accurately weighed and refluxed with 20 mL ethanol for 30 min. Finally, the solution was transferred to a 25 mL volumetric flask and replenished with ethanol for sufficient. The solution was filtered through a 0.45 µm membrane filter prior to HPLC analysis. The drug content was determined using the standard calibration curve developed with the concentration ranging from **6.75 - 108** µg/mL for schisandrin, **5.675 - 90.8** µg/mL for gomisin B and **56.5 - 104** µg/mL for schisandrin A, respectively. The stock and working solutions were stored at 4°C.

***HPLC conditions*:** Mobile phase: Acetonitrile (ACN) and water (H_2O)

Time (mins)	0-17	17-35	35-50	50-55	55-60
% ACN	50	50-75	75	75-50	50
% H_2O	50	50-25	25	25-50	50

Chromatography system: Gemini® C_{18} column (4.6 x 250 nm, 5 µm); flow rate: 0.8 mL/min; injection volume: 10 µL; detector: UV 254 nm, column temperature was set up at 25°C. Identify the retention times of the peaks corresponding to markers. The percentages of each lignan loading were calculated in the samples taken: Chromatography system

$$\textbf{Result (\%)} = \frac{C_t \times V \times P}{m \times 10 \times (100 - a)}$$

Where: C_t is the concentration of *sample solution* calculated by calibration curve (µg/mL); V (mL) is the volume of *sample solution*. m (mg) is the weight of the sample taken for analysis; B is the moisture content of the sample; P is the purity of the standard reference.

Dissolution studies

The USP type II (paddle apparatus) dissolution tester in Dissolution Tester DT 70 (Pharmatest, Germany) was used to evaluate the *in vitro* dissolution of lignans-loaded SD formulations. The rotation speed was set up at 100 rpm. Each formulation at the dose equivalent to 305 mg of crude extract was exposed to 900

mL of water as dissolution medium, maintained at 37 ± 0.5°C. At the interval times of 5, 10, 15, 30, 45, 60, 90, and 120 mins, 10 ml of dissolution sample was withdrawn and filtered through a 0.45 µm pore-sized PTFE syringe filter to determine the percentage of markers released by HPLC assay and the dissolution medium was replenished immediately with the same volume of fresh medium. Each sample was done in triplicate. The dissolution profiles of three lignans from the SD formulation were evaluated in water and compared to those from an untreated pure extract. For the comparison of dissolution profiles between formulations, the similarity factor (f_2) should be estimated by using the following formula:

$$f_2 = 50 \times log\left\{\left[1 + \frac{1}{n}.\sum_{t=1}^{n}(R_T - T_T)^2\right]^{-0.5} \times 100\right\}$$

Whereas f_2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the test and T(t) is the mean percent test drug dissolved at time t after initiation of the test. The f_2 values from 50 to 100 indicated that the difference in dissolution rates was considered insignificant.

All experiments were repeated in triplicate. The data were presented as means ± SD (standard derivation) and analyzed by Microsoft Excel 2019.

3. Results and discussion

Preformulation study

Table 1. Summary of the extract process

	Ripe fruit	Total Ethanol extract	Lignan-enriched extract
Lignan content (%)	0.58	1.25	5.48
Yield of recovery (%)	-	77.30	84.47

Table 1 summarized the results of extracting raw materials. The results obtained 5.48% of mixed lignans (SC, GB, SCA) from medicinal herbs with lignans content above 0.5% through two steps as mentioned in which the lignans content in the EtOAc fraction was 10 times higher than in raw materials. The lignan-enriched extract helps to facilitate the preparation process to increase the amount of drug loading per unit thus reducing the number of doses used.

Table 2. Preformulation study

Characteristics		SC	GB	SCA
Calibration curve[a]		y = 29598.83x + 15748.17	y = 25428.70x + 6799.29	y = 23523.66x + 14747.04
Correlation coefficient (r^2)		r^2 = 1.0000	r^2 = 1.0000	r^2 = 1.0000
Concentration range (µg/mL)		6.75 - 108	5.675 - 90.8	6.5 - 104
% loading		2.72 ± 0.08	1.08 ± 0.03	1.68 ± 0.06
Saturated concentration (µg/mL)		14.7	2.47	0.7
Log $P_{o/w}$		2.23	4.28	3.60
Dissolution (%)	5 min	15.93	-[b]	-[b]
	10 min	33.41	-[b]	-[b]
	15 min	51.06	-[b]	-[b]
	30 min	**61.90**	**3.21**	-[b]
	45 min	63.98	4.68	-[b]
	60 min	66.01	5.41	-[b]
	90 min	75.47	8.56	-[b]
	120 min	76.55	11.17	-[b]

[a] *y is the peak area (mAU*min) and x is the concentration of drug (µg/mL) (n=3);* [b] *Undefined.*

The calibration curves were obtained by plotting peak areas against concentrations (**Table 2**). The results of the regression analysis were shown in **Table 2.** Equations in the table represented the relationship between response areas and concentrations of three markers, where y stands for peak area and x for concentration. The three derivatives exhibited good linearity over the range tested with the correlation coefficients r^2 all above 0.99 as shown in the following Fig.s in **Table 2.**

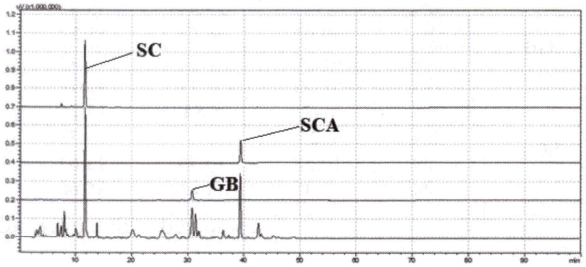

Fig. 1. Chromatography of SC, SCA, GB reference standards and lignans-enriched SS extract.

The results showed that the solubility of **SC, GB** and **SCA** in water at 25°C ± 0.5 was 14.7 mg/mL, 1.08 mg/mL and 1.68 mg/mL, respectively. **Table 2** shows logP values of **SC, GB** and **SCA** at room temperature, respectively. The logP value of **SC** was found to be 2.23 whereas the Fig. for **GB** and **SCA** were shown to be more lipophilic with logP values of 4.28 and 3.60, respectively. Thus, these markers could be classified into group of low solubility and high permeability according to BCS. Besides that, the accumulated dissolution of lignans in preformulation showed the release of below 70% of markers content within 30 minutes which raised the requirement for the amelioration of lignans solubility in preparations to enhance bioavailability.

The ratio of Tween 80 in the formulation

The effect of the Tween ratio on the solubility of lignans was investigated in **Table 3.**

Table 3. Effect of Tween 80 on the aqueous dissolution of SC, GB, and SCA in SD formulations

Markers	Tween 80	Dissolution (%) / min								f_2[c]
		5	10	15	30	45	60	90	120	
SC	0%	15.93	33.41	51.06	61.90	63.98	66.01	75.47	76.55	
	1%	49.82	73.25	84.24	91.16	91.62	94.01	94.04	93.71	26
	2%	49.20	65.09	76.11	82.94	85.84	87.81	89.21	89.81	31
	5%	47.78	68.13	80.74	94.37	97.47	98.18	99.90	100.00	26
	10%	79.5	95.1	99.1	101.1	100.9	101.1	101.5	100.9	18
GB	0%	-	-	-	3.21	4.68	5.41	8.56	11.17	
	1%	-	23.49	35.45	49.09	38.81	51.46	56.68	58.97	21
	2%	7.74	15.00	24.78	35.04	41.98	47.03	50.70	53.50	24
	5%	5.27	11.99	18.49	32.61	41.13	47.67	53.39	57.13	24
	10%	11.12	23.18	33.09	43.88	48.10	50.39	52.37	57.58	21
SCA	0%	-	-	-	-	-	-	-	-	
	1%	-	8.84	10.25	11.94	11.83	19.46	25.88	25.39	40
	2%	2.20	4.77	11.42	15.88	20.29	22.76	25.41	28.13	37
	5%	-	2.69	6.72	12.33	17.19	18.37	25.71	27.98	39
	10%	4.01	11.42	19.03	25.73	30.96	33.78	36.06	35.04	29

[c]: *compared with raw materials.* -: *Undefined.*

Obviously, the release of biologically active lignans from the untreated pure extract was low. The dissolution of all lignans was significantly promoted with a Tween 80 based-SD formulation. The results of the dissolution of lignans (**Table 3**) showed that when the ratio of Tween 80 was raised in the formula, the dissolution tend to increase and improve compared to the pure extract form ($f_2 <$ 50). **SC** has a solubility of over 70% after 30 min, but the solubility of **GB** or **SCA** is less than 70%, this may be due to the hydrophobic properties of the matrix making it difficult to diffuse the active ingredients in the medium dissolution. There was no difference in the dissolution profiles of **SC, GB,** and **SCA** in various ratios of Tween 80 in investigated samples. Simultaneously, a large amount of Tween incorporated in the formula can cause a semi-solid formation that is less suited to developing various dosage forms, including tablets, and capsules. Therefore, the study selected Tween 80 of 1% for further studies.

The ratio of PVP K30 in the formulation

The effect of PVP K30 on the dissolution of markers was demonstrated in **Table 4.**

Table 4. Release profiles of **SC, GB** and **SCA** from different formulations in water

Markers	PVP K30	Dissolution (%) / min								f_2[d]
		5	10	15	30	45	60	90	120	
SC	0%	49.82	73.25	84.24	91.16	91.62	94.01	94.04	93.71	-
	2%	81.21	86.04	87.36	86.30	83.56	88.79	86.15	85.66	38
	4%	97.02	92.71	98.98	102.36	100.37	98.73	99.49	100	28
	6%	96.50	96.82	98.47	98.02	96.13	99.14	94.37	97.75	28
GB	0%	-	23.49	35.45	49.09	38.81	51.46	56.68	58.97	-
	2%	30.02	46.74	55.27	62.12	61.95	66.69	60.06	64.27	36
	4%	41.38	46.38	77.42	82.27	83.48	82.52	82.46	82.30	23
	6%	51.32	52.11	42.79	74.13	74.45	82.58	74.64	78.03	26
SCA	0%	-	8.84	15.25	11.94	11.83	19.46	25.88	25.39	-
	2%	6.22	13.47	19.38	31.07	29.59	35.64	30.94	32.86	46
	4%	10.58	13.44	43.63	42.34	39.24	45.94	46.09	44.66	32
	6%	11.47	11.81	35.66	43.18	42.42	48.23	42.29	48.51	32

[d]: compared with the formulation containing 1% of tween 80.

The incorporation of PVP K30 in the SD of SS extract can be effective in facilitating the solubilization of biologically active lignans and promoting the faster and greater dissolution of

biologically active lignans due to hydrophilic matrix. Dissolution profiles of GB were higher when increasing the ratio of PVP K30 in the formula, demonstrating a significant difference with a lower PVP K30 as this carrier could facilitate the diffusion of markers in medium dissolution. However, the formula containing 4 or 6 % of PVP exhibited a similar dissolution profile. Simultaneously, too much incorporated PVP K30 per unit can increase humidity and enhance average mass. Therefore, PVP K30 of 4% was selected to prepare the SD of lignans enriched from SS extract.

4. Conclusion

The study was successful in the formation of solid dispersion loaded lignans-enriched *Schisandra sphenanthera* extract with tween 80 and PVP K30 promising for improving the dissolution of poorly soluble lignans into aqueous medium.

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EVALUATION OF THE SKIN IRRITATION AND ANTI-INFLAMMATORY ACTIVITY OF A GEL CONTAINING *PERILLA FRUTESCENS* EXTRACT AND *GLYCYRRHIZA URALENSIS* EXTRACT

Huynh Thi My Duyen *, Le Thi Minh Ngoc, Tran Thi Mong Tuyen, Duong Tuyet Ngan, Pham Thi Ngoc Linh, Nguyen Nhu Huynh, Nguyen Nhu Y, Mai Le Gia Ngan, Nguyen Ngoc Nguyen Trang, Lam Vi Trang

Can Tho University of Medicine and Pharmacy

*Corresponding author: htmduyen@ctump.edu.vn

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Summary

Evaluation of the Skin Irritation and Anti-Inflammatory Activity of a Gel Containing *Perilla frutescens* Extract and *Glycyrrhiza uralensis* Extract

The study prepared the herbal gel with 0.75% of carbopol 940, 0.85% of *Perilla frutescens* (PF) extract, 0.7% of *Glycyrrhiza uralensis* Fisch (GU) extract. and other excipients. *In vitro* testing showed that the product was non-irritating and safe; the anti-inflammatory activity of the gel had an IC_{50} value of 303.33 µg/mL. The total polyphenol content and flavonoid content were 2.9 mg GAE/g and 1.82 mg QCE/g, respectively. The research prepared and evaluated the skin irritation of the gel by the HET-CAM (Hen's EggTest on the Chorioallantoic Membrane) method. At the same time, the study assessed the anti-inflammatory activity and quantified polyphenols and flavonoids in the finished gel.

Keywords: *Perilla frutescens, Glycyrrhiza uralensis, Gel, Anti-inflammatory, HET-CAM, Irritation.*