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Extraction and Purification of Eriocitrin from *Mentha piperita*

[1]Duygu Mısırlı, [2]Merve Soy, *[1]**Zafer Ömer Özdemir**, [1]Mahfuz Elmastaş

[1] Health Sciences University, Hamidiye Faculty of Pharmacy, Hamidiye Pharmacy Program, Istanbul, Turkey.
[2] University of Health Sciences, Hamidiye Institute of Health Sciences, Pharmacognosy (PhD), Istanbul, Turkey.
* Corresponding author, e-mail: ozdemirz@gmail.com

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Abstract - Currently, the practice of using plants for treatment is a multidisciplinary field referred to as "phytotherapy." The presence of secondary metabolites in plants is one of the main reasons for their utilization in the pharmaceutical sector. Research assessing the scientific use of plants utilized in Traditional and Complementary Medicine (GETAT) inside modern medicine would enhance the healthcare system by delivering highly efficient pharmacological molecules with minimal adverse effects, potentially stimulating the country's economy. In this article, the levels of 16 specific phenolic compounds in *Mentha piperita*, *Mentha dumoretum*, *Mentha spicata* and *Mentha villosa nervata* were investigated and the purification of eriocitrin from *Mentha piperita* was attempted. Eriocitrin is a secondary metabolite that has been shown to have various benefits for human health. The process of purifying bioflavonoid combinations containing eriocitrin from local natural sources is becoming increasingly important. The HPLC analysis revealed that the butanol extract of *Mentha piperita* contained the highest concentrations of eriocitrin. Therefore, the purification process was carried out utilizing these extracts obtained from *Mentha piperita*. This research has yielded eriocitrin with a purity of 92%.

Keywords: Extraction, Mentha species, Chromatography, Eriocitrin

Mentha piperita'dan Eriositrin'in Ekstraksiyonu ve Saflaştırılması

Öz - Günümüzde, bitkileri tedavi amaçlı kullanma uygulaması "fitoterapi" olarak adlandırılan çok disiplinli bir alandır. Bitkilerdeki sekonder metabolitlerin varlığı, bunların ilaç sektöründe kullanılmasının başlıca nedenlerinden biridir. Geleneksel ve Tamamlayıcı Tıpta (GETAT) kullanılan bitkilerin modern tıpta bilimsel kullanımını değerlendiren araştırmalar, en az yan etkiye sahip yüksek verimli farmakolojik moleküller sunarak sağlık sistemini geliştirecek ve potansiyel olarak ülke ekonomisini canlandıracaktır. Bu makalede *Mentha piperita*, *Mentha dumoretum*, *Mentha spicata* ve *Mentha villosa nervata*'daki 16 spesifik fenolik bileşiğin düzeyleri araştırılmıştır ve *Mentha piperita*'dan eriositrin saflaştırılmasına çalışılmıştır. Eriositrin insan sağlığı için çeşitli faydaları bulunduğu gösterilmiş bir sekonder metabolittir. Yerel doğal kaynaklardan eriositrin içeren biyoflavonoid kombinasyonlarının saflaştırılması süreci giderek daha önemli hale gelmektedir. HPLC analizi, *Mentha piperita*'nın butanol özütünün en yüksek eriositrin konsantrasyonlarını içerdiğini ortaya koymuştur. Bu nedenle, saflaştırma işlemi *Mentha piperita*'dan elde edilen bu özütler kullanılarak gerçekleştirilmiştir. Bu araştırma sonucunda %92 saflıkta eriositrin elde edilmiştir.

Anahtar kelimeler: Ekstraksiyon, Mentha türleri, Kromatografi, Eriositrin

1. Introduction

Nowadays, treatment with plants is an interdisciplinary science known as "phytotherapy". The Green Wave or Green Medicine, known as the movement of returning to nature in treatment, has become a growing interest worldwide (Yadav et al., 2024). One of the primary factors for the use of plants in the pharmaceutical industry is the secondary metabolites they contain. These metabolites are used not only as raw materials for the pharmaceutical industry but also in cosmetics, food additives, agricultural pesticides, and many other chemical sectors. The use of herbal additives in various industrial fields is quite common in Europe. To enhance the efficacy of organic compounds

[1] Corresponding author: ozdemirz@gmail.com

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derived from natural sources and to develop modified new drugs, the isolation and characterization of secondary metabolites have gained importance, leading to significant research in this area in recent years. Although Türkiye has rich flora, it cannot utilize this wealth adequately due to the lack of scientific and technological applications. Consequently, Türkiye has not achieved its deserved place in the global market regarding herbal products. Studies evaluating the scientific usage of plants used in the field of Traditional and Complementary Medicine (GETAT) in modern medicine will contribute to the health system by introducing low-side-effect effective drug molecules and potentially boost the country's economy (Talhaoğlu, 2021; Uçar et al., 2020). It is known that flavonoid-structured secondary metabolites, which are widespread in plants, have been a particularly noteworthy group in recent years (Demirtas et al., 2013; Erenler et al., 2024).

There are 15 species of mint, including 6 hybrids, in the flora of Türkiye. Among these, the spearmint group (*M. spicata* and *M. villosa nervata*), rich in carvone, is used in spices, food, and cosmetics, while the peppermint group (*M. piperita*) is primarily used for pharmaceutical and essential oil production. The commercial value of naturally distributed Mentha species is limited. Among these species, the hybrid *M. dumetorum* is an interspecific hybrid of *M. aquatica* and *M. longifolia*. This species has been identified in the flora of Türkiye in recent years. Due to its limited distribution and less preferred aroma, studies on it are quite limited. Although it was not recorded in the flora of Türkiye researched by Davis, recent studies have identified it in the Black Sea region (Yesilada, 2005). In addition to its natural distribution in Türkiye, it has been noted that it is cultivated as an ornamental plant in Anatolia due to its more attractive appearance than other mint species. Cultural genotypes collected from various regions have been examined for yield and essential oil characteristics (Saka et al., 2024).

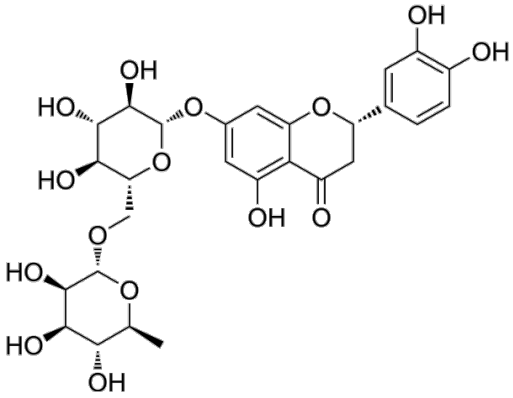

Figure 1. Structure of eriocitrin.

Studies on the phenolic compound content in mint species have identified numerous compounds. Rosmarinic acid, as with all species belonging to the Labiatae family, is an important phenolic acid in mint species. Additionally, eriocitrin is a highly valuable compound isolated in mint species (Akşit et al., 2014). Mint species have various uses beyond essential oils, including spices (*M. spicata*, *M. villoso nervata*) and herbal tea (*M. piperita*). Due to their antioxidant activities, plants have become important in functional food mixtures in preventive medicine in recent years. Among the phenolic acids in mint species, rosmarinic acid, caffeic acid, flavonoids such as eriocitrin, and luteolin are important antioxidants (Fatih et al., 2017; Teğin et al., 2022).

In the literature, articles related to citrus species are encountered in the purification of the eriocitrin compound. Citrus species are important due to the bioflavonoids they contain, which are used in the treatment of cancer, liver disorders, and many inflammation-related conditions. Scientific studies have shown that many plants with records of use in cardiovascular diseases, varicose veins, and hemorrhoid treatments contain flavonoid compounds. Numerous scientific studies have been conducted on the biological activities of flavonoids (Ángeles Ávila-Gálvez et al., 2021; Liu et al.,

2019). The health effects of these compounds vary depending on the amount consumed and their bioavailability (Ferreira et al., 2020).

Unlike citrus species, recent studies on the eriocitrin compound found in mint species report that it has no side effects but possesses anticancer, cholesterol-lowering, and antioxidant activities. Furthermore, it has been documented to counteract diet-induced hepatic steatosis, exhibit efficacy in the management of cardiovascular disorders, and be employed in the prevention of neurodegenerative conditions such as Alzheimer's and Parkinson's owing to its cholinesterase inhibitory properties (Ferreira et al., 2021; Guo et al., 2019; Kwon & Choi, 2020). Considering these studies, it is predicted that the eriocitrin compound will become a prospective raw material for the health, food, cosmetic, and pharmaceutical industries. Therefore, the production or purification of this compound will become an important issue in the future. Currently, it is observed that the research use of this compound is sold at high prices. The price of 1 mg of 98% pure eriocitrin for analytical purposes is €264 in chemical catalogs (Sigma Aldrich). Dietary supplements containing small amounts of eriocitrin, such as lemon bioflavonoid mixture capsules (containing 60 capsules), are sold online for prices ranging from €7-12. Hence, the purification of bioflavonoid mixtures containing eriocitrin from local natural sources is gaining importance.

The objective of this study is to extract compounds from four species of Mentha plants - *Mentha spicata*, *Mentha piperita*, *Mentha dumetorum*, and *Mentha villosa nervata* - using different solvents. The goal is to identify the species with the highest concentration of eriocitrin and subsequently purify the eriocitrin compound.

2. Experimental

The mint samples were acquired from Prof. İsa TELCİ, who is affiliated with the Faculty of Agriculture at Isparta University of Applied Sciences.

The procedures were carried out separately for each plant. 20 g of *M. dumetorum*, *M. villosa nervata*, *M. spicata*, and *M. piperita* plants were weighed. 600 mL of pure water was added to each, and after boiling for 30 minutes, the mixture was filtered. Another 600 mL of water was added to the remaining plants, and the process was repeated twice. Liquid-liquid extraction was initiated with each of the obtained water extracts. Additionally, the previously applied process was repeated, and this time the water extracts were subjected to lyophilization. HPLC analyses were performed after lyophilization.

The initial water extracts were subjected to liquid-liquid extraction first with ethyl acetate and then with butanol. The liquid-liquid extractions were performed in two repetitions. The first ethyl acetate liquid-liquid extraction was carried out at a ratio of 1:5 (water:ethyl acetate), and the second at a ratio of 1:2 (water:ethyl acetate). The solvents of the ethyl acetate extracts were removed using a Rotary Evaporator under low pressure. The last part, obtained after extracting with these two solvents, is referred to as the "Remaining Water Extract" and generally has a lower concentration of chemicals.

For quantitative analysis, a Shimadzu Nexera-i LC-2040C 3D Plus HPLC device was used. A DAD detector (scanned at 254 nm) was used for detection, and separation was performed using a Phenylhexyl 4.6 x 150 mm, 3 µm (UP) (GL Sciences Inter Sustain Made in Japan) C6 reverse phase column. The mobile phases were 0.1% formic acid/deionized water (Solvent A) and acetonitrile (Solvent B) (Merck, HPLC grade), following the pump program in Table 1. The flow rate of the mobile phase was set to 1 mL/min throughout the analysis. Samples and standards were injected into the device at 10 µL. The column temperature was set to 30 °C.

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Table 1. HPLC pump program.

Steps	Flow rate (mL/min)	Time (min.)	% Solvent B (acetonitrile)	% Solvent A (% 0,1 formic acid/deionize water)
Step 1	1.00	0,01	5	95
Step 2	1.00	7	9,5	90,5
Step 3	1.00	20	17	83
Step 4	1.00	35	40	60
Step 5	1.00	40	0	100
Step 6	1.00	40,01	Stop	

Using the method described in Table 1, 16 phenolic compounds were analyzed. The wavelength at which each phenolic compound exhibited maximum absorbance was determined, and all were scanned at their respective maximum wavelengths.

Since there was no detection of Vanilic acid and Salicylic acid in the mint species examined, these acids are not given in the Table 2.

3. Results and Discussions

Following the extraction procedure outlined in the experimental section. The results of the analysis of 16 phenolic compounds are presented in Table 2.

Table 2. HPLC Analysis Results of Lyophilized Water Extracts, Ethyl Acetate Extracts, Butanol Extracts, and Remaining Water Extracts (Values are given as means ± standard deviation)

			Mentha dumetorum **mg/g**	*Mentha villosa nervata* **mg/g**	*Mentha spicata* **mg/g**	*Mentha piperita* **mg/g**
1	**Gallic Acid**	Lyophilized water extract	1.79±0.417	0.677±0.027	0.82±0.036	0.43±0.018
		Ethyl acetate	0.581±0.011	0.177±0.006	0.152±0.007	0.202±0.001
		Butanol	1.187±0.005	0.622±0.022	0.507±0.020	0.226±0.005
		Remaining Water Extract	1.43±0.217	0.569±0.021	0.675±0.037	0.472±0.012
2	**4-Hydroxyibenzoic Acid**	Lyophilized water extract	0.025±0.000	0	0	0
		Ethyl acetate	0	0	0.097±0.001	0
		Butanol	0	0	0	0
		Remaining Water Extract	0	0	0.135±0.018	0
3	**Chlorogenic Acid**	Lyophilized water extract	1.545±0.411	2.039±0.813	2.307±0.915	1.774±0.107
		Ethyl acetate	12.335±1.717	24.037±1.717	22.898±1.917	17.317±1.007
		Butanol	0	1.789±0.403	1.504±0.210	0.425±0.033
		Remaining Water Extract	0	0	0,163	0
4	**Caffeic Acid**	Lyophilized water extract	0.032±0.000	0.167±0.003	0.419±0.045	0.031±0.000
		Ethyl acetate	0	0	0	0
		Butanol	0	0.717±0.025	0.509±0.097	0.209±0.012

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		Remaining Water Extract	0	0	0	0
4	**Epicatechin**	Lyophilized water extract	0	0.548±0.032	0	0
		Ethyl acetate	0	0.539±0.065	0.379±0.067	0.919±0.081
		Butanol	0	0	0	0
		Remaining Water Extract	0	0	0	0
6	**p-Coumaric Acid**	Lyophilized water extract	0	0.244±0.013	0.033±0.000	0.041±0.000
		Ethyl acetate	0.028±0.000	0	0	0
		Butanol	0	0.258±0.005	0	0
		Remaining Water Extract	0	0	0	0
7	**Ferulic Acid**	Lyophilized water extract	0	0.061±0.000	0.178±0.010	0
		Ethyl acetate	0	0	0	0
		Butanol	0	0.226±0.023	0.072±0.000	0.018±0.000
		Remaining Water Extract	0	0	0	0
8	**Eriocitrin**	Lyophilized water extract	**132.599**±13.497	0.239	4.323±0.437	**198.936**±11.616
		Ethyl acetate	**285.342**±15.623	0	9.769±0.967	**336.036**±16.417
		Butanol	**369.717**±17.417	0	7.587±0.987	**389.486**±19.417
		Remaining Water Extract	0	0	0	**6.204**±0.697
9	**Rutin**	Lyophilized water extract	12.519±1.417	3.949±0.918	3.219±0.618	8.526±0.717
		Ethyl acetate	34.417±6.915	1.838±0.317	3.96±0.417	14.779±3.567
		Butanol	51.857±7.419	3.319±0.818	14.021±5.234	27.632±8.498
		Remaining Water Extract	0	0	0.317±0.007	3.791±0.187
10	**Rosmarinic Acid**	Lyophilized water extract	43.078±0.417	93.892±8.643	112.465±9.413	41.45±0.989
		Ethyl acetate	406.523±20.619	907.247±43.717	713.634±37.417	346.336±19.369
		Butanol	36.302±7.455	179.327±8.634	200.115±9.917	31.002±3.428
		Remaining Water Extract	0.6±0.007	3.804±0.098	6.448±0.537	1.413±0.088
11	**Apigenin-7-glucoside**	Lyophilized water extract	0.953±0.063	1.562±0.319	1.096±0.413	0.462±0.068
		Ethyl acetate	3.053±0.735	1.141±0.228	1.878±0.419	0.506±0.098
		Butanol	3.567±0.652	2.054±0.605	1.776±0.619	0.646±0.058

		Remaining Water Extract	0	0.718±0.081	0.543±0.023	0.194±0.022
12	**Cinnamic Acid**	Lyophilized water extract	0.06±0.000	0	0	0
		Ethyl acetate	0	0	13.967	0
		Butanol	0	0.369±0.074	0.029±0.000	0
		Remaining Water Extract	0	0.029±0.002	0.071±0.001	0.121±0.010
13	**Quercetin**	Lyophilized water extract	0.179±0.029	0.164±0.005	0.669±0.079	0.47±0.028
		Ethyl acetate	3.476±0.088	2.091±0.098	3.968±0.187	3.731±0.117
		Butanol	0	0.428±0.087	0.359±0.058	0.183±0.056
		Remaining Water Extract	0.153±0.013	0.192±0.023	0.757±0.037	0.588±0.026
14	**Naringenin**	Lyophilized water extract	0.398±0.035	0.176±0.018	1.785±0.185	0.067±0.003
		Ethyl acetate	5.327±0.095	0.388±0.078	8.811±0.789	2.368±0.058
		Butanol	0	0.016±0.001	0.791±0.019	0
		Remaining Water Extract	0	0.118±0.091	1.566±0.213	0

The table shows that in lyophilized water extracts, the highest concentration of phenolic compounds was found in *Mentha piperita* (198.936±11.616 mg/g extract) and *Mentha dumetorum* (132.599±13.497 mg/g extract) with eriocitrin. Additionally, rosmarinic acid levels were also high compared to other phenolic compounds and among the other species, with the highest concentrations found in *Mentha villosa nervata* (93.892±0.417 mg/g extract) and *Mentha spicata* (112.465±9.413 mg/g extract).

The table also indicates that in ethyl acetate extracts, the highest concentration of phenolic compounds was rosmarinic acid in *M. villosa nervata* (907.247±43.717 mg/g extract) and *M. spicata* (713.634±37.417 mg/g extract). High levels of rosmarinic acid were also observed in other species (*M. dumetorum*: (406.523±20.619 mg/g extract), *M. piperita*: (346.336±19.369 mg/g extract). In *M. villosa nervata* and *M. spicata*, aside from rosmarinic acid, the highest phenolic compound was chlorogenic acid (24.037±1.717 mg/g extract) and (22.898±1.917 mg/g extract, respectively). Following rosmarinic acid, eriocitrin was found to be the highest phenolic compound in *M. dumetorum* (285.342±15.623 mg/g extract) and *M. piperita* (336.036±16.417 mg/g extract). In these two plant species, rutin was also found to be high (*M. dumetorum*: (34.417±6.915 mg/g extract), *M. piperita*: (14.779±3.567 mg/g extract).

In butanol extracts, the highest concentration of phenolic compounds was also eriocitrin, found in *M. dumetorum* (369.717±17.417 mg/g extract) and *M. piperita* (389.486±19.417 mg/g extract). Additionally, besides eriocitrin, rutin was also found to be high in these two species *M. dumetorum*: (51.857±7.419 mg/g extract), *M. piperita*: (27.632±8.498 mg/g extract). Rosmarinic acid levels were higher in *M. villosa nervata* (179.327±8.634 mg/g extract) and *M. spicata* (200.115±9.917 mg/g extract).

The findings reported here are in agreement with the results that were acquired from the previous research.

In their study, Kapp et al. examined the qualitative and quantitative polyphenolic contents in the infusions of 27 commercial peppermint (*M. piperita* L.) tea samples sourced from 10 different countries using HPLC–UV-MS/MS analysis (Kapp et al., 2013).

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In another study conducted by Athanasiadis et al., deep eutectic solvents (DES) composed of glycerol-choline chloride (GL-ChCl), 60% aqueous ethanol (AqEt), and water were used as extraction solvents. Peppermint (*M. piperita* L.) samples, dried and packaged in plastic, air-tight containers, were obtained from local stores in Greece and analyzed using HPLC. The analytical polyphenolic composition of the extracts produced with GL-ChCl, AqEt, and water revealed that eriocitrin was the predominant compound in all extracts. The yields of eriocitrin were 36.60 ± 1.99 mg g^{-1} dm, 35.42 ± 2.22 mg g^{-1} dm, and 23.65 ± 1.88 mg g^{-1} dm, respectively (Athanasiadis et al., 2023).

It was observed that, consistent with findings from previous studies, eriocitrin emerged as the predominant polyphenolic compound (Areias et al., 2001; Athanasiadis et al., 2023; Atoui et al., 2005; Dorman et al., 2003; Duband et al., 1992; Fecka & Turek, 2007; Guédon & Pasquier, 1994; Kapp et al., 2013; Sroka et al., 2005).

Consequently, this investigation found that the greatest concentration of the phenolic component in the remaining water extracts was eriocitrin in *Mentha piperita* (6.204 mg/g extract), consistent with the findings in the literature. Rosmarinic acid concentrations were determined to be elevated in *Mentha spicata* (6.448 mg/g extract).

The butanol extract of *Mentha piperita* was found to have the highest concentrations of eriocitrin, as shown by the results of the HPLC analysis. Following this, the process of purification was carried out with the use of these extracts that were generated from *Mentha piperita*.

3.1. Purification Process

The butanol extract was first processed in a rotary and then in a lyophilized (HyperCOOL, Korea) to become powder.

The powdered extract of *M. piperita* was dissolved in water at a concentration of 1 mg/mL in a volume of 9 mL and loaded onto a 40 cm long chromatographic column with a 2 cm internal diameter, packed with Sephadex LH-20 (General Electric (GE) Healthcare (Cytiva)). The purification process was conducted at a flow rate of 0.1 mL/min. The eluent was collected in 20 mL fractions in test tubes at the column exit, and the water from these tubes was subsequently removed by lyophilization. Analytical HPLC was performed on a C6 reverse-phase column, resulting in the isolation of eriocitrin in pure form in fractions 36 and 37. The HPLC chromatogram indicated that the eriocitrin achieved 92% purity.

A sample solution of 1000 ppm concentration was prepared from the powdered extract and analyzed by HPLC (Shimadzu Nexera-i LC-2040C 3D Plus) on a C6 reverse-phase column Phenylhexyl 3 µm, 4.6 mm x 150 mm (GL Sciences InterSustain, Japan). The analysis was performed with a DAD detector, scanning at 280 nm.

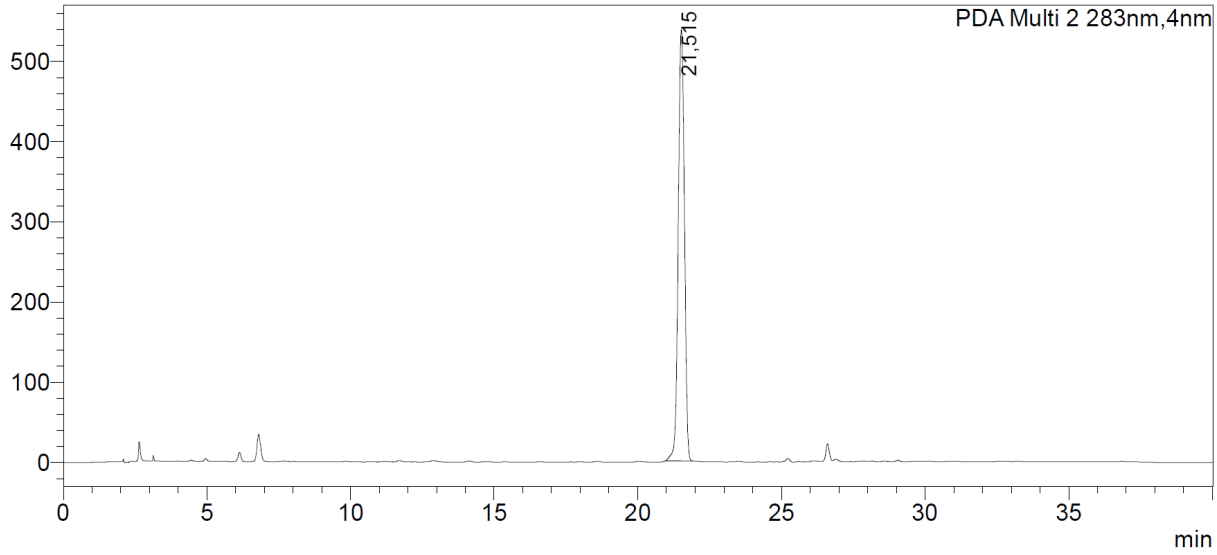

Figure 2. The HPLC chromatogram of eriocitrin obtained from tube 36.

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4. Conclusions

In this study, industrial scale grinding tests were carried out for the fabrication of nano calcite. The normal capacity of the mill used in the tests is 20 tph. However, it was not possible to produce nano-sized calcite with this capacity. Therefore, the capacity of the mill has been reduced. In other words, the amount of calcite feed is reduced. This increases the contact time between the calcite and the balls. When the residence time of Calcite in the mill was increased by 4 times, the fineness (d_{90}) of the products obtained fell below 4 microns. When the mill capacity was 20, 10 and 5 tph, respectively, the fineness of the products was 60, 20, and 3.8 microns, respectively. These results were obtained in case of grinding with conventional balls. In case of using Cylpebs instead of conventional balls, the product fineness was 30, 10 and 1.3 microns, respectively. According to these results; the fineness of the products is inversely proportional to the mill capacity. As the mill capacity is reduced, finer products are obtained. This is due to increased grinding time and material-to-ball contact.

As a result, mill capacity is an important operating parameter in the fabrication of nano-sized calcite. It is not possible to fabricate nano-sized material with a conventional ball mill operated with normal capacity (20 tph). If the capacity is reduced by 75%, it is possible to produce nano-sized material. Furthermore, cylpebs should be used instead of conventional balls in this grinding process. Cylpebs gives finer products than conventional spherical balls.

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