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Development of Spectrophotometric Method for The Determination of Mesalazine as Pure Form and in Tablets

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Abstract

This method involves development of a highly sensitive spectrophotometric procedure to estimate mesalazine as pure substance and in the tablets. This particular procedure was focused on the diazotization of mesalazine with an excess quantity of sodium nitrite ($NaNO_2$) in an acid medium using HCl solution to produce a corresponding diazonium compound which reacts with 8-hydroxyquinoline reagent in an alkaline solution of NaOH to yield read-orange azo dye which is soluble in water and showed maximum absorption peak at the wavelength of 500 nm against the blank solution. The calibration graph was linear and compatible to Beer's law over the concentration range from 0.25 to 12.5 µg/ml with an exceptional determination coefficient (R^2= 0.9994) and apparent molar absorptivity 2.88×10^4 $L.mol^{-1}cm^{-1}$. The limits of detection (LOD) and quantitation (LOQ) were premeditated and found to be 0.2023 and 0.6524 µg/ml, correspondingly. A relative error percent (accuracy) and the relative standard deviation (RSD%) was also calculated and found to be in the range -3.84% - 2.70%, and 0.17% - 1.94%, correspondingly. No interferences were observed from other ingredients that may be exist in the tablets. The stoichiometry of the resulting azo dye has been examined and the experimental results revealed that the mole ratio of mesalazine to 8-hydroxyquinoline is 1:1. The advised procedure was successfully applied for the determination of mesalazine in its pharmaceutical form (tablets).

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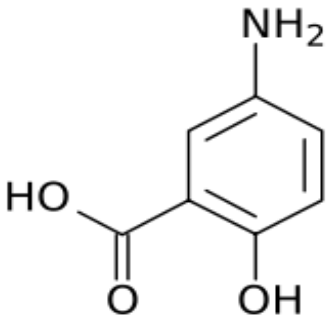
1. Introduction

Mesalazine (MESZ) or mesalamine, is a light grey powder. It is practically not soluble in alcohol but, it is little soluble in water. It can be dissolved in dilute hydrochloric acid and sodium hydroxides solutions (British Pharmacopoeia, 2013). MESZ was chemically known as 5-amino salicylic acid. It has melting point of 280°C. The chemical structure of MESZ was exemplified in the following (Scheme 1) (Cartwright, 2016).



Scheme 1. Mesalazine

($C_7H_7NO_3$)

M.Wt.= 153.135 g/mol

MESZ was used in the treatment of chronic bowel and ulcerative colitis which is a gathering of autoimmune diseases that cause large intestine inflammation (Zayed & Farrag, 2016). The anti-inflammatory mesalazine effect was achieved by the process of inhibiting the conversion of arachidonic acid in the mucosa, by stopping cyclooxygenase enzyme (Zawada et al, 2017). Also, the MESZ can be used to treat hyperemesis gravidarum in pregnant women as a second choice (Pasternak et al, 2013).

A variety of diverse spectrophotometric approaches have been issued for the approximation of MESZ in its pharmaceutical preparations. Most of the aforementioned procedures involved oxidative coupling reactions with thymol in the existence of sodium meta periodate (Salih & Mohammed, 2020), phenothiazine in the presence of potassium sulphate (K_2SO_4) as oxidant (Shehab & Muhammed, 2020), pyrocatechol and K_2SO_4 (Shihab, 2011), histidine in the presence of N-bromosuccinimide (NBS) (Zakaria, 2019), 8-hydroxyquinoline and N-(1-naphthyl) ethylenediamine (NNED) in alkaline solution (Zakaria, 2013). Others depended on the diazotization reaction of MESZ and coupling with some reagents for instance, 2,6-dihydroxytoluene (Aziz & Sultan 2019), resorcinol (Madhavi et al, 2011) and phlorogycinol (Hamdon et al, 2012). A condensation reaction was also applied to estimate MESZ via spectrophotometric methods by using reagents of salicylaldehyde (Anumolu et al, 2019) and p-dimethylaminocinnamaldehyde (Sama et al, 2011). Charge transfer reactions with alizarin red sulphonate (Altayib et al, 2014) and p-bromanil (Al-Ramadhani & Al-Mtioti, 2019), as well as ion-pair complex formation between the MESZ and bromothymol blue (Nair et al, 2015) have also been employed for the estimation of MESZ.

Numerous techniques have also been used for estimating MESZ in some biological liquids and pharmaceutical forms which included; cyclic voltammetry using sodium dodecyl sulfate modified carbon paste electrode (Tanuja et al, 2018), RP-HPLC (Rao & Sekhar, 2013), fluorescence probe (Guang et al, 2015) and electrochemical oxidation method for MESZ at poly (glutamic acid) modified glassy carbon electrode (Kumar et al, 2017).

This investigation describes the ideal conditions to develop a sensitive spectrophotometric method to determine MESZ in water via coupling of 8-hydroxyquinoline with diazotization MESZ in an alkaline solution of NaOH to form an orange water

soluble azo dye and to explore its applicability in tablets.

2. Materials and Methods

The chemical materials and reagents used in this research displayed a considerably high degree of purity and were acquired from the BDH, Fluka and Merck companies.

Stock solution of MESZ (500 µg/ml): A 0.0500 g of MESZ was weighted and set in nearby 5 ml of DW and with the identical solvent the volume was completed up to 100 ml in a calibrate flask and saved in dark bottle.

MESZ standard solution (50 µg/ml = 3.265×10^{-4} M) was prepared by taking a suitable volume of the stock solution and diluted by DW in a calibrated flask.

Solution of 8-hydroxyquinoline solution *(*1% w/v*):* A 1.00 g of 8-hydroxyquinoline reagent was dissolved in a small quantity of DW and the same solvent was used to bring the volume to 100 ml in a calibrated flask. The solution was then saved in a brown container.

Solution of sodium nitrite (0.2% w/v) (2.898×10^{-5} M): A 0.2000 g of $NaNO_2$ was dissolved in a minimal quantity of DW and the volume was then completed to 100 ml with the identical solvent.

HCl solution (1M): It was prepared by diluting 8.47 ml of concentrated hydrochloric acid to 100 ml with DW.

Solution of sulphamic acid (0.5%): A 0.50 g of the sulphamic acid was weighed and dissolved in a 100 ml DW using a calibrated flask.

Solution of sodium hydroxide (1M): The solution was prepared by diluting 100 ml of the standard solution of NaOH (10 M) (BDH) with DW to 1 L and placed in a plastic bottle.

2.1. Analysis of MESZ in tablets

Solution of Awasalazine and Pentasa tablets (50 µg/ml)

Five tablets of Awasalazne (400 mg MESZ exist in each tablet) or Pentasa (500 mg MESZ in each tablet) were finely grinded, mixed will and weighted exactly to quantity comparable to 0.010 g of MESZ and then was dissolved with 5 ml ethanol and completed to 40 ml with DW with slight heating. The solution was then filtered and completed with DW to 100 ml using a calibrated flask. The working solution of MESZ (50 µg/ml) was prepared by diluting with DW.

3. Results

3.1. Preliminary investigations

On treatment of MESZ with an excess quantity of $NaNO_2$ solution in presence of HCl solution the corresponding diazonium ion was formed. The relating diazonium ion was then coupled with 8-hydroxyquinoline in a basic solution of NaOH to produce colored azo dye. (Figure 1)

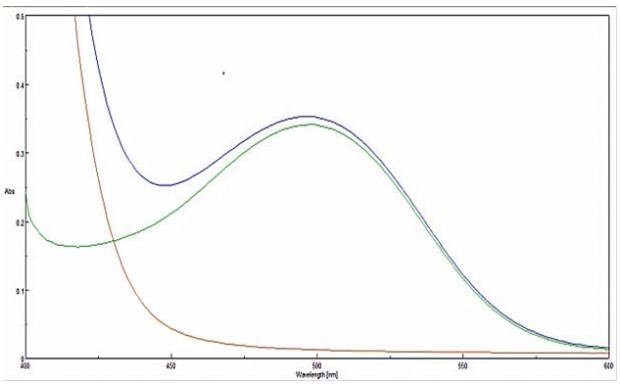


Figure 1: Initial spectrum for the resulting dye

3.2. Study of optimum condition

Effect of acid type and its amount on absorbance

Acidity is necessary for the completion of diazotization process. Therefore, the influence of varying quantities (0.5-3.0 ml) of several acids (1M) (such as H_2SO_4, HCl, HNO_3, HCOOH and CH_3COOH) on absorbance of the resulting azo dye was examined. The results are illustrated in Figure 2 and revealed that 1.0 -1.3 ml of 1M HCl solution exhibit maximum absorbance conforming to other acids. Therefore, 1ml of 1M HCl with standing time for 2 minutes to complete the diazotization reaction were established for the subsequent experiments.

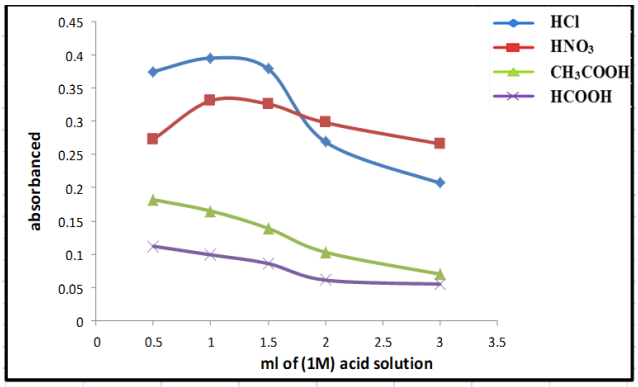


Figure 2: Effect of various acids on absorption of the resulting azo dye

Effect of sodium nitrite amount and the time on absorbance

The influence of several quantities of $NaNO_2$ solution from 0.2 to 2.0 ml at different waiting times 1-7 minutes on absorbance was investigated. The results are nominated in Figure 3 and indicated that the diazotization reaction of MESZ was accomplished after 5 minutes after the addition of 1.5 ml of 0.2% $NaNO_2$ solution, because this amounts of $NaNO_2$ give the highest absorbance. Therefore, 1.5 ml has been chosen for the next experiments.

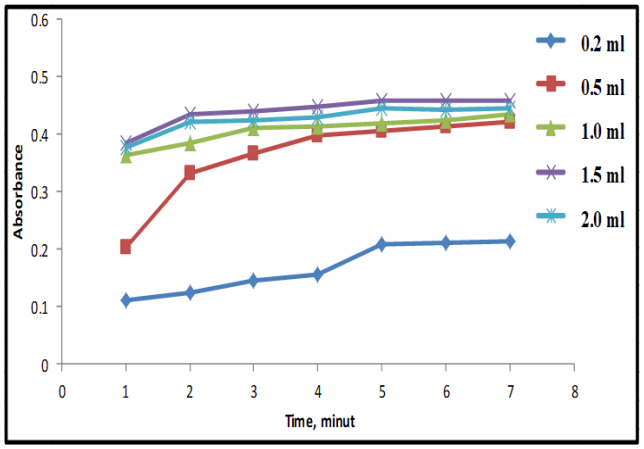


Figure 3: Effect of sodium nitrite amount and time on absorbance

Influence of sulphamic acid amount

The influence of several quantities 0.1-0.3 ml of sulphamic acid (0.5%) on the absorbance of the resulting azo dye have been also studied. Figure 4 show that 0.2 ml of sulphamic acid (0.5%) with occasional shaking for 4 minutes was sufficient to remove the excess of $NaNO_2$ (Clayden et al, 2001) Therefor, 0.2 ml of 0.5% sulphamic acid was followed for the all subsequent experiments.

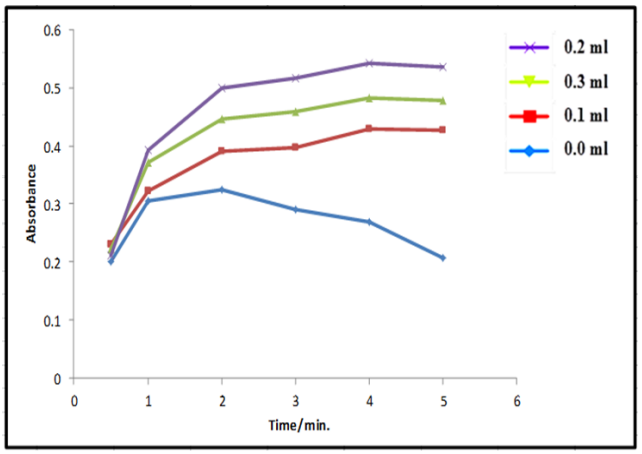


Figure 4: Influence of sulphamic acid quantities and the time on absorption

Effect of 8-hydroxyquinoline amount

The influence of several quantities from 0.5 to 2.5 ml of 8-hydroxyquinoline solution on the magnitude intensity of absorption of the producing dye was examined.

The data in Figure 5 reveal that the quantity 2.0 ml of 8-hydroxyquinoline are enough to be the ideal amount for showing high absorbance with excellent determination coefficient (R^2 = 0.9996) for coupling reaction with diazonium compound of MESZ, therefore, 2ml of 8-hydroxyquinoline (1%) it has been selected for subsequent investigation.

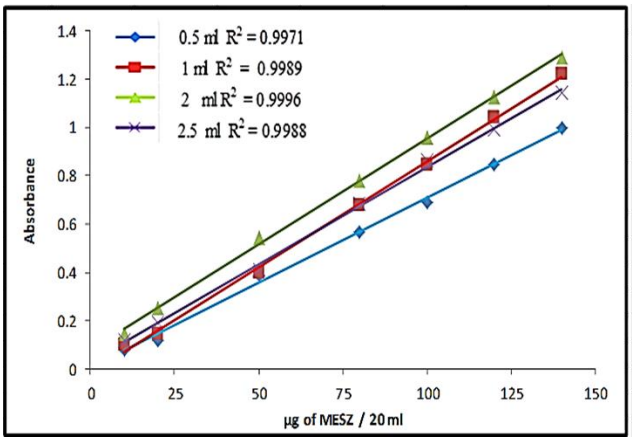


Figure 5: Effect of 8-hydroxyquinoline amount on absorbance

Effect of coupling reaction time

The influence of time on the coupling of diazotized MESZ with 8-hydroxyquinoline reagent was carried out by measuring the absorbance of azo dye at room temperature at different time before the addition of DW to complete the final volume. The results Figure 6 illustrate that the coupling reaction of diazotized MESZ with 8-hydroxyquinoline requires at least 7 minutes to give high intense colour and high absorbance values.

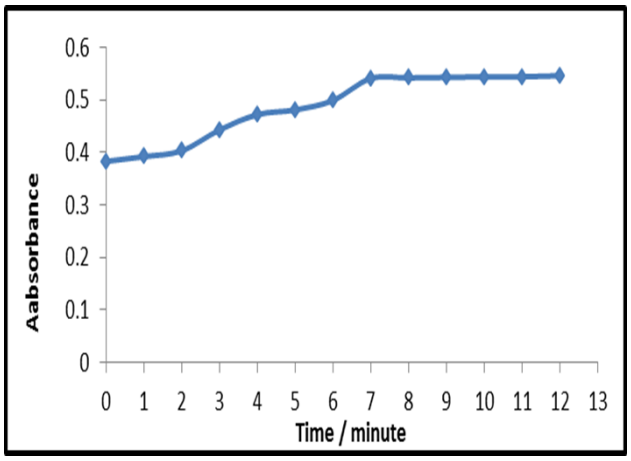


Figure 6: Influence of coupling reaction time on absorbance

Effect of base type and its amount

To obtain an intense color of azo dye, the coupling reaction of diazotized MESZ with 8-hydroxyquinoline was performed in an alkaline solution. Therefore, the influence of several quantities from 0.5 to 3.0 ml of various weak and strong bases (1M) on the intensity of absorption of the dye was performed.

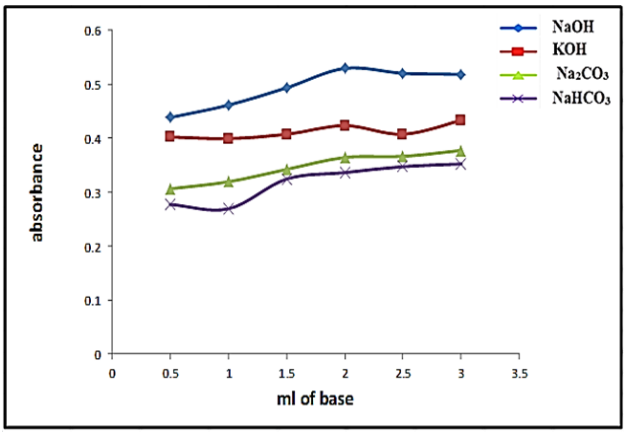


Figure 7: Effect of alkaline solution on absorbance

The results in Figure 7 explain that the solution of sodium hydroxide (1M) show high sensitivity than the other bases, and the results also illustrate that 2 ml of

sodium hydroxide (1M) is the optimal amount for the reaction therefore, it was selected for subsequent investigation.

Colour stability of the azo dye formed

Under optimal conditions, the time effect on the permanency of the colour of the resulting azo dye was performed at 499 nm by studying two diverse amounts of MESZ (50 and 150 µg /20ml).

The results in Figure 8 reveal that the colour stability of the resulting azo dye reaches its maximum absorbance at laboratory temperature and remains stable for at least one hour.

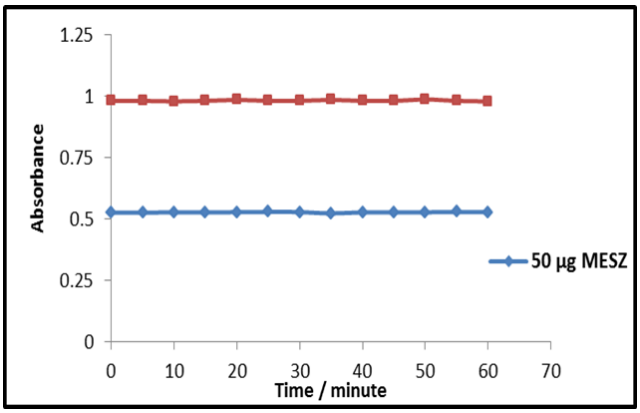


Figure 8: Stability of azo dye with time

Final absorption spectrum

Under optimum conditions, the coupling of 8-hydroxyquinoline with the diazotized MESZ in an alkaline solution of NaOH an orange colored, water soluble azo dye was formed that showed a peak with high absorbance at wavelength of 499 nm, where as the blank solution shows a minor absorbance at the same wavelength (Figure 9).

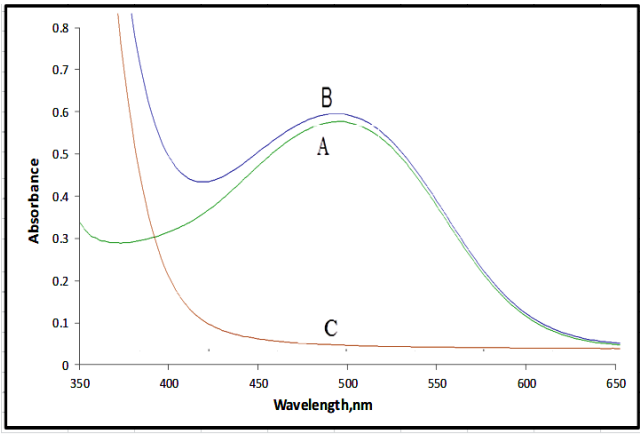


Figure 9: Absorption spectra of 2.5 µg/ml MESZ treated agreeing to the suggested method vs.(A) blank, (B) DW and (C) blank recorded vs. DW

3.3. Suggested method and calibration curve

To a sequence of 20 ml calibrated flasks, 0.1-7 ml of 50 µg/ml pure MESZ solution and 2 ml of 0.1% $NaNO_2$ was added and followed by 1ml of 1M HCl solution. The solutions were mixed thoroughly and set aside constant at room temperature for 2 minutes. After that 0.2 ml of 0.5% sulphamic acid solution was then added and mixed well. A 2 ml of 8-hydroxyquinoline reagent (1%) was added, mixed well and left for 7 minutes. Finally, 2 ml of sodium hydroxide solution (1M) was added and the volumes of all calibrated flasks were completed by DW. The absorbance of the sample solutions was measured at 499 nm versus blank solution prepared in the same manner but without the drug. A relationship between the absorbance and the concentration was plotted to obtain a straight line cover the concentration range from 5 to 250 µg MESZ/20 ml (Figure 10). The molar absorptivity (Ɛ) and the Sandell's sensitivity were calculated and found to be 2.88×10^4 l/mol.cm. and 0.0065 µg/cm^2 respectively.

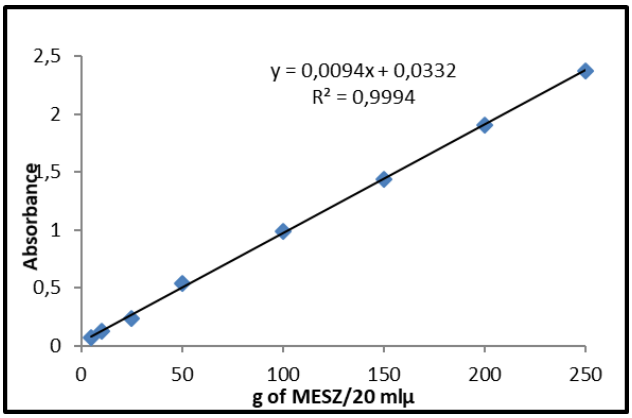


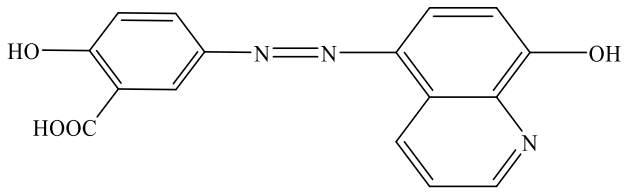
Figure 10: The calibration curve for MESZ determination

4. Discussion

Stoichiometry of the azo dye

The stoichiometry of the resulting azo dye was studied under established conditions by using the continuous variation and molar ratio methods (De Levie, 1997). The acquired results in Figure 11 show that the dye was produced by (1:1) a combination ratio of diazotized MESZ and 8-hydroxyquinoline.

According to the results obtained in Figure 11, the chemical structure of the azo dye can be represented as in (Scheme 2).



Scheme 2: The chemical composition of the azo dye

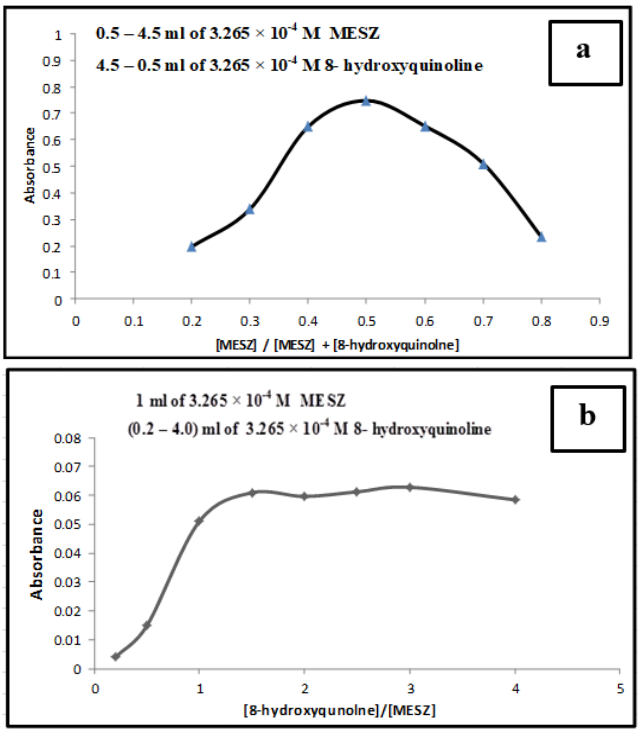


Figure 11: Plots of (a) A continuous variation and (b) molar ratio of the resulting azo dye.

Statistical analysis

The collection of data obtained by applying the proposed method such as Beer's law limits, molar absorption (εmax), accuracy (% recovery), precision (RSD), conditional stability constant, LOD and LOQ values are listed in Table 1. These results indicate that the proposed method Sensitive and precise. The linearity of the method was also proven by calculating the regression equation and the corresponding estimation factor (R^2), which represents good linearity for the proposed method and these data are presented in Table 1.

Application

The applicability of the proposed procedure for the assessing MESZ in two type of tables (Pentasa and AwaSalazine) was applied for four different amounts

20, 50, 100 and 200 µg of MESZ in a total volume 20 ml of each tablet. The results are listed in Table 2.

Table 1. Optical characteristics and statistical data for the proposed method

Parameter	Data
Beer's law range	0.25- 12.5 µg/ml
λmax	500 nm
εmax	2.82 ×10⁴ l/mol.cm
Range of recovery*	96.2% - 102.7%
Relative error range*	- 3.84% - 2.7%
RSD*	≤ 1.94 %
Sandall's sensitivity ,	0.00434 µg/cm²
Determination coefficient (R^2)	0.9994
Average of stability constant (K)	0.37×10⁷ l/mol
LOD ,	0.202 µg/ml
LOQ ,	0.652 µg/ml
Sandell sensitivity	0.00531

*Average of five determinations

Evaluation of recommended procedure

We have verified the efficacy of the proposed procedure according to the standard addition methods and demonstrated that the recommended method can be effectively useful to assay the MESZ without any effect of foreign species. The findings are shown and listed in Figure 12 and Table 3.

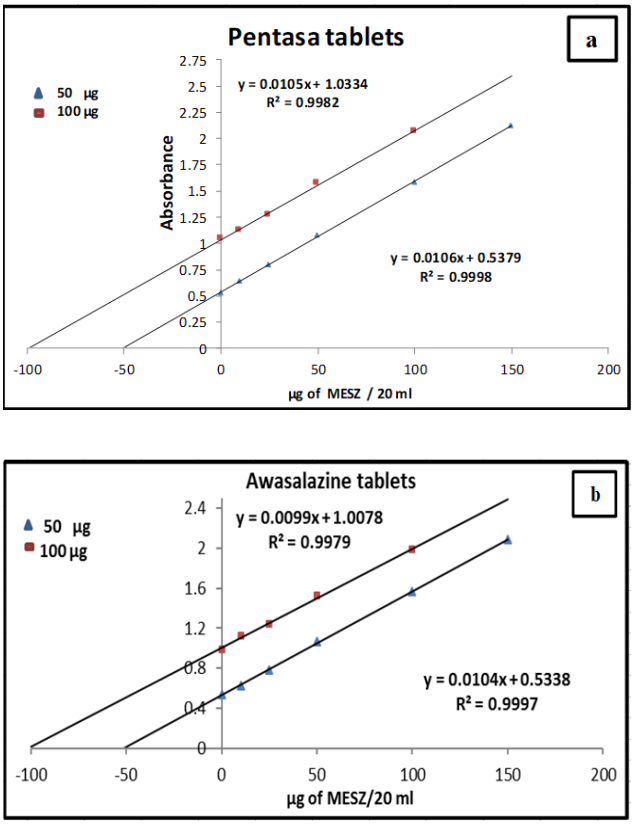


Figure 12: Calibration graphs of standard addition methods for analysis of MESZ in (a) Pentasa and (b) Awasalazne tablets

Table 2. Application of the method

Pharmaceutical Preparation	Certified Value	MESZ Found (µg)	Relative Error (%)*	Recovery (%)*	Measured Value	RSD *	t*
Pentasa tablet (Turkey)	500 mg/tab.	20.80	4	104.00	520 mg/tab.	2.17	---
		51.11	2.42	102.42	512.1 mg/tab.	1.83	1.88
		101.28	1.28	101.28	506.4 mg/tab.	1.94	1.79
		198.96	-0.52	99.48	497.4 mg/tab.	3.01	---
AwaSalazine tablet (Iraq)	400 mg/tab.	20,54	2.70	102.7	410.8 mg/tab.	1.54	---
		49.26	-1.48	98.52	394.08 mg/tab.	1.83	1.91
		96.16	-3.84	96.16	384.64 mg/tab.	0.98	1.68
		195.74	-2.13	97.87	391.48 mg/tab.	2.62	---

*Average of five determinations

Table 3: The results of standard addition method

Pharmaceutical Preparation	MESZ Present (µg)	MESZ Measured (µg)	Recovery (%)
Pentasa tablet	50	50.74	101.49
500 mg MESZ/tablet (Turkey)	100	98.42	98.42
AwaSalazine tablet	50	51.32	102.65
400 mg MESZ/tablet (Iraq)	100	101.79	101.79

Table 4. Compare the proposed method

Parameter	Present Method	Literature Method*
Type of reaction	Diazotization and coupling	Charge transfer complex
Reagent	8-hydroxyquinoline	p-bromanil
Λ_{max}(nm)	500	346
Medium of reaction	Basic	Basic
Beer's law range (ppm) (µg/ml)	0.25-12.5	0.48-12
Molar absorptivity (L/mol.cm)	$2.82x10^4$	$6.5x10^3$
RSD (%)	≤1.94	≤1.7
Colour of the producte	orange	orange
Correlation coefficient (R^2)	0.9994	0.9987
Recovery (%)	96.2-102.7	≥98.04
Relative error (%)	-3.84-2.70	-1.1- -0.29
K (l/mol)	$0.37x10^7$	--------
Sandell sensitivity (µg/cm^2)	0.00531	0.0235
LOD (µg/ml)	0.202	0.053
LOQ (µg/ml)	0.652	0.176

* (Al-Ramadhani and Al-Mtioti, 2019)

Compare the proposed method

Some spectroscopic analytical variables of the proposed method for sulfadiazine estimation were compared with the same variables of other spectroscopic methods, and the results were recorded in Table 4.

5. Conclusion

A spectrophotometric method was used for estimating MESZ through diazotization coupling reaction. The method was based on the coupling of 8-hydroxyquinoline reagent in alkaline solution of NaOH with diazotized MESZ to produce a water soluble azo dye which showed maximum absorption at 500 nm. The procedure is easy, swift, sensitive, low-cost and highly selective. In addition, it does not involve temperature, control of pH or solvent

extraction steps. It is also precise enough to be effectively accepted as an alternative to the existing colorimetric methods with an acceptable result. The linearity of calibration curve covers the concentration range from 0.25 to 12.5 µg/ml with an exceptional molar absorptivity 2.88×10^4 $L.mol^{-1}cm^{-1}$. The limits of detection and quantitation were premeditated and found to be 0.2023 and 0.6524 µg/ml, correspondingly. A relative error percent (accuracy) was also calculated and found to be in the range -3.84% - 2.70%. The development approach was successfully applied for the analysis of MESZ in tablets.

Conflicts of interest

There is no conflict of interest.

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Breastfeeding Problems and Affective Factors During Postpartum Period

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Abstract

This study aims to examine breastfeeding problems experienced by mothers with 0-1 month old babies and the factors affecting them. The research population consists of breastfeeding mothers with 0-1 month old babies who applied to a State Hospital Clinics of Gynecology and Pediatrics. In data collection, the study used "Demographic Question Form" and "Breastfeeding Experience Scale". Data was collected face to face via questionnaire. Mothers who gave birth on the 33-37th weeks, those who do not have breastfeeding experience, those who did not breastfeed their baby within the first half hour, those who breastfed their babies as soon as they cried, those who use pacifiers or bottles and formula and supplementary, those who experience breastfeeding problems and those whose babies stayed in intensive care unit were found to experience bigger problems with breastfeeding ($p<0.05$). In conclusion, it was determined that mothers who gave birth on the 33-37th weeks, those who do not have breastfeeding experience, those do not breastfeed their baby in the first half hour, those who use a pacifier or bottle, those who give formula or supplementary food to their baby and those who face problems with breastfeeding have greater breastfeeding problems. It was also found compared to the mothers breastfeeding in the first hour or after an hour, the ones breastfeeding in the first half hour faced considerably less breastfeeding problems. The study revealed that compared to mothers breastfeeding their babies once every two or three hours, those breastfeeding their babies as soon as their baby cried experienced more breastfeeding problems.

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1. Introduction

Breastfeeding has numerous advantages for both mothers and infants. World Health Organization (WHO) recommends breastfeeding babies in the first half of full hour after birth and relying only on breast milk up until 6-month period (World Health Organization, 2020). Early start of breastfeeding helps regular production of breast milk by strengthening the bond between mother and the newborn. Therefore, it is recommended that the newborn is placed on mother's breast right after they are born; in addition, other than breast milk, no other sort of pre-breastfeeding (any kind of food/liquid) is recommended (Yüzügüllü et al., 2018). Türkiye Demographic and Health Surveys 2018 data demonstrates that although rate of breastfeeding babies is 98% in Türkiye; as opposed to recommendations, children younger than 6 months of age is breastfed at a rate of only 41%. However, rate of relying only on breastfeeding decreases with age: while it is 59% among 0-1 month old babies, it decreases to 45% when they become 2-3 months old, culminating in a 14% when they are 4-5 months old. Most mothers stop or terminate breastfeeding due to breastfeeding-related problems they face during postpartum period (Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, 2019).

The start and continuation of breastfeeding is affected by numerous factors. Various studies have found that particularly breastfeeding problems faced by mothers have adverse effects on the process of breastfeeding (Karaçam & Sağlık, 2018). Literature has shown mothers usually experience difficulty inbreastfeeding in the early postpartum period (Almqvist-Tangen et al., 2012; Mortazavi et al., 2014; Tokat et al., 2015). While flat-inverted nipples, redness on the nipple, pain and cracks on the nipple are regarded as the most common problems, concern over insufficiency of milk, baby's low gain weight, mother's negligence of breastfeeding methods and techniques, engorgement and early solid feeding are among the less common breastfeeding problems (Taş Arslan & Yeniterzi, 2013; Tokat et al., 2015; Karaçam & Sağlık, 2018; Uyanık et al., 2022). With detection of these problems, their affective factors and interventions according to the results, it is possible to increase the rate of breastfeeding children. Increase in the breastfeeding period has many advantages for both mother's and infant's health (Karaçam & Sağlık, 2018). This study aims to determine breastfeeding problems experienced by mothers with 0-1 month old babies and the factors affecting them.

2. Materials and Methods

This research was descriptively conducted for the purpose of examining the breastfeeding problems faced by mothers with 0-1 month old babies.

2.1. Population and sample

The research population consists of breastfeeding mothers with 0-1 month old babies who applied to a State Hospital Clinics of Gynecology and Pediatrics. In the calculation made on the basis of the Breastfeeding Experience Scale mean scores (24.6±7.04) (Uyanik et al., 2022) of mothers in 2nd postpartum week, the minimum number of samples were found to be 190.

In order to determine the sample size, calculations were made in accordance with the formula where the number of individuals in the population is unknown.

$$n=\frac{t^2 x \sigma^2}{d^2}=\frac{1.96^2 x 7.04^2}{1^2}=\frac{3.8416 x 49.5616}{1}=190$$

In the formula; n: The number of individuals to be taken into the sample.

t^2: The theoretical value found in the t table on specific degree of freedom and detected level of error (value 1.96 with 5% margin of error).

σ: Sample standard deviation (SD)

d^2: ± deviation to be made according to the average

Inclusion criteria;

- Having a 0-1-month-old baby
- Volunteering to take part in the research

Exclusion criteria;

- Mothers who have never breastfed babies,
- Mothers with diseases that will prevent breastfeeding,
- Mothers using drugs that will prevent breastfeeding
- Babies with health problems that will prevent sucking mother's nipple
- Hospitalized mothers or babies.

2.2. Data collection

2.2.1. Data collection form

In data collection, the study used "Demographic Question Form" and "Breastfeeding Experience Scale" which were developed by the researchers reviewing the literature (Yüzügüllü et al., 2018; Uyanık et al., 2022). In Demographic Question Form, 37 questions related to individuals' age, level of education, marital status, perceived income levels, profession, obstetric and breastfeeding characteristics were asked.

2.2.2. Breastfeeding Experience Scale

Developed by Karen Wambach in 1990, Breastfeeding Experience Scale (BES) is used in the assessment of mother's breastfeeding experience. It is a 30-item scale that measures breastfeeding results in terms of early breastfeeding issues/experiences, nutritional practices/patterns and breastfeeding time (Wambach, 1993).

The study of Turkish validity and reliability of the first part of the scale (18 items) was carried out by Uyanık (Uyanık et al., 2022). The Cronbach Alpha value of the scale was found to be 0.776. The first 18 items in the scale measures the presence/absence and the severity of common breastfeeding difficulties in the early postpartum period. All items are five likert type and the scores range among (1) "not at all" and (5) "unbearable". The total score range from 18 to 90 and higher scores refer to increasing severity of the problem. The scale has five sub-dimensions, which are concerns over nipples (three items: pain in the nipples, cracks in the nipple and symptoms and findings of infection in the nipples), concerns over the process (five items: fatigue while breastfeeding, leaking milk from the nipple, frequent breastfeeding of the baby, baby falling asleep while breastfeeding, fragility in the nipples), mechanical concerns (five items: mother's feeling nervous and overwhelmed, nervousness of the baby while breastfeeding, baby's difficulty in grasping the nipple, placing the baby in the correct position while breastfeeding), concerns over inadequate amount of milk (three items: concern that the baby does not take adequate amount of milk, concern about baby's weigh gain, concern that the

mother does not have adequate amount of milk) and social concerns (two concerns: feeling shy about breastfeeding outdoors and in crowded environments, difficulty in managing work and breastfeeding at the same time). In our study, The Cronbach Alpha value of the scale was found to be 0.876.

2.2.3. Data collection process

For the research, breastfeeding mothers, who applied to clinics of gynecology and pediatrics were reached. Informed consent forms were received from these women. Data was collected face to face via questionnaire. Data collection process was completed among April 1, 2023-April 15, 2023. Data collection time for each women took an average of 10 minutes.

2.3. Statistical analysis

The data collected during the research was assessed by a package data program (SPSS 23.0 (Statistical Package for Social Sciences, drive 24.0, for Windows) in a computerized environment. In the analysis of the data, descriptive statistics such as number and percentage, t-test, one-way analysis of variance (ANOVA) and Bonferroni were performed depending on the variables. The suitability of the data for normal distribution was determined by evaluating the skewness and kurtosis coefficients. Linear regression (step by step) analysis of factors affecting breastfeeding problems was alsoperformed. For statistical significance, the alpha level was set at 0.05. The Cronbach-α coefficient was used to evaluate the reliability of the scale used in the study.

2.4. Ethical aspect of the research

Ethical approval for the research was received from Gazi University Ethics Committee (Date: 23.03.2023, Number: E-77082166-604.01.02-619080). Informed consents were received from participants. The research was conducted in accordance with Helsinki Declaration.

3. Results

Characteristics of mothers and infants are listed in Table 1. 48.9% of the women are high school graduates and 77.4% are unemployed. 49.5% of them perceive their income and outcome levels as equal.

Table 1. Characteristics of mothers and infants

Characteristics	$\bar{X} \pm$ **SD**	**(Min-Max)**
Age	27.17 ± 4.97	18-41
Number of pregnancies	2.02±0.98	1-6
Number of birth	1.88±0.87	1-6
Birth weight	3092.11±353.83	2100-3950
Baby age (in month)	16.33±7.72	2-30

Mothers who gave birth on the 33-37th weeks, those who do not have breastfeeding experience, those who did not breastfeed their baby within the first half hour, those who breastfed their babies as soon as they cried, those who use pacifiers or bottles and formula and supplementary, those who experience breastfeeding problems and those whose babies stayed in intensive care unit were found to experience bigger problems with breastfeeding ($p<0.05$) (Table 2).

Table 2. Obstetric and breastfeeding characteristics of mothers and infants and their effects on the Breastfeeding Experience Scale (BES) mean scores

Characteristic	n	%	BES $\bar{X} \pm SD$	Test and p values
Mode of delivery				
Vaginal	104	54.7	43.56±14.16	t:0.072
C-section	86	45.3	43.44±9.82	p:0.943
Birth week				
Week 33-37	21	10.9	48.61±12.00	t:2.025
Week 37-41	169	79.1	42.87±12.28	**p:0.044**
Breastfeeding experience				
Yes	124	65.3	41.94±11.53	t:-2.426
No	66	34.7	46.45±13.37	**p:0.016**
First breastfeeding time				
First half hour[a]	175	92.1	42.41±11.87	F:9.957
First hour[b]	10	5.3	54.20±11.22	**p:0.000**
Longer than first one hour[c]	5	2.6	60.40±10.21	diffrence: a-b. a-c
Receiving support in the first breastfeeding	11	5.8	38.45±9.36	F:2.870
No	169	88.9	43.39±12.29	p:0.059
Midwife/Nurse	10	5.3	51.10±13.90	
Companion				
Frequency of feeding the baby				
When s/he cries[a]	84	44.2	46.88±12.88	F:5.927
Once every two hours[b]	98	51.6	40.92±11.70	**p:0.003**
Once every three hours[c]	8	4.2	39.75±3.19	diffrence: a-b
Frequency of breastfeeding at night				
1-3 hours	178	93.7	42.90±11.55	t:-0.39
4-5 hours	12	6.3	42.98±11.70	p:0.969
Use of pasifier or bottle				
Yes	52	27.4	46.71±13.31	t:-2.203
No	136	71.6	42.29±11.88	**p:0.029**
Baby staying in intensive care for a period of time	5	2.6	63.60±6.22	t:3.813
Yes	185	97.4	42.96±12.03	**p:0.000**
No				
Experience of breastfeeding problems				
Yes	31	16.3	49.46±12.99	t:3.260
No	159	83.7	42.25±1.86	**p:0.01**
Use of formula or supplementary food				
Yes	29	15.3	48.06±14.22	t:2.179
No	161	84.7	42.68±11.85	**p: 0.031**

It was found that compared to mothers who breastfed their babies in the first full or a longer hour, those who breastfed in the first half hour experienced significantly less problems. Mothers who breastfed their babies as soon as they cried stated they experienced more breastfeeding problems than those who breastfed their babies once every two or three hours ($p<0.05$) (Table 2).

In order to determine breastfeeding-related problems, a multi-variable linear regression analysis was performed, which indicated that failure to breastfeed in the first half hour increased breastfeeding problems approximately 11 times while breastfeeding as the baby cried increased breastfeeding problems 8 times. It was also found that staying in the intensive care unit increased breastfeeding problems approximately 15 times and giving formula or supplementary food increased breastfeeding problems approximately 6 times. The modal explains 21% of breastfeeding problems (Table 3).

Table 3. Linear regression (stepwise) analysis of factors affecting the breastfeeding problems

Variables	**B**	***SE***	**β**	***p***	***R²***	***Adj R²***
First breastfeeding time	10.720	3.136	.235	.001	0.228	0.211
Frequency of baby feeding	-7.796	1.650	-.314	.000		
Baby staying in ıntensive care for a while	-15.334	5.265	-.199	.004		
Use of formula or supplementary food	-5.907	2.301	-.172	.011		

B: regression coefficient, SE: standard error , β: odds ratio , Adj R^2: adjusted R^2 , *$p<0.05$

4. Discussion

Many studies demonstrate that postpartum breastfeeding problems are quite common (Şahin et al., 2013; Karaçam & Sağlık, 2018). Breastfeeding problems in the postpartum period is described as one that negatively affects breastfeeding times and babies' nutrition with mother's milk. These results demonstrate breastfeeding problems must be more emphasized in terms of maternal and infant health.

Literature suggests breastfeeding experience affects breastfeeding process and expectations in the first six months (Santacruz-Salas et al., 2020). Compared to mothers with breastfeeding experience, mothers with no breastfeeding experience were found to face more breastfeeding problems. Similar to our study, the study conducted by Şencan et al. (2013) pointed out 25,3 % of the mothers are inexperienced, which makes up breastfeeding problems. The study conducted by Yanıkkerem et al. (2014), likewise, indicated that compared to mothers with breastfeeding experience, mothers with no breastfeeding experience have greater social and mechanical concerns together with concerns over the relevant process and inadequacy of milk. All these in mind, it might be considered that previous

breastfeeding experiences and information make later breastfeeding experiences far easier.

Due to their negative effects, use of pacifiers and bottles is not recommended (Batista et al., 2018; Yakar et al., 2020; Yeşilçiçek Çalık et al., 2017). Our study also found mothers relying on pacifiers and bottles tend to face more breastfeeding problems ($p<0.05$). A randomized controlled study found a negative correlation among early use of pacifiers and breastfeeding problems (Howard et al., 2003). Tanrıkulu et al. (2012), in their study, claimed that use of pacifiers or bottles in the first six months reduced mothers' breastfeeding times. Our study results examines the current situation but fails to determine whether breastfeeding problems occur before or after using pacifiers or bottles. Nonetheless, it is clear that mothers who experience problems with nipples or breastfeeding tend to prefer feeding with bottles, which makes it more difficult for the baby to get used to the nipple again.

Mother's milk and baby formula are fundamental food sources for 0-6 month old babies. Due to newborns' immature gastrointestinal system, inadequate digestion, impaired absorption of proteins, lipids and lactose, mild digestion problems are usually seen in infancy. The component differences of baby formulas from mother's milk increase the possibility of mild digestion problems in babies fed with formula. Moreover, mothers who give formula or supplementary food to their babies experience problems with breastfeeding (Tanrıkulu et al., 2012; Jiang et al., 2022). Thus, it is not recommended to feed babies with formula or any other supplementary food (Yılmaz, 2019). It was found in our study that mothers using formula or supplementary food experienced more breastfeeding problems ($p<0.05$). In the study conducted by Tanrıkulu et al. (2012) it was found that the breastfeeding times of mothers who give their babies formula or supplementary food in the first six months considerably decreased.

Mother milk is the most appropriate source of nutrition for infants and premature babies. It is more likely for mothers of premature babies to experience nutritional problems due to such additional difficulties as mother-baby separation, baby's failure to suck the nipple and inadequate breast milking skills. The separation of mothers registering into intensive care units and premature babies might affect mother-baby bond and prevent mothers from breastfeeding (Cacho et al., 2017). Our study found mothers who gave birth on 33-37th weeks and whose babies stayed in intensive care units had bigger breastfeeding problems. The study conducted by Lima et al. (2019) demonstrated there was a considerable decrease in babies' rate of feeding on only mother's milk after discharge from newborn intensive care units and underlined constancy of counseling in order to prevent weaning in early period.

Early start of breastfeeding is significant for both infant and maternal health. WHO recommends breastfeeding babies in the first hour after birth. The concern that the milk is inadequate and the baby is not full leads mothers to breastfeed their babies more often. Our study found mothers who breastfeed their babies in the first half hour after birth experience significantly less breastfeeding problems than those who breastfeed in the first hour or after an hour. Bostancı & Sevil (2015), in their study, revealed only

18% of mothers breastfed their babies whenever they wished. Şen & Koçakoğlu (2022) pointed out the rate of mothers breastfeeding in 2 hour intervalsis 71,3%. In our study, it was determined 92.1% of the mothers start breastfeeding in the first half hour. Many factors such as mode of delivery, skin-to-skin contact, baby's birth weight, level of family education and traditional practices might affect the first breastfeeding time (Bolat et al., 2011; Cantürk & Kostak, 2020).

Our study also found higher breastfeeding problems scores for mothers who considered to be experiencing breastfeeding problems. Many mothers stop or terminate breastfeeding due to problems with breastfeeding in the postpartum period. Similar to our study results, literature revealed mothers who claimed facing breastfeeding problems are concerned about all sorts of issues from lack of milk to breast problems, from problems in the process to social problems (Almqvist-Tangen et al., 2012; Gönenç & Vural, 2015; Tokat et al., 2015; Yılmazbaş et al., 2015; Feenstra et al., 2018). Feenstra et al. (2018) divided breastfeeding problems into seven categories: The baby cannot grasp the nipple; sore, injured and/or cracked nipples, insufficient milk, too much milk, mastitis, doubt and other breastfeeding problems.

5. Conclusion

Mothers who gave birth on the 33-37th weeks, those who do not have breastfeeding experience, those who did not breastfeed their baby within the first half hour, those who breastfed their babies as soon as they cried, those who use pacifiers or bottles and formula and supplementary, those who experience breastfeeding problems and those whose babies stayed in intensive care unit were found to experience bigger problems with breastfeeding It was also found that compared to the mothers breastfeeding in the first hour or after an hour, those breastfeeding in the first half hour faced considerably less breastfeeding problems. The study revealed that compared to mothers breastfeeding their babies once every two or three hours, mothers breastfeeding their babies every time their baby cried experienced more breastfeeding problems. In addition, failure to breastfeed in the first half hour increased breastfeeding problems 11 times while breastfeeding as the baby cries increased breastfeeding problems 8 times. Also babies' stay in the intensive care increased breastfeeding problems 15 times and giving formula or supplementary food increased breastfeeding problems 6 times.

In order to maintain a healthy breastfeeding process, it is crucial to give information about the use of pacifiers and bottles and the solution methods for midwives and nurses, who are in the closest contact with mothers among those providing the most common healthcare services. Healthcare professionals must inform mothers about breastfeeding the baby in the first half hour and not giving formula or any supplementary food in the first six months. So as to manage the breastfeeding process in a healthy manner, it is significant to enhance relevant sensitivity of midwives and nurses and to include information about breastfeeding problems and their solutions in the courses provided to mothers.

Conflicts of interest

The authors declare no conflicts of interest.

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Review Article

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Role of Apolipoproteins in Neurodegenerative Diseases

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Abstract

Since lipids are insoluble in water, they are carried in the blood as particles called lipoproteins. Lipoproteins consisting of lipids and proteins are multicomponent complexes. The classification of lipoproteins, which are divided into several main groups such as low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) and chylomicrons, is based on their density, size, lipid and apolipoprotein content. Apolipoproteins are the protein component of lipoproteins that carry lipids from the blood to various tissues of the body for metabolism and utilisation. Apolipoproteins play an important role in lipid metabolism. They regulate many metabolic enzymes and interact with lipoprotein receptors. Numerous studies have shown that apolipoprotein phenotype, different allelic polymorphism and apolipoprotein gene mutation can affect metabolism and utilisation of blood lipids and consequently trigger the onset and development of atherosclerosis, hyperlipidaemia, cerebrovascular and cardiovascular diseases. Furthermore, apolipoproteins have been associated with neurodegenerative diseases and different apolipoprotein polymorphisms have been evaluated as risk factors or protective agents in different neurodegenerative diseases. This review presents evidence from some studies linking apolipoproteins with Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration disease.

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1. Introduction

Water-insoluble lipids are carried in the blood in the form of particles known as lipoproteins. Lipoproteins consist of a hydrophobic triglyceride/cholesterol ester core surrounded by a single amphiphilic phospholipid layer with embedded apolipoproteins (Dai et al., 2023). Lipoproteins consisting of lipids and proteins are involved in transporting triglycerides and cholesterol in the blood (Ross & Pawlina, 2011). It is divided into several main groups, including low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) and chylomicrons (Ross & Pawlina, 2011). Classification is based on the density, size, lipid and apolipoprotein content of lipoproteins (Tóth et al., 2020). Apolipoproteins are synthesised in various organs, especially in the liver and intestine (Table 1). Changes in the expression levels, function and spatial structure of apolipoproteins have been closely associated with various diseases (Liu et al., 2021). Numerous studies have shown that apolipoprotein phenotype, different allelic polymorphism and apolipoprotein gene mutation can affect metabolism and utilisation of blood lipids and consequently trigger the onset and development of atherosclerosis, hyperlipidaemia, cerebrovascular and cardiovascular diseases (Liu et al., 2021; Richardson et al., 2020). Some apolipoproteins have been reported to be related to neurodegenerative diseases (Reichert et al., 2020b) (Table 1). The aetiology of various neurodegenerative diseases is not clear because there are different neurodegenerative diseases and the central nervous system is made up of different cell populations with unique functions (Mathieu et al., 2020; Reichert et al., 2020a; Reichert et al., 2020b).

Here, we present evidence from some studies linking apolipoproteins to neurodegenerative diseases with a high prevalence in the general population. These studies are predominantly human studies and were selected by searching PubMed and Google Scholar databases using various combinations of the name of the apolipoprotein type and the name of a common neurodegenerative disease.

2. Apolipoproteins and neurodegenerative diseases

This Apolipoproteins include subfamilies A, B, C, D, E, L, F, H, M, N and R, each with different functions (Liu et al., 2021). Beyond their basic functions such as regulation of lipid transport and structural stabilisation of lipoproteins, apolipoproteins play important roles in lipid metabolism through the organisation of a number of metabolic enzymes and molecular interactions with lipoprotein receptors (Liu et al., 2021; Ramasamy, 2014; Tóth et al., 2020). Apolipoproteins are both amphipathic molecules and regulators of the lipoprotein system and are metabolised via receptors, enzymes and transporters (Bahrami et al., 2019). The low-density lipoprotein receptor (LDLR), a cell surface receptor, mediates the uptake and catabolism of plasma lipoproteins containing apolipoprotein B (apoB) or apolipoprotein E (apoE) (Brown & Goldstein, 1986). The main task of this receptor is to remove LDL from the bloodstream (Brown & Goldstein, 1986). The blood-brain barrier effectively blocks the uptake of lipoprotein-bound cholesterol from the bloodstream, so that cholesterol levels in the brain are independent of those in peripheral tissues (Björkhem & Meaney, 2004). It has been reported that some cholesterol in

Table 1. Some apolipoproteins related to neurodegenerative diseases

Apolipoprotein	Synthesis	Lipoprotein	Neurodegenerative Disease
ApoA-I	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons, VLDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Bergt et al., 2006; Johansson et al., 2017; Kawano et al., 1995; Kuriyama et al., 1994; Liu et al., 2006; Merched et al., 2000; Saczynski et al., 2007; Paula-Lima et al., 2009; Wisniewski et al., 1995) Multiple sclerosis (Murali et al., 2020; McComb et al., 2020) Amyotrophic lateral sclerosis (Thompson et al., 2022) Frontotemporal degeneration disease (Kim et al., 2018)
ApoA-II	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons, VLDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Kuriyama et al., 1994) Frontotemporal degeneration disease (Kim et al., 2018)
ApoA-IV	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons (Dominiczak & Caslake, 2011)	Huntington's disease (Huang et al., 2011)
ApoB (ApoB-48, ApoB-100)	Intestine (ApoB-48), liver (ApoB-100) (Dominiczak & Caslake, 2011)	Chylomicrons (ApoB-48), chylomicron remnants (ApoB-48), VLDL (ApoB-100), IDL (ApoB-100), LDL (ApoB-100) (Dominiczak & Caslake, 2011)	Alzheimer's disease (Choi et al., 2016; Namba et al., 1992; Tóth et al., 2020) Parkinson's disease (Fang et al., 2019; Lehnert et al., 2012; Wei et al., 2013) Huntington's disease (Chang et al., 2023) Amyotrophic lateral sclerosis (Thompson et al., 2022) Frontotemporal degeneration disease (Kim et al., 2018)
ApoC-I	Intestine, liver (Dominiczak & Caslake, 2011)	Chylomicrons, VLDL, HDL (Dominiczak & Caslake, 2011)	Frontotemporal degeneration disease (Kim et al., 2018)
ApoC-III	Intestine, liver (Dominiczak & Caslake, 2011)	Chylomicrons, VLDL, HDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Adunsky et al., 2002; Muenchhoff et al., 2017; Shih et al., 2014; Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020)
ApoD	Astrocytes, oligoastrocytes, Schwann cells, pericytes (Rassart et al., 2000)	HDL (Fyfe-Desmarais et al., 2023)	Parkinson's disease (Waldner et al., 2018) Multiple sclerosis (Reindl et al., 2001; Navarro et al., 2018)
ApoE(ApoE-IV)	Intestine, liver, brain, spleen, kidney, adrenals and other (Dominiczak & Caslake, 2011)	Chylomicron remnants, mature VLDL, VLDL remnants, LDL and HDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Farrer et al., 1997; Hong et al., 2020; Koizumi et al., 2018) Parkinson's disease (Mata et al., 2014; Real et al., 2023; Tsuang et al., 2013) Multiple sclerosis (McComb et al., 2020) Amyotrophic lateral sclerosis (Leoni et al., 2019) Frontotemporal degeneration disease (Su et al., 2017)
ApoH	Liver (Leduc et al., 2008)	Chylomicron, VLDL (Nakaya et al., 1980)	Alzheimer's disease (Misra et al., 2021; Öhrfelt et al., 2011)
ApoJ (Clusterin/CLU)	Testis, prostate, brain (Vitali et al., 2014)	HDL (Vitali et al., 2014)	Alzheimer's disease (Calero et al., 2000; Foster et al., 2019; Zlokovic et al., 1996) Parkinson's disease (Lenzi et al., 2020; Lin et al., 2021; Maarouf et al., 2012; Přikrylová Vranová et al., 2010; Zhang et al., 2012) Multiple sclerosis (van Luijn et al., 2016)

the brain is absorbed by the blood-brain barrier as lipoprotein-bound cholesterol (Balazs et al., 2004; Vitali et al., 2014). Atherosclerotic changes can occur in the entire vascular system, including the blood vessels associated with the brain (Tóth et al., 2020). The structure of the brain capillaries is favourable for the maintenance of proper neural function (Tóth et al., 2020). Endothelial cells, which are the basic cellular components of the blood brain barrier, are characterised by the lack of fenestrae, low transcytosis rate, tight junctions and the presence of selective transporters (Fanning & Anderson, 2009; Tóth et al., 2020). Blood brain barrier dysfunction is usually accompanied by morphological changes such as impaired tight junctions, basement membrane changes and pericyte loss (Tóth et al., 2020). Dyslipidaemia is a known risk factor for intracranial atherosclerosis (Park et al., 2011; Turan et al., 2010). Brain endothelial cell function may be affected by the increased production of arachidonic acid metabolites that occur under hyperlipidaemia (Tóth et al., 2020). Lipolysis products of triglyceride-rich lipoproteins can also increase blood brain barrier permeability through disruption of intercellular connections, which in turn induces apoptosis and affects lipid bulk morphology and composition (Eiselein et al., 2007; Wang et al., 2008). Reactive oxygen species may also be involved in endothelial cell damage caused by triglyceride-rich lipoproteins (Antonios et al., 2008; Wang et al., 2008) Most signs suggestive of a blood brain barrier with a deconstructed and altered structure and permeability are observed in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), chronic traumatic encephalopathy and HIV-1-associated dementia (Sweeney et al., 2018).

Deposits of apolipoprotein A-I (apoA-I) and amyloid beta (Aβ) have been found in the human brain and it has been described that these deposits can be detected in the cerebrospinal fluid (CSF) of Alzheimer's patients (Paula-Lima et al., 2009; Wisniewski et al., 1995). In a study, it was reported that CSF apoA-I level decreased in Alzheimer's patients and this was associated with cognitive function and AD (Johansson et al., 2017). In another study, a high level of apoA-I in the serum was associated with a decreased risk of dementia (Saczynski et al., 2007). It has been reported that decreased apoA-I levels are associated with cognitive decline in AD patients (Kawano et al., 1995; Merched et al., 2000). In a study involving a group of patients with sporadic late-onset Alzheimer's dementia, a group of patients with vascular dementia and a control group, it was reported that HDL-cholesterol levels were lower in both groups of patients compared with the control group, and that apoA-I and apolipoprotein A-II (apoA-II) levels decreased in both groups of patients, especially in the vascular dementia group, and that the apoA-I/A-II ratio increased in both groups of patients (Kuriyama et al., 1994). Many studies have reported decreased serum and plasma apoA-I concentrations in AD patients, while some have reported unchanged apoA-I levels (Bergt et al., 2006; Liu et al., 2006; Merched et al., 2000). Serum apolipoprotein B-100 (apoB-100) is normally unable to cross the blood-brain barrier, but the pathological changes in the blood-brain barrier seen in AD may allow various serum-derived proteins to enter the brain (Tóth et al., 2020). In a study, it was observed that apoB-100 protein

accumulated in neurofibrillary tangles and senile plaques in the brains of Alzheimer's patients (Namba et al., 1992). In a study of cognitively normal elderly individuals, it was reported that serum triglycerides and apoB were associated with cerebral Aβ deposition, but total cholesterol, LDL-cholesterol, HDL-cholesterol and apoA-I levels were not associated with cerebral Aβ deposition (Choi et al., 2016). The role of apolipoprotein C-III (apoC-III) in the pathogenesis of AD is not clear, although some studies suggest that it may play a role (Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020). In a study, it was stated that apoC-III may be the main pathogenic factor of AD after Aβ and tau (Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020). Some studies have shown a positive correlation between decreased apoC-III levels and cognitive performance in AD patients (Muenchhoff et al., 2017; Shih et al., 2014). It has been suggested that apoC-III can bind circulating Aβ and that plasma apoC-III levels are decreased in patients with AD (Adunsky et al., 2002; Shih et al., 2014). ApoE is an apolipoprotein expressed in central nervous system and apolipoprotein E-IV (apoE-IV) protein encoded by the e4 allele is genetically associated with AD (Farrer et al., 1997). In a genome-wide association study of AD, apoE was reported to have profound effects on Aβ42-related phenotypes (Hong et al., 2020). In one study, it was shown that APOE-ε4 may negatively affect the microvascular functions in brain, thus contribute to impairing white matter and cognitive function (Koizumi et al., 2018). Apolipoprotein H (apoH, beta-2-glycoprotein 1), which prevents the activation of blood coagulation, is a lipid-binding protein (Misra et al., 2021). In one study, it was stated that the amount of apoH was significantly increased in CSF samples of those with moderate to severe AD (Öhrfelt et al., 2011). However, in a proteomic study using CSF samples from Alzheimer's patients and controls, it was reported that a significant decrease in the amount of apoH was detected in the CSF of Alzheimer's patients compared to controls (Misra et al., 2021). Apolipoprotein J (apoJ, clusterin, CLU), a ubiquitous glycoprotein that can interact with many different molecules, has been reported to be associated with amyloid (Calero et al., 2000). Studies have shown that CLU binds Aβ peptides, prevents their aggregation and provides their clearance by various means (Foster et al., 2019; Zlokovic et al., 1996).

About 30% of people with PD are reported to develop PD dementia during the course of the disease (Lehnert et al., 2012). In a study, it was reported that apoB-100 was significantly decreased in Parkinson's patients compared to non-demented controls (Lehnert et al., 2012). In a retrospective study, serum lipid and lipoprotein levels of Parkinson's patients were investigated and it was shown that significantly lower serum triglyceride, VLDL-cholesterol and apoB values were found in Parkinson's patients (Wei et al., 2013). It has also been reported that higher apoB, total cholesterol, LDL-cholesterol and triglyceride levels are associated with a lower risk of PD (Fang et al., 2019). In a study of healthy controls and PD patients with mild to moderate neurological impairment, a correlation between apolipoprotein D (apoD) and PD stage was reported (Waldner et al., 2018). The link between AD and the APOE-ε4 allele has led to studies investigating the links between PD and apoE polymorphisms (Huang et al., 2004). It has been reported that apoE is not a PD susceptibility gene, but although PD is clinically defined by motor

symptoms, many patients develop dementia within years after diagnosis (Aarsland et al., 2003; Hely et al. 2008; Hughes et al., 2000; Tsuang et al., 2013). As a result of a study, it was reported that the APOE-ε4 allele is an important determinant for cognitive function in PD (Mata et al., 2014). However, it has been reported that apoE genotype is not correlated with brain amyloid burden in autopsy patients with PD (Gomperts et al., 2013). In a recent study, APOE-ε4 allele was identified as an important risk factor in the development of PD dementia (Real et al., 2023). PD is a progressive neurodegenerative disorder characterised by the loss of dopamine-secreting dopaminergic neurons and the accumulation of α-synuclein (α-syn) (Lenzi et al., 2020). Clusterin (CLU) is a molecular chaperone and has been described to prevent Aβ accumulation in AD, but its role in the pathogenesis of PD is not yet known (Lenzi et al., 2020; Zlokovic et al., 1996). The study of CLU showed that CLU co-localised with α-syn in biopsies from patients with α-synucleinopathies and was an α-syn-related protein (Sasaki et al., 2002). Studies have shown that CLU expression is upregulated in CSF and serum samples from Parkinson's patients (Maarouf et al., 2012; Přikrylová Vranová et al., 2010; Zhang et al., 2012). In a recent study, it has been reported that CLU gene polymorphism is associated with PD and high levels of CLU are expressed in the plasma of PD patients (Lin et al., 2021).

Cholesterol biomarkers have been reported to be important for monitoring brain damage and disease progression in MS (Browne et al., 2014; Murali et al., 2020; Weinstock-Guttman et al., 2011). In a prospective longitudinal study of healthy controls, patients with progressive MS and patients with relapsing-remitting MS, increases in apoA-I and HDL-cholesterol were reported to be protective in MS (Murali et al., 2020). ApoD, which is involved in the removal of lipids in neurodegeneration, has been reported to be found at high levels in MS patients (Reindl et al., 2001). However, in a different study, a clear decrease in apoD expression was found in human multiple sclerosis plaques (Navarro et al., 2018). In a prospective longitudinal study of patients with relapsing-remitting MS and patients with progressive multiple sclerosis, it was reported that apoA-I and apoE may be associated with grey matter damage in multiple sclerosis (McComb et al., 2020). It has been reported that chromogranin A (CgA) and CLU expression is increased in reactive astrocytes in MS white matter lesions, which indicates that CgA and CLU, as neuroinflammatory mediators, may be CSF markers in MS patients (van Luijn et al., 2016).

HD has been reported to be associated with changes in lipid composition and impaired lipoprotein metabolism (Chang et al., 2023). In the study in which control and Huntington's patient groups were included, it was reported that prothrombin, apolipoprotein A-IV (apoA-IV), haptoglobin levels were higher in the CSF of Huntington's patient group compared to the control group (Huang et al., 2011). It has been reported that weight loss occurs in both the early and advanced stages of HD and that high levels of apoA-IV in the CNS inhibit food intake and stabilise body weight in the long term (Huang et al., 2011). In a study, it was reported that plasma levels of total cholesterol, apoB, apoB-particle number and LDL components were lower in people with presymptomatic HD and symptomatic HD (Chang et al., 2023).

In a study on ALS, it was reported that changes in neurofilaments and apoE were observed in bulbar-onset fast progressing ALS compared to limb-onset fast progressing ALS (Leoni et al., 2019). In another study, high HDL and apoA-I levels were associated with a decreased risk of ALS, whereas high total cholesterol:HDL ratio, LDL and apoB levels were associated with an increased risk of ALS (Thompson et al., 2022).

In a study, it was reported that APOE-ε4 was associated with an increased risk of frontotemporal lobar degeneration (FTLD) in all genetic models, whereas there was no significant association between APOE-ε2 allele and FTLD in most genetic models and subgroup analyses (Su et al., 2017). At the end of a study, it was reported that apoA-I and apoA-II levels decreased, apoB levels did not change, but apolipoprotein C-I (apoC-I) level decreased in behavioral variant frontotemporal dementia (bvFTD) patients compared to controls. In addition, it was reported that apoB:apoA-I ratio and standard lipid ratios were significantly increased in bvFTD patients compared with AD patients and controls (Kim et al., 2018.

3. Conclusion

Mothers The functions of apolipoproteins involved in lipid metabolism have been associated with neurodegenerative diseases. However, there are inconsistent findings in studies and different apolipoprotein polymorphisms have been evaluated as risk factors or protective agents in different neurodegenerative diseases. This points to specificities in the mechanisms that cause neurodegenerative diseases. Therefore, further and comprehensive studies on apolipoproteins are required both to elucidate the mechanisms of the development of neurodegenerative diseases that seriously worsen the quality of life of people and to slow down and reduce the neurodegeneration process. Studies in this direction will contribute to the development of new clinical and pharmacological treatments.

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Conflicts of Interest

The authors declare that there is no conflict of interest between them.

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