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Agaroz Jel Elektroforezinde DNA Konsantrasyonunun Bant Yoğunluğu ve Çözünürlüğü Üzerine Etkisi

Effect of DNA Concentration on Band Intensity and Resolution in Agarose Gel Electrophoresis

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ÖZET

Amaç: Agaroz jel elektroforezi (AJE) nükleik asitlerin ayrıştırılması, tespiti ve saflaştırılması için yaygın kullanılan bir yöntemdir. Moleküler araştırmalarda ve biyoteknolojik uygulamalarda yoğun bir şekilde kullanılmaktadır. AJE' de bant çözünürlüğü ve bant kalitesi araştırmacılar için önemli etkenler arasındadır. Şuana kadar, tarak kalınlığı, jel konsantrasyonu, voltaj ve tamponlar gibi birçok faktörün AJE' de bant çözünürlüğü ve bant kalitesini etkilediği rapor edilmiştir. Fakat AJE' de DNA konsantrasyonun bant çözünürlüğü ve ışımaları üzerine etkisi belirsizdir. Bu nedenle, bu çalışmanın amacı DNA konsantrasyonun AJE sonuçları üzerine etkisini detaylı olarak araştırmaktı.
Materyal ve Metot: DNA boyut belirteçlerinin ve PCR ile elde edilen spesifik DNA fragmentlerinin farklı konsantrasyonları analiz edildi, fakat; yüklenen toplam DNA miktarı değiştirilmedi. Ayrıca, DNA konsantrasyonun AJE üzerine etkileri farklı kalınlıkta ve genişlikte dizayn edilen jel taraklarıyla da araştırıldı**.**
Bulgular: DNA konsantrasyonunun jel çözünürlüğünü etkilemediği gözlemlendi ve bu etki tarak kalınlığı ve genişliği tarafından da değiştirilmedi. Ayrıca, 2-kat seyreltme bant ışımalarını etkilemezken 8-kat seyreltme tüm test edilen DNA fragmentlerinin bant ışımalarını önemli bir şekilde etkiledi.
Sonuç: Örnekleri en az 8-kat konsantre etme, ince ve dar jel tarakları kullanma AJE'de istenilir sonuçlar için kullanılabilinir.

Anahtar Kelimeler: Agaroz jel elektroforezi, DNA konsantrasyonu, Bant Kalitesi, Bant ışıması, Jel çözünürlüğü.

ABSTRACT

Objective: Agarose gel electrophoresis (AGE) is a widely used method for separating, identifying, and purifying nucleic acids. It has been used intensively in molecular researches and biotechnological applications. In AGE, band resolution and band quality are important parameters for researchers. Until now, many factors such as comb thickness, gel concentration, voltage and buffers have been reported to influence resolution and band quality in AGE. However, effect of DNA concentration on band resolution and intensity in AGE is unclear. Therefore, aim of the study was to investigate the effect of DNA concentration on AGE results in detail.
Material and Method: Different concentrations of DNA Marker and specific DNA fragments obtained by PCR were analyzed, but the loaded total DNA quantity was not changed. Furthermore, the effect of DNA concentration on AGE was also investigated by designed gel combs with different thicknesses and wideness.
Results: It was shown that DNA concentration did not affect gel resolution, and the effectwas not changed by comb thickness and wideness. Also, 2-fold dilution did not affect band intensities while 8-fold dilution significantly affected band intensities of all tested DNA fragments.
Conclusion: Concentrating samples, at least 8-fold, and using thin and narrow gel combs can be used for desired results in AGE.

Keywords: Agarose gel electrophoresis, DNA concentration, Band quality, Band intensity, Gel resolution.

INTRODUCTION

Agarose gel electrophoresis (AGE) is a simple and highly effective method in electrophoresis of DNA fragments. It has been widely used for separating, identifying, and purifying nucleic acids and proteins since the 1960s (Bachvaroff and McMaster, 1964; Ross, 1964; Thorne, 1967; Philippsen and Zachau, 1972; Serwer, 1983; Stellwagen, 2009;

Greaser and Warren, 2012; Li and Arakawa, 2019; Sürmen et al., 2020). In practice, it is mainly used for DNA studies, and it is a simple and easy way of separating DNA fragments of varying sizes ranging from 100 bp to 25 kb (Sambrook and Russell, 2001).

In the electrophoresis process, DNA is forced to migrate in agarose gel matrices with an electric current towards to the anode pole since the charge of DNA molecules is negative due to the sugar-phosphate backbone on DNA. DNA molecules move through the gel matrices depending on their sizes. Larger DNA fragments migrate more slowly than smaller fragments because longer fragments pass gel pores more difficult (Helling et al., 1974). Migration of DNA molecules is affected by many factors including size of DNA molecule, agarose concentration, DNA conformation, applied voltage, electric field, temperature, staining techniques, agarose type, and electrophoresis buffer (Aaij andBorst, 1972; Sharp et al., 1973; Johnson and Grossman, 1977; Serwer, 1983; Mathew et al., 1988; Lai et al., 1989; Lee et al., 2012).

In AGE, resolution which is the ability to separate two different lengths of DNA fragments, and band quality are very important parameters for researchers. These are required to better interpretation of gel results, which may affect time and resources management. Resolution and band quality can be affected by several factors. Agarose gel concentration is the main factor affecting gel resolution. It determines pore sizes in gel and affects the mobility of the DNA. Increased concentration of agarose results in increasing resolution. Gel and comb thickness are the other factors influencing resolution and band quality. Thin combs are advised forbetter resolution, sharper DNA bands and desired band intensities, while the thin gel is feasible for short DNA fragments (Lee and Bahaman, 2012). Also, the applied voltage affects resolution and band quality. Higher voltages increase buffer temperature, which results in low gel resolution. Also, higher voltages cause band streaking in the longer DNA fragments (≥12-15 kb), whereas low voltages give rise to dispersion and diffusing small DNA fragments (≤1 kb) (Lee and Bahaman, 2012). Furthermore, the intercalation of dyes affects gel resolution, changing the negative charge of the DNA molecule, gel background, and band intensity, which is a very important factor for desired band intensity (Sharp et al., 1973; Lee and Bahaman, 2012; Green and Sambrook, 2019). However, the effect of loaded DNA concentration on resolution and band quality remains unclear.

The aim of the present study was to investigate the effects of DNA concentration on gel resolution and band intensity using different concentrations of DNA samples. For the sample, DNA Marker and PCR amplified DNA fragments were used. These samples were diluted at different levels and loaded into the agarose gel, but the loaded total DNA quantity was not changed. Here, the relationship between comb shape and sample concentration was also investigated by using designed combs and different concentrations of the sample.

MATERIAL and METHODS

DNA sample preparation

In this study, a 100-1000 bp DNA Marker (MR65, Blirt, Poland) was used to show the dilution effect on DNA fragments from 100 to 1.000 bp. DNA marker was diluted by using 1x loading buffer which was prepared by 5 volumes of deionized water and 1 volume of 6x loading dye (6xGreen loading dye). Diluted samples were tested in AGE, but the loaded total DNA quantity was not changed.

To obtain and study specific DNA fragments, PCR was used. In PCR, the plasmid pUC19 was used as template DNA. pUC19 was isolated from the *E. coli* DH5α by using a plasmid DNA isolation kit (Exprep Plasmid SV, Genall). Briefly, the stock culture of the strain was streaked onto the LB plate (10.0 g/L tryptone, 10.0 g/L NaCl, 5.0 g/L yeast extract, 15 g/L agar) containing ampicillin (50 µg/ml) and incubated at 37ºC. Next, a single colony was inocu-

lated in LB medium containing ampicillin, and incubated over night at 37ºC and 200 rpm. Then, the cultures were centrifuged at 10.000 x g for 3 min and cells were harvested. Following the plasmid DNA isolation kit's protocol, pUC19 DNA was purified.

For PCR amplification of 101 bp, 300 bp, 500 bp, 700 bp and 899 bp DNA fragments, a set of primers was designed (Table 1). Designed primers were cheeked as described previously by Arslan (2020).

PCR amplification of the fragments was carried out using the Taq Polymerase kit (Solisbiodyne). For each PCR reaction, final conditions were: 1×buffer BD, 1.5 mM MgCl2, 1 U FIREPol® DNA Polymerase (Solis Biodyne, Estonia), 200 µM dNTPs (Solis Biodyne, Estonia), 250 nM primer and 2 ng of DNA template (pUC19) in a 20 µL reaction volume. Then, each PCR reaction was carried out in a single run in a thermal cycler (Table 2).

Before loading PCR products (PCRp), an appropriate volume of 6xloading dye was added to the PCR tubes. Then, PCRp was diluted 2, 4 and 8-fold by using 1x loading dye and loaded into well.

Table 1. Primers used in the study.

PCR product (bp)	Direction	Sequence (5'->3')
101	Forward	GGAAACAGCTATGACCATG
	Reverse	GTATCACGAGGCCCTTTC
300	Forward	AATACGCAAACCGCCTCTC
	Reverse	GTAAAACGACGGCCAGTG
500	Forward	GGAAACAGCTATGACCATG
	Reverse	GTATCACGAGGCCCTTTC
700	Forward	GGAAACAGCTATGACCATG
	Reverse	ACGGAAATGTTGAATACTCATAC
899	Forward	AATACGCAAACCGCCTCTC
	Reverse	ACGGAAATGTTGAATACTCATAC

Quantification of DNA samples

DNA quantities of PCR products and DNA Marker were determined by using a Qubit™ .3.0 Fluorometer (Invitrogen). For this purpose, a Qubit™dsDNA HS assay kit (Invitrogen) was used. By following the manufacture's protocol, 198 µl working solution was prepared in 500 µl PCR tubes. Then, 2 µl DNA samples were added into the tubes, and DNA concentrations (ng/ul) were determined.

Table 2. Cycling conditions for amplification of target fragments.

Step	Temperature	Time	Cycles
Initial denaturation	94ºC	3 min	1
Denaturation	94ºC	20 sec	
Annealing	55ºC	25 sec	30
Extention	72ºC	50 sec	
Final extention	72ºC	5 min	1

Comb preparation

To show the link between the effect of sample concentration and comb shape, new combs with different thicknesses and wideness were designed and prepared from metal plates by laser cutting (Figure 1). Combs having 3 mm and 6 mm thickness were used to show the effect of sample concentration and comb's thickness (Figure 1a), while combs with 3 mm and 5 mm wideness were used to determine the effect of sample concentration and comb's wideness (Figure 1b).

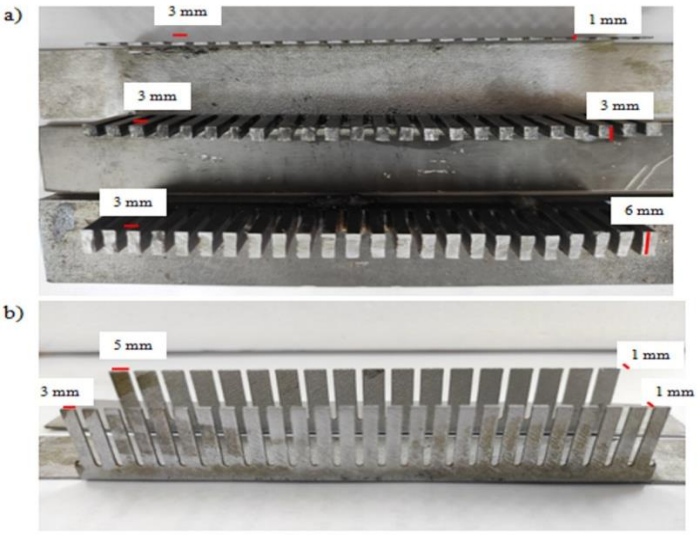

Figure 1. Comb shapes used in the study. (a) Comb thickness was increased from 1 mm to 3 mm and 6 mm. (b) Comb wideness was 3 mm and 5 mm

Agarose gel electrophoresis

In the study, 2% agarose gel was used. To prepare the gel, 2 g agarose (LE standard) was weighed and added in 100 ml 1xTBE buffer (10.8 g (w/v) tris base, 5.5 g (w/v) boric acid, 0.93 g (w/v) EDTA in 1 liter distilled water, pH≈8). The solution was heated using a microwave oven for 3 min. Then, the melted agarose was cooled until about 55 ˚C at room temperature. To stain DNA samples, gel staining was applied (pre-casting). For this purpose, 5 µl (1 µl/20 ml) a fluorescent dye (Eurosafe, Euroclone) was added into cooled agar (about 55 ˚C), and mixed-well, and then poured onto gel tray with designed-combs. Electrophoresis was carried out at 90 volts (V) for 70 min and gels were visualized under ultraviolet (UV) light using a transilluminator.

Quantification of AGE results

To quantification of the gel results, Image J software was used (Schneider et al., 2012). Using Image J, band intensities of each DNA fragment were analyzed and quantified. Photographs were uploaded to the program, and images were adjusted based on brightness and contrast. Then, analysis was carried out. Obtained data were represented as fold of the-control group's intensity value.

Statistical analysis

Obtained quantitative data were analyzed by using R 'stats' package, where a student's t-test was used to determine the significance level between groups (R Development Core Team, 2017).

RESULTS

In the study, firstly, 2.5, 5, 10-fold dilutions of DNA Marker (124.77±1.90 ng/µl) were assessed (Figure 2). According to the results, it was realized that no significant difference was detected in resolutions, indicating that resolution is not affected by DNA concentrations. The different results were observed in the band intensities. In higher quantities (4 µl), 2.5-fold dilution of the sample did not affect band intensities whereas 5-fold dilution caused a detectable difference in DNA fragments that were shorter than 300 bp (Figure 2a). When 2 µl DNA Marker and its dilutions were assessed, 5-fold dilution slightly affected band intensities whereas 10-fold dilution caused a detectable difference in 300 bp and shorter DNA fragments (Figure 2b). Therefore, a further detailed investigation was designed to study specific DNA fragments.

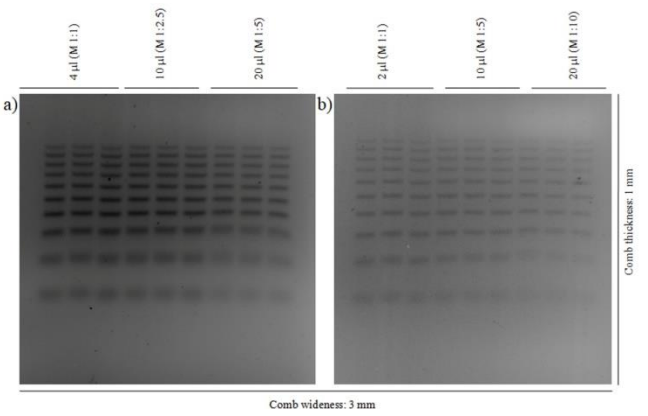

Figure 2. Triplicate electrophoresis results of 4 µl (a) and 2 µl (b) DNA marker (M), and its indicated dilutions, in where loaded total quantity was the same.

To study in detail the band intensity differences, single DNA fragments (101, 300, 500, 700 and 899 bp) were obtained by PCR and analyzed deeply according to the length of DNA fragments. DNA concentrations in PCR products were detected as 13±0.2 ng/µl, 28±0.1 ng/µl, 53±1.41 ng/µl, 50±0.7 ng/µl, 25±0.35 ng/µl, 53±1.41 ng/µl for 101 bp, 300 bp, 500 bp, 700 bp and 899 bp, respectively (Figure 3).

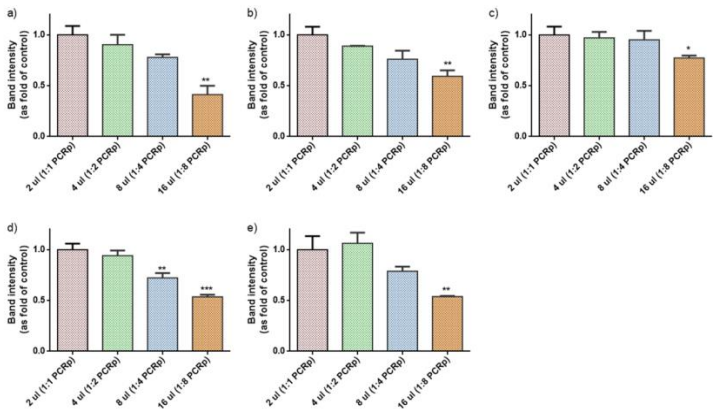

Figure 3. Quantitative analysis of band intensities of (a) 101 bp, (b) 300 bp, (c) 500 bp, (d) 700 bp and (e) 899 bp

DNA fragments, using image J program. Band intensities were shown as a fold of the control group's band intensity. Data represent mean and standard deviation in groups (n=3). Statistical significance level was indicated as *, ** and *** for P-value<0.05, <0.01 and<0.001, respectively.

Each PCR product (PCRp) was diluted 2, 4 and 8-fold and assessed separately (data not shown). Studying with specific fragments gave rise to deeply analyzing band intensities for each fragment. Band intensities of each DNA fragment were determined by Image J software (Figure 4). According to the results, 8-fold dilution of PCRp significantly decreased band intensities of all tested DNA fragments. The only intensity of 101 bp DNA fragment decreased more than 2-fold (Figure 3a). Band intensities of 101 bp, 300 bp, 500 bp and 899 bp DNA fragments were not affected in 4-fold dilution level, whereas the intensity of 700 bp DNA fragment was affected. As shown in quantitative data, 2-fold dilutions of all tested DNA fragments did not affect band intensities.

To investigate the link between the effect of DNA concentration and the shape of the comb, DNA Marker and its dilutions were loaded into wells with different thicknesses and wideness. Results showed that increasing sample-well thickness decreased resolution. However, sample dilutions did not affect the resolution (Figure 5).

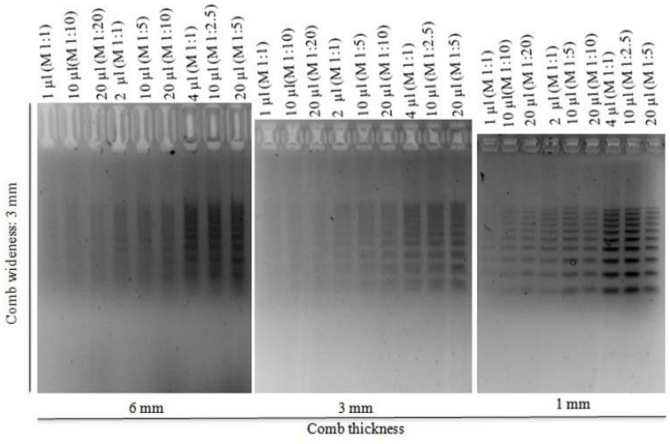

Figure 4. AGE results of DNA marker (M) and its indicated dilutions in the increasing sample-wells thicknesses, in which thickness was 6 mm (left), 3 mm (center) and 1 mm (right) whereas comb wideness was 3 mm for all the combs.

Furthermore, the effects of DNA concentration and comb wideness were also checked. The increasing wideness of the comb decreased band intensities compared to that of narrow combs, and the resolution was not affected (Figure 5). Here, it was shown that thin and narrow combs could be preferred for better band intensity and resolution.

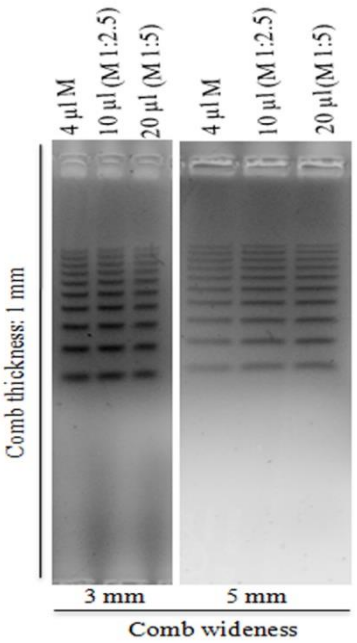

Figure 5. Effect of increasing comb wideness and DNA concentration on gel results, where loaded total DNA quantities were the same. DNA Marker (M) and its indicated dilutions were tested.

DISCUSSION

AGE is a very simple and useful technique in molecular researches to separate and evaluate DNA fragments. In AGE, resolution and band quality and/or intensity are important to evaluate of interest, and the effect of DNA concentration on AGE has not been studied in detail, yet. Here, a detailed study was carried out to investigate the effect. Studying with DNA Marker, which has 100-1000 bp length of DNA fragment, and PCR amplified specific fragments (101, 300, 500, 700 and 899 bp) showed that 2-fold dilution did not affect band in-

tensities (Figure 2 and Figure 3). However, 8-fold dilution decreased band intensities of all tested DNA fragments even the loaded DNA quantity was the same. The intensities of the 101 bp DNA fragments decreased more than 2-fold compared to the other fragments (Figure 3a). This could be due to the easy diffusing of shorter DNA fragments in agarose gel (Lee and Bahaman, 2012). In 4-fold diluted samples, only 700 bp PCR amplified fragment's band intensity decreased significantly whereas in 500 bp PCR amplified fragment was not affected at 4-fold dilution. This difference could be due to the difference in the initial quantitative of 500 and 700 bp PCRp. Therefore, 4-fold dilution can be significantly affected by initial quantities and the result may change. Here, it can be concluded that at least 8-fold concentration of DNA samples can be used to increase band intensities and better results. Evaporation and ethanol precipitation have been used to concentrate samples (Moore and Dowhan, 2002). Using these techniques, concentrated samples can be obtained, which may provide desired band intensity in AGE.

For the resolution of gel, agarose gel concentration and sample-well thickness should be considered (Slater and Noolandi, 1989; Smith, 1993; Lee and Bahaman, 2012). Sample-wells thickness is defined by used comb thickness. Increasing the sample-well thickness enables researchers to load more convenient way. However, increased thickness of the sample-well or combs causes a decrease in the gel resolution (see Figure 4 and (Lee and Bahaman, 2012)). On the other hand, thin wells are important for both resolution and band quality and require the lover volume of the sample compared to the thicker ones. However, thin sample-well causes difficult applications, leading to losing time and work. In practice, combs with 1.5 and 1 mm thickness are very common. Since sample loading into the well lower than 1 mm thickness is almost impossible, new approaches have been described for easy loading and desired resolution and band intensity. A patent application was described by Branko Kozulic (patent no: US5800691A). However, this approach did not gain wide usage. For the solution of this problem, it can be proposed that "using diluted sample and larger sample-well may be a practical solution for easy sample loading and desired resolution and band quality". However, the results obtained in this study showed that sample dilution did not affect resolution in thicker wells (Figure 4). Therefore, using thin combs is the only choice for the best resolution and band quality.

In the study, it was also shown that using narrow-combs resulted in higher band intensity in the same volume and concentration of samples (Figure 5). This shows that the height of the loaded sample in the sample-well is important, and this is not affected sample concentration. Using combs with wide teeth limits the working sample amount in the same gel. Therefore, using narrow combs is more practical for desired band intensity and working with more samples in the same gel in AGE.

In the literature, there are three methods to stain DNA in AGE. These methods are pre-loading, pre-casting and post-stain (Hall, 2020). In pre-loading technique, samples are stained during loading, in where stain, loading dye and sample are mixed and loaded into the sample well. In the pre-casting technique, the stain is added to molted agar, and then the gel is cast, which is mostly used technique. In the post-stain technique, gel electrophoresis is carried out, and then the gel is soaked within a stain solution (Hall, 2020). In the current study, a pre-casting staining technique was applied. Also, the pre-loading staining technique was checked, but the method is not appropriate with the used DNA stain in the study. Even though the post-stain technique is an important way for more appropriate sizing of DNA fragments, the technique is time-consuming and costly (Sigmon and Larcom, 1996; Miller et al., 1999; Huang and Fu, 2005; Huang et al., 2010; Hall, 2020). It should be noted that in the current study, pre-casting method was applied; therefore, the obtained result can be dependent pre-casting technique.

To conclude, gel resolution is not affected by DNA concentration, and this effect is not depend on comb thickness and wideness. 8-fold sample dilution significantly affects band intensity while 2-fold dilution does not. For better band intensity and resolution, thin and narrow combs are the only choice. Concentrating samples at least 8-fold can be used for desired band intensity in AGE.

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Ethical Statement

This study does not present any ethical concerns.

Conflict of Interest

The authors declare that there is no conflict of interest.

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