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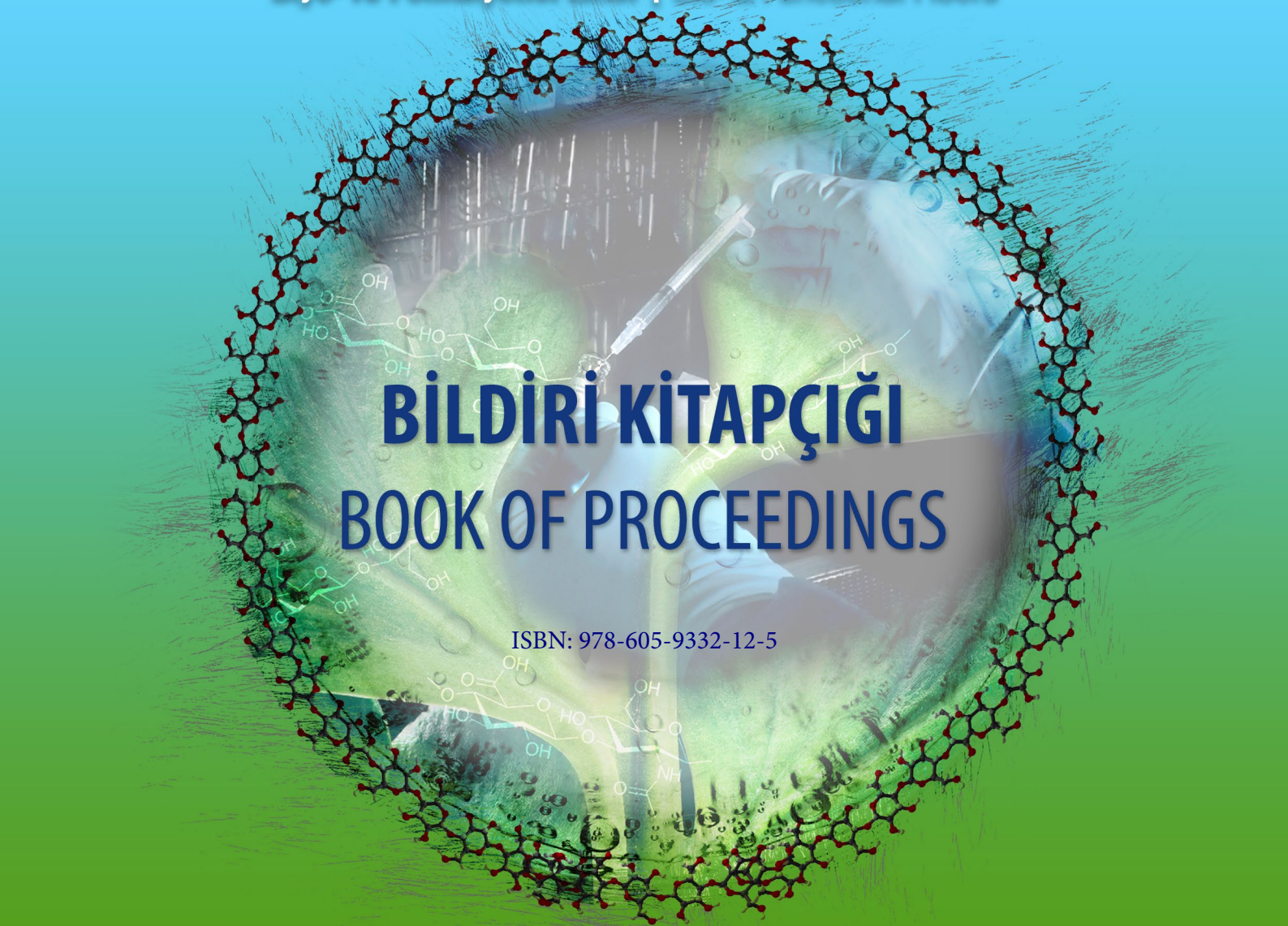

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Adsorption challenge in the PDMS-based microfluidic systems for drug screening application

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SUMMARY
Drug screening is one of the demand areas due to close and direct dependency on human health. On the other hand, recently microfluidic systems have been increasingly used for drug development and screening purposes. However, this system has some challenges such as adsorption issue which can effect pharmacokinetic–pharmacodynamic (PK-PD) of the drugs. Thus, in this research, the issue was characterized and evaluated by UV-Vis spectrophotometry and FTIR spectroscopy devices as a model drug of cisplatin. Despite of strong relationship between logP and adsorption, and the very low value of logP in the drug candidate, the results for both apical and basal planes of the microfluidic chip confirmed the adsorption. In the UV-Vis spectrophotometry, the basal plane show 5%, and 10% higher adsorption compared to apical and control polydimethylsiloxane (PDMS)-based microfluidic. Additionally, the FTIR patterns were a good coincide with UV-Vis results.

PURPOSE
The main purpose of this research is to prepare a PDMS-based microfluidic platform for the investigation of surface adsorption in the target drug analysis experiments. Today, this system has frequently been implemented as an alternative to animal-based trials for the drug development and study of disease. Failure in the similarities between animals and human resulted to the attraction and motivation of researchers to rapidly move toward microfluidics-based organ-on-a-chip system [1-7]. On the other hand, using new and state-of-art technologies lead to new hurdles such as surface adsorption. Therefore, in this work, we focused on the adsorption issue. Finally, the prepared system is characterized by various devices for evaluation adsorption effect on the obtained results.

INTRODUCTION
Drug development and screening in recent years get more attention due to their significance and effect on human beings. Till today, conventional animal-based methods are performed for introducing a new drug in the market, but these routes faced big challenges i.e., 10-15 years to develop as well as spending approximately 2.6 billion dollars per each drug [8]. To overcome the challenges, crucial needs for emerging new platforms have not been ignorable. Therefore, the microfluidic organ-on-a-chip (OOC) system was discovered [9] and has been under improvement by diverse research groups [10-12]. The minimum cost of developing and using drugs from the initial stage to the market, portability, ease of access, best similarities with human structure, and reliability of the obtained results compared to animal trials are

classified as some advantages of this system [11, 13]. By benefiting from the advantages, different drug investigations have been carried out for OOCs applications [14]. In this research, the above-mentioned platform was performed for simulation liver-on-a-chip (LOC) and cisplatin was used as a drug candidate for the investigation of adsorption.

Regarding to the literature, diverse polymer types of materials have been implemented in microfluidic platforms [15, 16]. Currently, PDMS was the most attractive one concerning to the other owing to transparency, almost non-toxicity, best compatibility in biological applications in addtion to flexibility, permeability and inexpensively [17-19].

Despite using the PDMS-based LOC facilitating and paving the way for a drug study, on the other side, other drawbacks, for instance, adsorption and absorption of small molecules due to the hydrophobic property of PDMS surface, are one of the reason to be investigated. To hinder these important barriers, therefore, some research groups provide coating, doping, grafting, and extraction effective routes [20, 21]. More detail about these methods was reviewed and exists in the literature [22, 23]. In addition to the above-mentioned pathways, in some cases, the researchers completely replaced PDMS polymer with alternatives such as polylactic [24], poly(methyl methacrylate) (PMMA), poly(carbonate) (PC) [25], high-density polyethylene (HDPE), and low-density polyethylene (LDPE) [26], and so on.

EXPERIMENTAL

Material: In this work, Cisplatin (Cas No: 15663-27-1, Product No: 479306) was used as a model drug. PDMS and PMMA were utilized for the fabrication of apical and basal channels of the chip, and to fix as well as prevent any misorientation in the channels and membrane. Polyethylene terephthalate (PET) membrane without a cell line was selected for this research as a preliminary investigation.

Analysis: Fourier transform infrared spectroscopy (FTIR), and ultraviolet-visible (UV-Vis) spectrophotometry was employed for in detail characterization of the molecular structure and existence of chemical groups on the chip's channels and the samples. The FTIR and UV-Vis spectrophotometry was performed in the 200-4000 cm^{-1}, and 190-1100 nm ranges, respectively.

Method: The apical and basal planes of the chip were initially poured into the home-made prepared mold by mixing the prepolymer and cross-linker with 10:1 w/w. Then the well-known soft lithography followed in the clean room; vacuumed the molded PDMS, and finally heat for overnight for the curing process. After curation, the prepared polymer was unmolded and kept for the chip formation procedure.

The prepared polymers were carefully cleaned with acetone a few times, then a high-resolution camera was employed for precise in-situ mounting of the basal and apical channels, and basement membrane. The drug candidate in our case passed through the basal channel. The schematic of this process was visualized in Fig. 1.

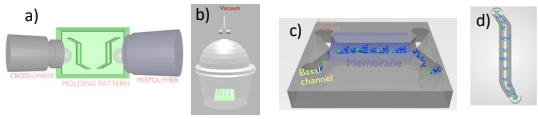

Figure 1. The schematic representative of preparation of the chip by using soft lithography

EXPERIMENTAL RESULTS AND DISCUSSIONS

The FTIR spectrum of the chip is displayed in Fig. 2. Also, the magnified section in the measured range is illustrated. It is obviously seen the intensity of the transmittance in the apical and basal plane is lower than control PDMS. Significantly, the transmittance value in the apical plane is higher than in the basal plane which demonstrated adsorption of the employed cisplatin drug when moving through the channel in the PDMS surface. A similar discussion was also reported by other works [22, 27]. In addition, it was noticed that there is no change in the location of the peaks that emerged in the control, basal and apical planes of the PDMS chip.

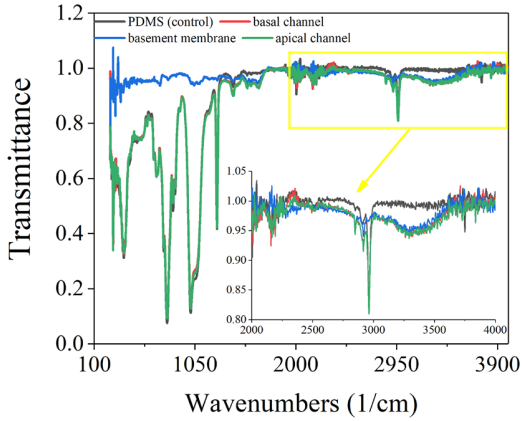

Figure 2. The FTIR spectrum of the basal, apical, and basement membrane of the fabricated chip using cisplatin drug after 7 days

The UV-Vis spectrophotometry of the control, basal and apical planes of the PDMS were depicted in Fig.

3. The change in the transmittance values of both channels is clearly clarified. The mean values of the transmittance were calculated 130%, 125%, 120% for control, apical, and basal PDMS planes in the 300-1100 nm wavelength range. It is seen that the minimum transparency was obtained in the basal plane which supported the FTIR results. To as best of our knowledge, there is a reverse relationship between transmittance and absorbance. So, this reduction exhibited adsorption of the drug onto the PDMS surface causing a reduction in the transmittance.

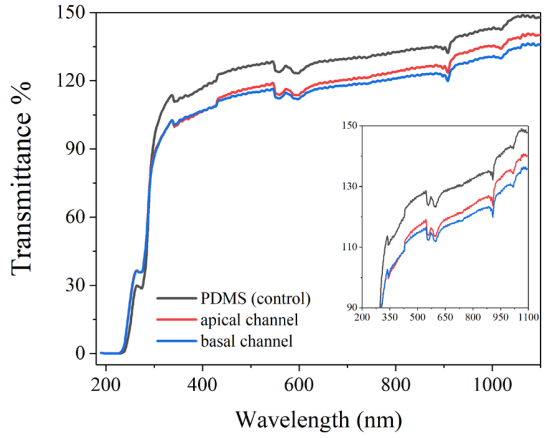

Figure 3. The UV-Vis spectrum of the fabricated chip using cisplatin as a model drug after 7 days

The adsorption of drugs in these types of experiments is highly related to the octanol/water concentration or partition coefficient or logP. The exact value of this parameter is known for most drugs but, should depend on experiment conditions [28]. The parameter can alter from -4 to 5 value, that the higher value declared lipophilic properties of a drug. This increase in the logP value inferred higher adsorption in PDMS while regarding the works published by V. Novohradsky et al. the cisplatin has logP = -2.25 [29] demonstrates lower adsorption by the PDMS surfaces among other drugs. The adsorption in this system also probably due to the low amount of sample.

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CONCLUSIONS

The cisplatin was successfully used as a model drug for understanding adsorption in the PDMS-based microfluidic system. The chip was fabricated using PMDS and PET-based membrane without a cell line for at least 7 days. Regarding the suitable analyses which were performed in this work, despite lower logP in the selected drug the adsorption was observed. In both UV-Vis and FTIR measurements, the obtained results were confirmed to reduce the intensity of the transmittance values of the basal, apical channels of the prepared chip. This research investigation highly recommended the usage of diverse routes introduced in this work for improvement in this challenge of obtaining reliable and repeatable results.

SUGGESTIONS FOR FURTHER WORK

The adsorption by the PDMS-based microfluidics leads to a serious change in the results obtained after the tests, then according to the works in the literature and our best knowledge, it is highly recommended to use a layer between the selected drug and PDMS surface or altered the surface properties of the used polymer material. This process has effectively and significantly behaved as a barrier for reduction or in some cases minimizing the adsorption to overcome the challenge and access close and reliable results for widespread of the platform in more applications.

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