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Polysaccharide-based films for transdermal drug delivery systems

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Polysaccharide-based materials are derived from plants and can be blended with other bioactive materials to enhance their properties, resulting in improved drug release, stability, bioavailability, and target specificity. Polysaccharides are known to exhibit delayed color development, reduced acidity, and increased firmness in drug materials. Therefore, it is necessary to study the mechanisms underlying their kinetics to understand their high activities, potencies, and specificities when used in pharmaceutical products.

The present study aims to investigate the potential of various polysaccharides as transdermal films to control the release of donepezil hydrochloride, a drug commonly used to treat Alzheimer's disease. For this purpose, pectin and guar gum were used as a polysaccharide-based polymer matrix for the transdermal films. The drug release kinetics was determined by analyzing samples taken at various time intervals using a UV spectrophotometer. *In vitro*, drug release studies were performed for donepezil hydrochloride by using a Franz diffusion cell which simulates human skin. To investigate release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models which include zero order, first order, Higuchi and Korsmeyer-Peppas. The results in the present work confirm the controlled release of donepezil hydrochloride and the polysaccharide content of the transdermal patch can extend the release of donepezil hydrochloride. Therefore, the study's results suggest that pectin and guar gum have potential as new materials for developing treatments for Alzheimer's disease and other diseases that require continuous drug release.

Keywords: Drug delivery**,** Donepezil hydrochloride, Polysaccharide, Alzheimer

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative condition that predominantly affects the elderly population. While most of the treatment for Alzheimer's disease is administered orally, this treatment method has disadvantages for elderly patient groups with difficulties in memory and swallowing. Transdermal drug delivery systems offer advantages over oral dosage forms in the management of various diseases [1-4].

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional methods of administering drugs due to their numerous advantages. Unlike oral administration, TDDS allow for controlled and sustained release of drugs through the skin over an extended period. This controlled release ensures a constant dosage, improves therapeutic efficacy, and minimizes fluctuations in drug concentration. Additionally, transdermal administration is non-invasive, eliminating the need for invasive procedures and reducing the risk of complications and infections associated with traditional methods [5, 6].

The convenience of transdermal patches or topical applications also enhances patient compliance by simplifying the drug regimen and reducing the frequency of dosing.

Moreover, transdermal administration enhances the bioavailability of the drug and improves therapeutic efficacy by bypassing the organs responsible for first-pass metabolism [7-9].

Transdermal drug delivery systems typically consist of three main components: a drug reservoir, a polymer matrix, and a skin adhesive layer. The polymers used in TDDS must possess biocompatibility, biodegradability, and suitable mechanical properties. Recently, polysaccharides like pectin and guar gum have gained attention as promising candidates for transdermal drug delivery systems. These polysaccharides exhibit desirable properties such as biocompatibility, biodegradability, and ability to form a gel-like matrix, facilitating sustained drug release and improved skin adhesion. The inclusion of other bioactive ingredients such as plasticizers, antimicrobial agents, or therapeutic drugs can further enhance the properties of transdermal drug delivery systems [10, 11].

The aim of the present study was to develop a transdermal drug delivery system for controlled release of donepezil hydrochloride which is mainly used in the treatment of Alzheimer’s disease. For this purpose pectin, guar gum, glycerol, and boric acid were used in the formulation of transdermal patches. The *in vitro* drug release studies were carried out

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using a Franz diffusion cell for donepezil hydrochloride loaded films at pH 7.4.

MATERIALS AND METHOD

Materials

Pectin and guar gum were purchased from Benosen Company. Glycerol, used as a plastizer, was purchased from Tekkim Kimya. Boric acid was supplied from Eti Maden and donepezil hydrochloride was supplied by Abdi İbrahim Medicine Company, Turkey.

Transdermal film preparation

Transdermal films were prepared by using the solvent casting technique. Guar gum and pectin were used as polysaccaharide-based polymers and they were weighed and then dissolved in distilled water under stirring using a magnetic stirrer for a duration of thirty minutes to ensure proper dissolution and uniformity. After this period, glycerol was added as a plastizer, boric asit as an antibacterial agent and donepezil hydrochloride as a drug. The formulation of the polysaccharide-based transdermal films is summarized in Table 1.The final solutions were kept at rest for another 2 h to eliminate the bubbles formed. To obtain the films, 14 g of the solution was poured onto circular Petri dishes (12 cm in diameter) and dried for 72 h at 37 ◦C. Schematic presentation of the experimental procedure can be seen in Figure 1.

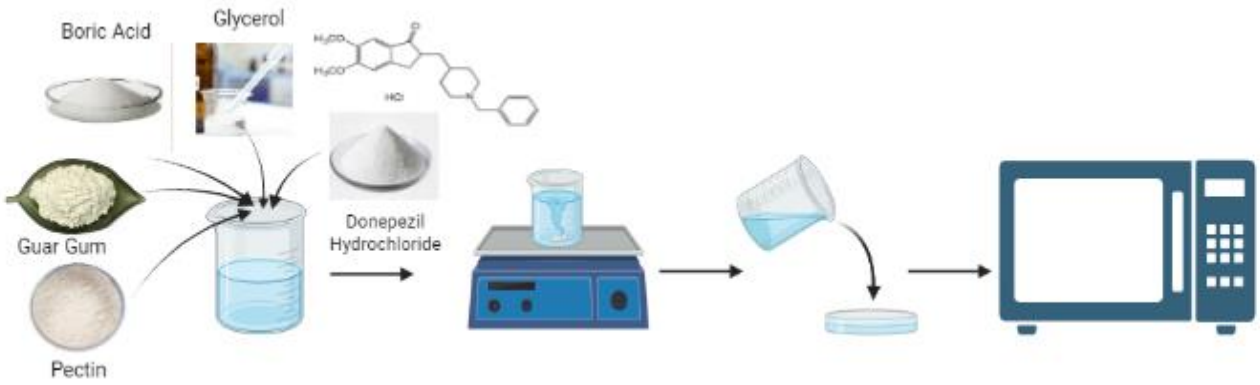

Figure 1. Schematic presentation of the experimental procedure for preparing transdermal films

Table 1. Formulation of transdermal films

Film code	2% Pectin (ml)	2% Guar gum (ml)	Glycerol (% w/v)	Boric acid (% w/v)	Donepezil - HCl (% w/v)
PGB-1	100	-	2	0.1	1.43
PGB-2	75	25	2	0.1	1.43
PGB-3	50	50	2	0.1	1.43
PGB-4	25	75	2	0.1	1.43
PGB-5	-	100	2	0.1	1.43

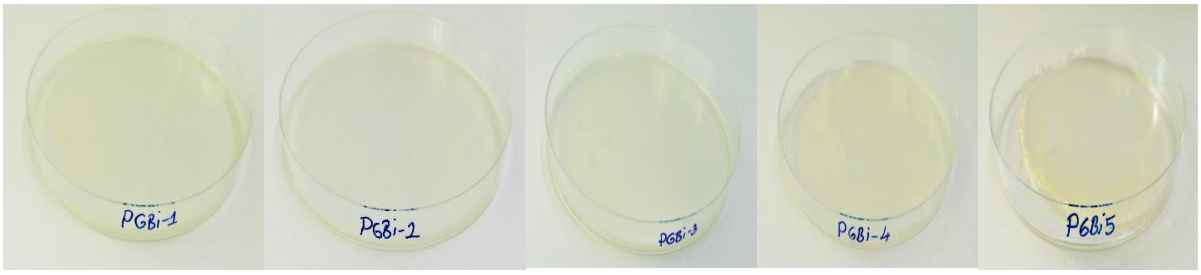

Figure 2. The dried state of the films

Table 2. Release kinetic models

Release kinetic modeling	
Zero-order model	$Q=Q_o+k*t$
First-order model	$Q/Q_o=1-e^{(-k*t)}$
Higuchi model	$Q=k*t^{1/2}$
Korsmeyer-Peppas model	$Q/Q_o=k*t^{n}$

RESULTS

Drug release experiments

In vitro, drug release studies were conducted with a vertical Franz diffusion cell shown in Figure 2. Transdermal film samples prepared by guar gum and pectin were placed in the membrane section of the Franz cell. Cellulose acetate membrane filters, with a diameter of 47 mm and a pore size of 0.45 µm, were prepared and placed in a pH 7.4 phosphate buffer (PBS) solution to mimic the skin. The prepared films were positioned on the cellulose acetate membrane filter, sandwiched between the diffusion cell cover and the receiver chamber. The top of the diffusion cell cover and the tip of the sampling tube were covered with parafilm to prevent evaporation. The diffusion cell was maintained at 36.8°C to represent body temperature by incubating under shaking at 100 rpm. Drug release was achieved in the diffusion cell for 8 hours. The hourly samples were collected and analyzed using a UV-vis spectrophotometer based on the absorbance at 270 nm. A linear calibration curve was constructed at a concentration range of approximately 0-40 mg/L with R^2 value of 0.9996.

Kinetic behavior of drug release

Drug release kinetic behavior graphs are used to understand the release of drugs from a formulation over time. These graphs typically plot the cumulative percentage of drug released *versus* time. The shape of the graph can provide information about the drug release mechanism and kinetics. Different models can be used to fit the experimental data and interpret the drug release kinetics. It includes first-order, zero-order, Korsmeyer-Peppas and Higuchi models. Factors that can affect drug release kinetics include the composition and morphology of the carrier, surface morphology, and molecular structures of the polymers. Understanding the drug release kinetics is important in formulating drugs with desired delivery and predicting the behavior of the formulated drug *in vivo*. Therefore, the kinetics of donepezil hydrochloride drug release during the pH 7.4 phosphate buffer permeability study were determined using the zero-order, first-order, Higuchi equation and Korsmeyer-Peppas equations. The equations for the release kinetic models are given in Table 3 below.

Q is the amount of drug dissolved in time, Q_0 is the initial amount of drug in the solution, k is the zero order release constant expressed in units of concentration/time [11-13].

R^2 regression coefficient values found by using the kinetic model equations are shown in Table 3. According to the table, the highest R^2 values were observed in Higuchi and Korsmeyer-Peppas release kinetics. As a result, it was seen that the films fit the Korsmeyer-Peppas model and the release mechanism was examined through this model. The results are shown in Table 3.

The controlled release behavior of the drug from polymer matrices was characterized by the Korsmeyer-Peppas equation. The values of the emission exponent (*n*) obtained from the slope of log t *versus* %log emission plot indicate that the release mechanism is working. Table 4 presents the *n* values of the five films obtained using the provided equation. The experimental findings indicate that the release of the drug from PGBI-5 film formulations adheres to the Fickian diffusion mechanism, as evidenced by the values of *n* being less than or equal to 0.45. Moreover, during instances of abnormal drug release, a combination of Fickian diffusion and polymer chain relaxation/erosion within the hydrated layers of the matrix is observed. The involvement of additives is believed to contribute to the overall release process by influencing these two mechanisms. In contrast, film formulations PGBI-1, PGBI-2, PGBI-3, and PGBI-4 exhibit a non-Fickian mechanism, as indicated by their *n* release exponent values falling within the range of $0.45<n<0.89$. Consequently, it can be inferred from these results that the drug release process is dependent on both drug diffusion and polymer relaxation, signifying the interplay between these factors.

Table 3. Regression coefficients according to release kinetic models

Film code	Zero-order kinetic model	First-order kinetic model	Higuchi kinetic model	Korsmeyer – Peppas kinetic model
PGB-1	0.5492	0.3234	0.7478	0.88829
PGB-2	0.5313	0.3339	0.7622	0.8656
PGB-3	0.6129	0.443	0.8149	0.9244
PGB-4	0.6898	0.462	0.884	0.9459
PGBİ-5	0.708	0.452	0.9139	0.911

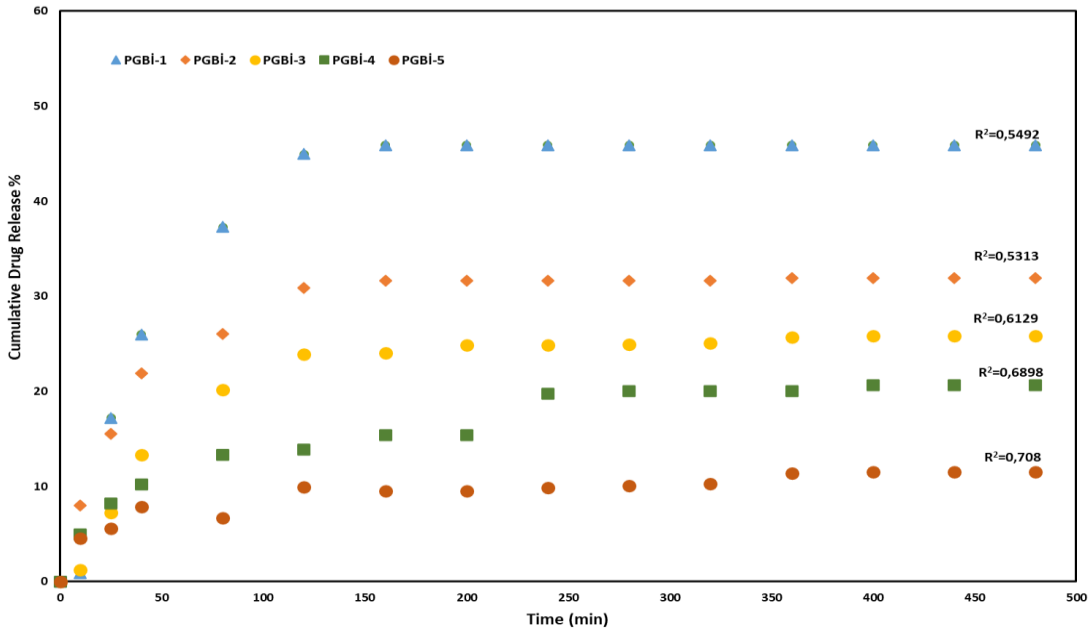

Figure 3. Zero-order kinetic model

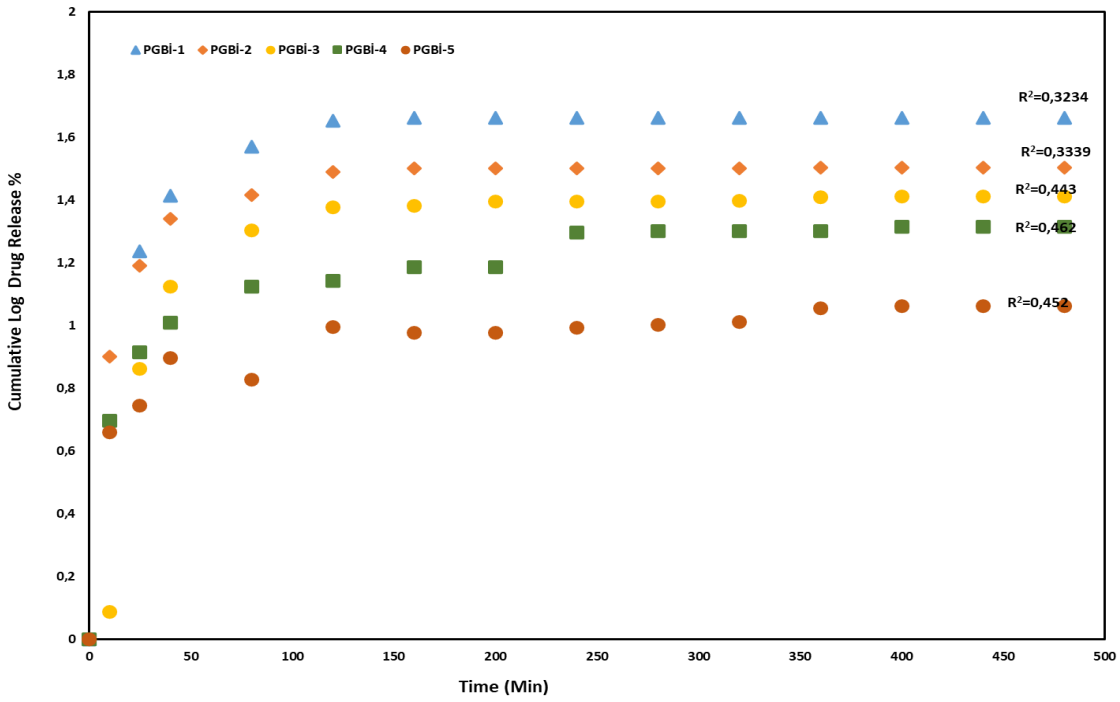

Figure 4. First-order kinetic model

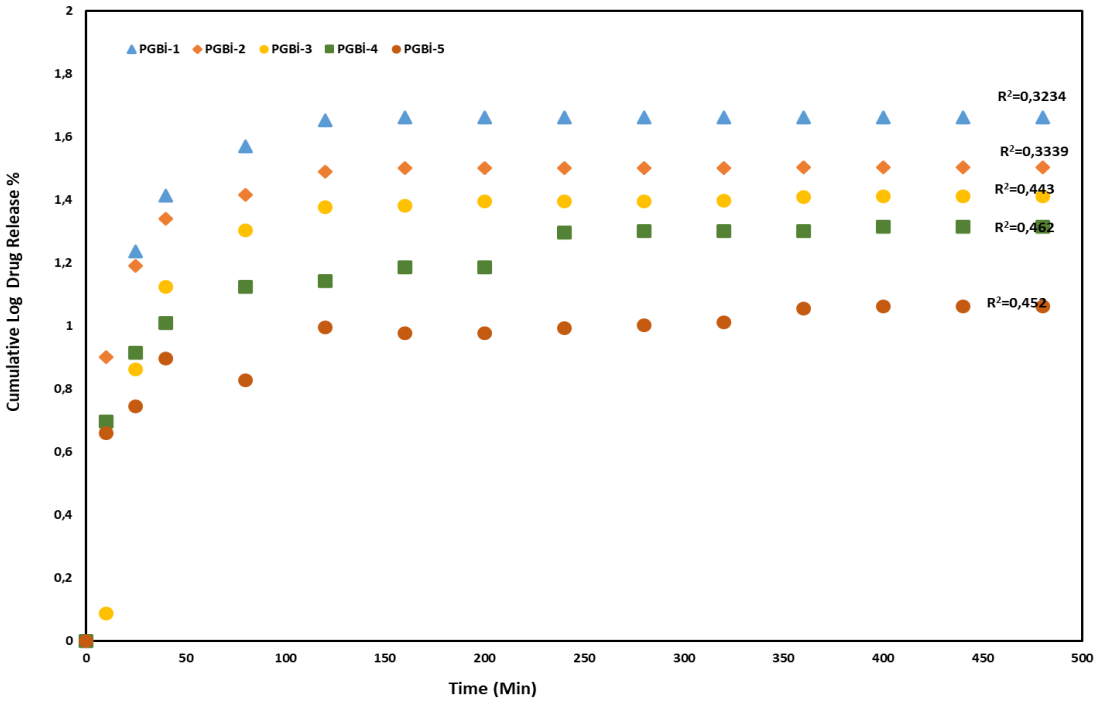

Figure 5. Higuchi kinetic model

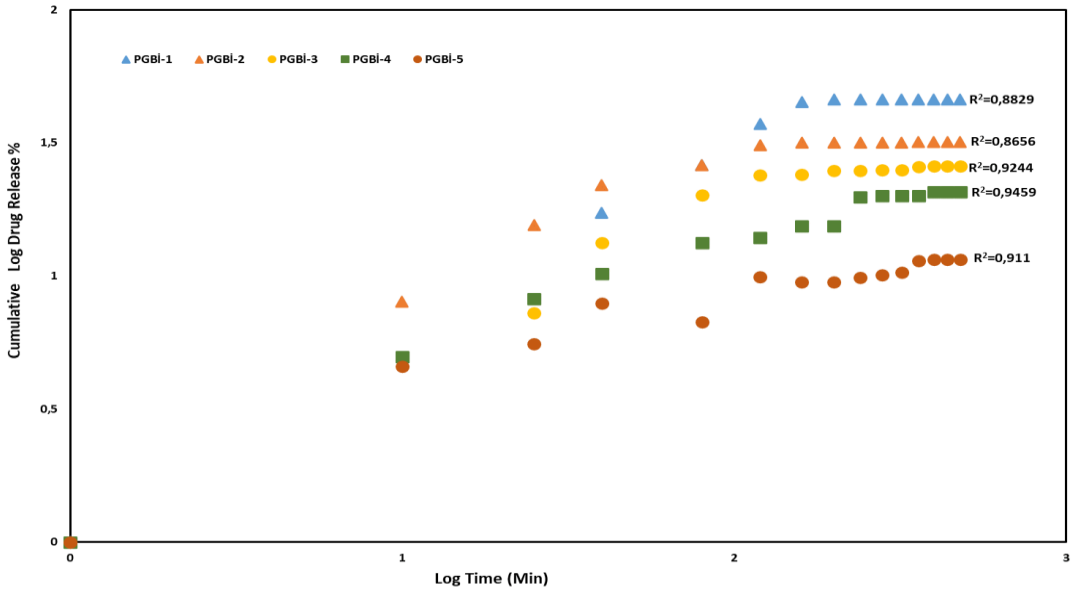

Figure 6. Korsmeyer - Peppas kinetic model

Table 4. Korsmeyer-Peppas release kinetic values

Film codes	*n*	k
PGBI-1	0.5842	0.2652
PGBI-2	0.5015	0.3107
PGBI-3	0.5193	0.1479
PGBI-4	0.4667	0.1686
PGBI-5	0.3476	0.1845

DISCUSSION

In this study, five different transdermal patches were successfully synthesized by incorporating varying ratios of substances and plasticizers. The introduction of different substances resulted in distinct release rates among the patches. To evaluate the drug release profiles, all patches were subjected to an 8-hour analysis in a pH 7.4 environment. Utilizing UV spectroscopy, the results revealed that the patch designated as PGBI-1 exhibited the highest release rate, measuring at 47.19%. Notably, the other patches demonstrated release rates of 33.54% for PGBI-2, 26.96% for PGBI-3, 20.68% for PGBI-4, and 10.67% for PGBI-5. These findings establish a clear correlation between the incorporated substances and the resulting drug release rates, underscoring the significance of formulation optimization for transdermal patches.

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