PREPARATION OF TRANSDERMAL FILMS FOR CONTROLLED RELEASE OF DONEPEZIL HCL

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ABSTRACT
Transdermal drug delivery systems, also known as "patches" have been attracted a great deal of attention for the past few decades since it delivers the drug through the skin in a predetermined and controlled. Transdermal delivery is a viable alternative to conventional oral therapy and provides a controlled drug release by increasing patient compliance and avoiding first-pass metabolism. Donepezil Hydrochloride is an active pharmaceutical ingredient for Alzheimer's disease (AD) It has been widely used by oral route. But this type of treatment may have some disadvantages when a chronic neurological disorder is present because of the patient's unwillingness to swallow and forgeting to take or carry pills in the day. So, transdermal patches can be used as an alternative treatment for AD.
The aim of this study was to develop a transdermal drug delivery system for controlled release of Donepezil HCl. For this purpose, hydroxyethyl cellulose/sodium alginate/gelatin combined with polyvinylpyrrolidone (PVP) and PEG-400 in the formulation of transdermal patches. Transdermal patches were prepared by Franz diffusion cell method. Hydroxyethyl cellulose, sodium alginate and gelatine as matrix-forming agent and transcutol as plasticizer was in the transdermal films. Fourier transform infrared (FT-IR) spectroscopy) was used to characterize the films. In vitro drug release studies were performed for donepezil hydrochloride-loaded hydrogels at 7.4. To study the 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 investigation confirm the controlled release of Donepezil HCl and sodium alginate content of transdermal patch can extend the release of donepezil. The study demonstrates that the fabricated transdermal system of Donepezil HCl can be considered as a suitable alternative of the oral route. Also studies have shown promising results, further studies are needed for pharmacokinetic evaluation.
Keywords: Transdermal Films

Introduction

The permeation of drugs through the skin offers promising route for treatment of some illness due the fact that skin is the largest organ of the human body (Javadzadeh, 2017; Groeber, 2011). Transdermal drug delivery systems have several important advantages over traditional systems including avoidance of the first-pass metabolism, longer duration of action, reduction in dosing frequency and good patient compliance. Additionally this type treatment is an alternative for people who forget or unable to take pills (specially fornauseated or unconscious patients). For this reasons, delivering drugs through the skin for treatment of diseased states is gaining increasingly great importance. However, the skin's low permeability limits the number of drugs (Escobar-Chávez, 2012; Badilli, 2018). There is a clear need to develop transdermal drug delivery systems like asthma, hypertension, diabetes, epilepsy, Alzheimer etc (Madan, 2015).

Skin can be accepted as a multilayered biomembrane and the transport of drug through the skin is a complex process. This process can be divided into three steps: penetration, permeation, and resorption. with particular absorption Among the various skin layers, the stratum corneum is the upper most layer of the skin and provides barrier to against drug absorption. To overcome this passive barrier system, chemical penetration enhancers are used (Encyclopedia of Toxicology, 2014; Bartosova, 2012; Pham, 2016). The physicochemical properties of the drugs are very important for absorption of drug into the skin (Albash, 2019).

Before the in vivo evaluation, in vitro drug release experiment can give reliable information about drug release from a transdermal patch. Although there is a number of methods can be used to evaluate drug release from the transdermal formulation, the Franz-diffusion cell widely used to investigate the efficiency of transdermal drug delivery systems in vitro (Al Hanbali, 2019; Salamanca, 2018). It determines important relationships between skin, active pharmaceutical ingredients and formulation (Franz, 1975; Senol, 2018). The image of the Franz difussion cell is given in Figure 1.

The aim of the present study was to develop a transdermal drug delivery system for controlled release of Donepezil HCl which is mainly used in the treatment of Alzheimer's disease. Alzheimer's disease is a type of dementia and

irreversible brain disorder that affects 6%-8% of people over the age of 65 years (Senol, 2018; Sozio, 2012). For this aim polyvinylpyrrolidone (PVP), hydroxyethyl cellulose (HEC), sodium alginate, gelatine and PEG-400 were used in the formulation of transdermal patches. Prepared films characterized by using FT-IR spectroscopy. The in vitro drug release studies were carried out using Franz diffusion cell for Donepezil hydrochloride loaded films at pH 7.4.

Figure 1. The image of Franz Diffusion Cell

The Study

Films were synthesized using PVP, HEC, Na alginate and gelatine polymers. The total film weight prepared is 10 grams. For this, all the components were added to the beaker and mixed in a magnetic stirrer. The films were then transferred to a glass petri dish and kept at room temperature for 24 hours and then kept in the oven at 40°C for 48 hours. Three formulations were developed by varying the polymer and keeping the drug load constant. Drug release started using the films taken out of the oven, Franz Diffusion Cell. Cellulose acetate membrane filter was used as a section taken from the film according to the mouth of the Franz Diffusion Cell and as a skin. pH 7.4 was used to represent blood and placed at the receptor site of the diffusion cell. The temperature was kept constant at 37°C. Drug release was achieved in the diffusion cell for 72 hours. The hourly samples were read in the UV Spectrophotometer and the percentage amount of drug release was measured. Synthesized polymers were prepared as shown in Table 1.

Table 1. Formulation design of PVP transdermal patches

Films	PVP	HEC	Na Alginate	Gelatine	PEG 400	pH 7.4	Transcutol	Distilled Water	Donepezil HCl
1	0.3	10			6.4	19.3	4.3	59.6	0.1
2	0.3		10		6.4	19.3	4.3	59.6	0.1
3	0.3			5	6.4	19.3	4.3	64.6	0.1

Findings

Characterization of PVP Films

Fourier transform infrared (FT-IR) spectroscopy was used to characterize the PVP transdermal patch. Figure 2 shows the photograph of film 1. The photograph also illustrates the relatively smooth surfaces of the PVP film.

Figure 2. Photograph of PVP Film 1

The FT-IR spectra of PVP are presented in Figure 3. The FT-IR spectrum of PVP had a peak at ~3420 cm^{-1} which indicates O-H stretching. The peaks at ~2950 and ~1650 cm^{-1} proved the existence of asymmetric stretching of CH_2 and stretching of C-O, respectively. The peaks at ~1020 and ~570 cm-1 were attributed to the CH2 rock and N-C=O bending, respectively (Figure 3, Film 1). The bands at ~1590 cm^{-1} and ~1410 cm^{-1} corresponded to asymmetric and symmetric carboxyl group stretching vibration, respectively for sodium alginate (Figure 3, Film 2). Film 3 in Figure 3 shows FTIR spectrum of the gelatin showed that the peaks at ~1640 cm^{-1} was due to C=O stretching. C–H stretching at ~920 and 2850 cm^{-1}.

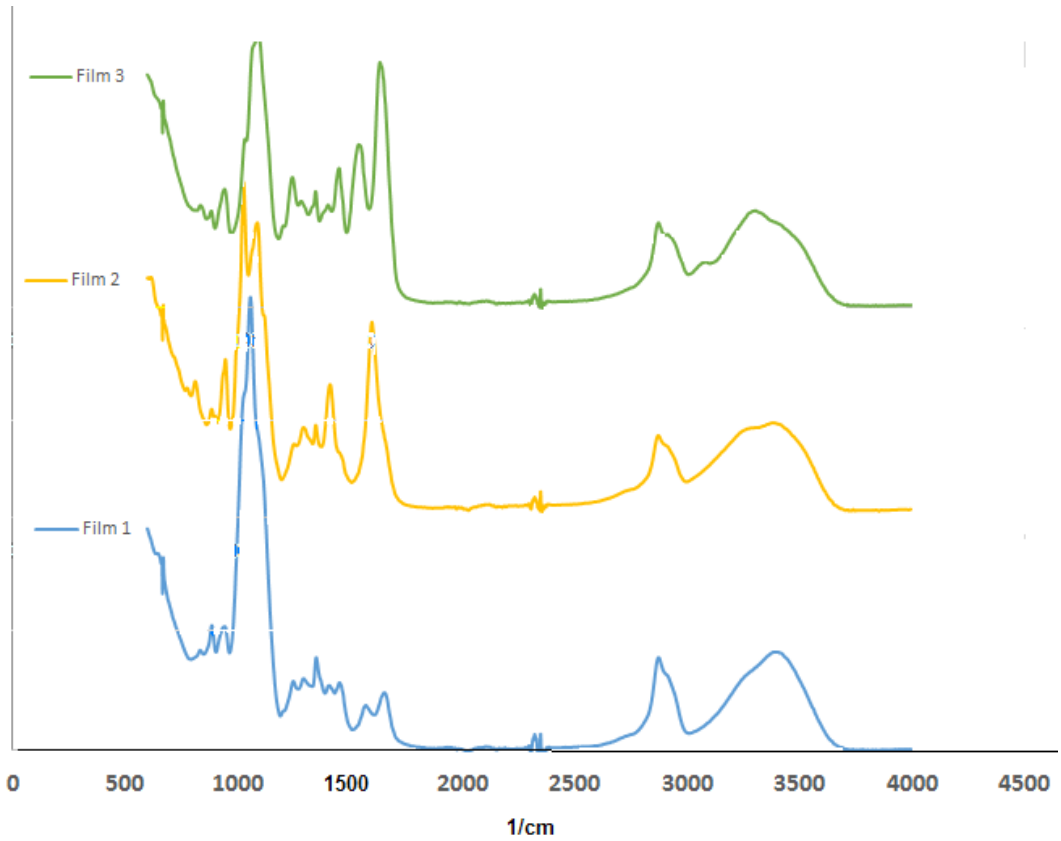

Figure 3. FT-IR analyses of PVP-based films.

In vitro drug release studies

The interaction of the films with donepezil hydrochloride at pH 7.4 and 37 ºC was seen in Figure 4. Donepezil HCl release studies were performed UV–Vis spectrophotometer at 270 nm. It has been found that film of sodium alginate show the highest release ratio with ~48%.

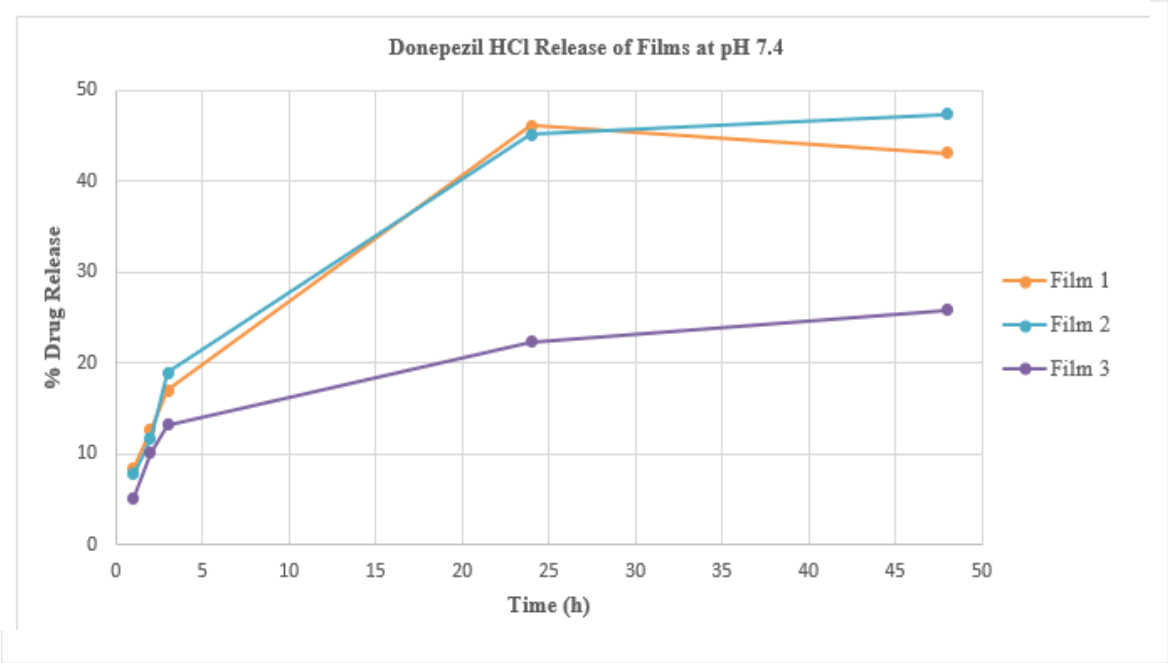

Figure 4. Donepezil HCl Release of Films

Drug Release Kinetic

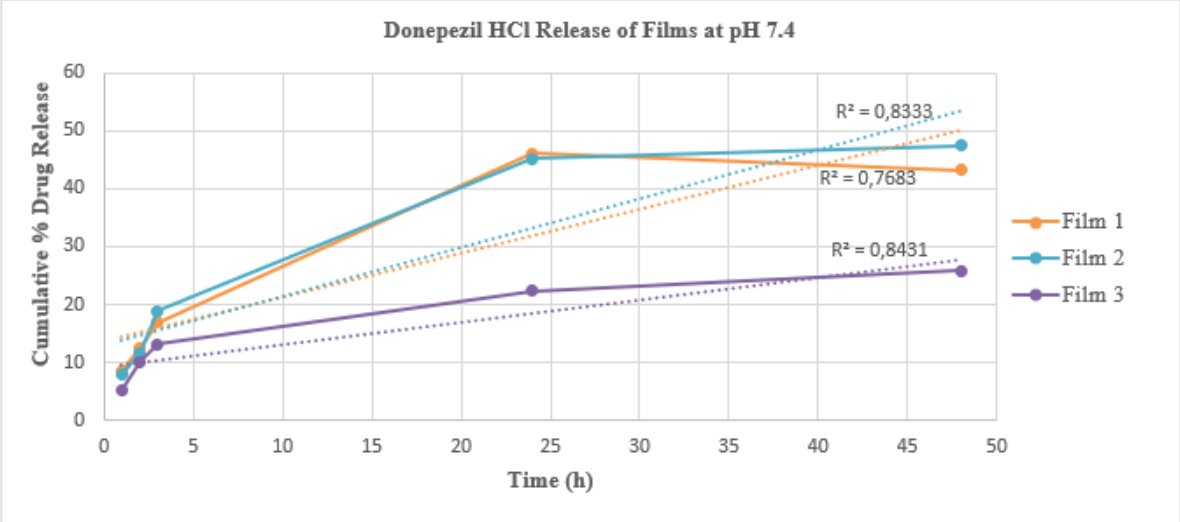

Figure 5. Zero Order Kinetic Model

The in vitro dissolution data of various formulation was analyzed by fitting the obtained data into various kinetic model to explain the release kinetics. Mathematical models that describe the kinetics of drug release from a transdermal patch include Higuchi, first order, zero order, and Peppas and Korsmeyer models. After data are collected and introduced into these models, the model that fits the data best is used to determine the mechanism of kinetic drug release (Dash, 2010). The kinetic profiles of PVP films are shown in Figure 5-8. According to the kinetic data, Higuchi kinetic Model were fitted suitable for all 3 films. Drug-release kinetics for films best corresponded to the Higuchi Kinetic model with good correlation with data with R^2 values varying between 0.89-0.93.

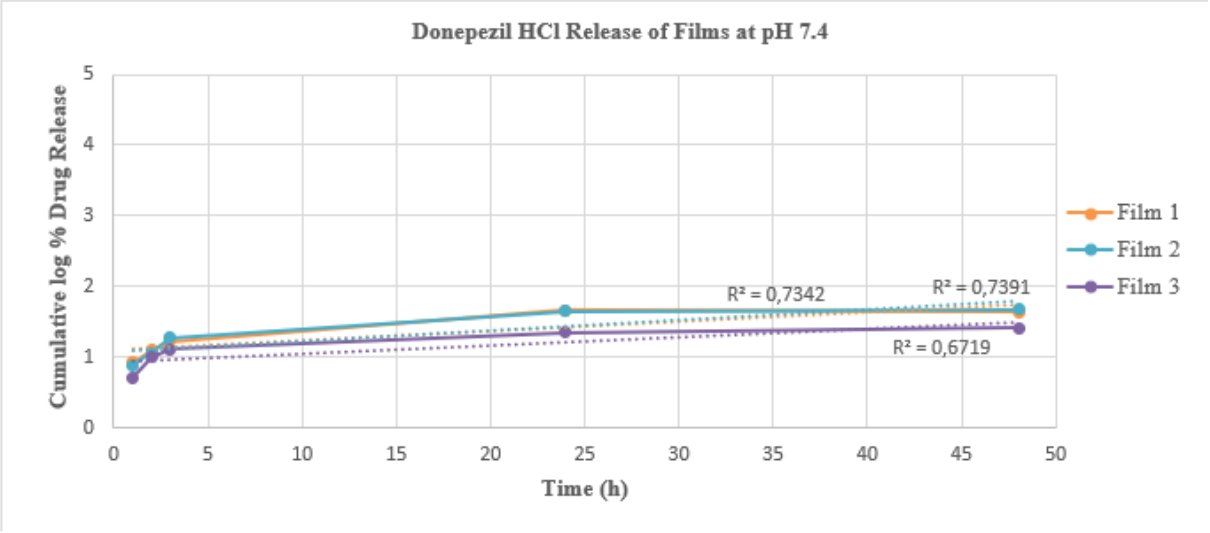

Figure 6. First Order Kinetic Model

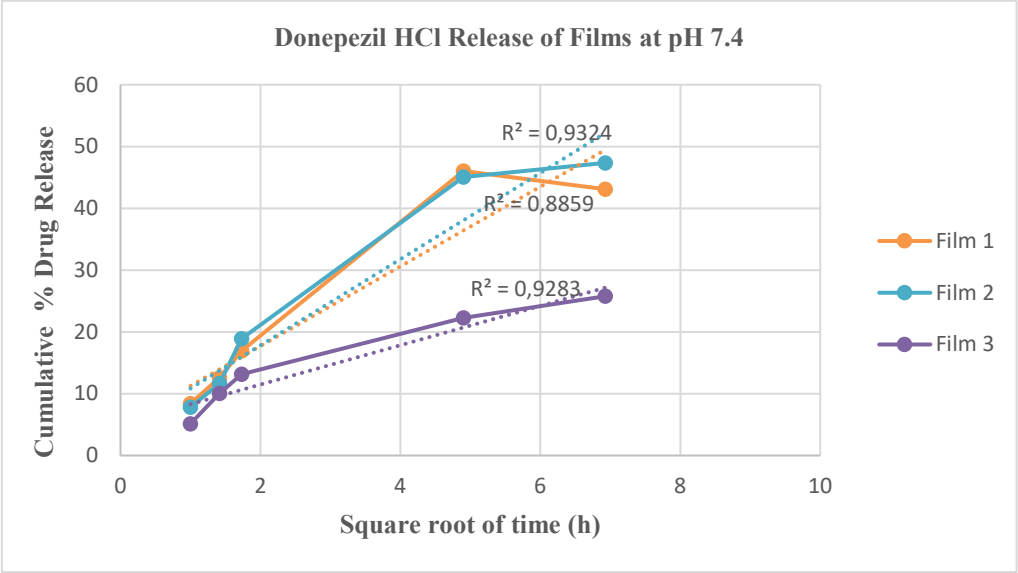

Figure 7. Higuchi Kinetic Model

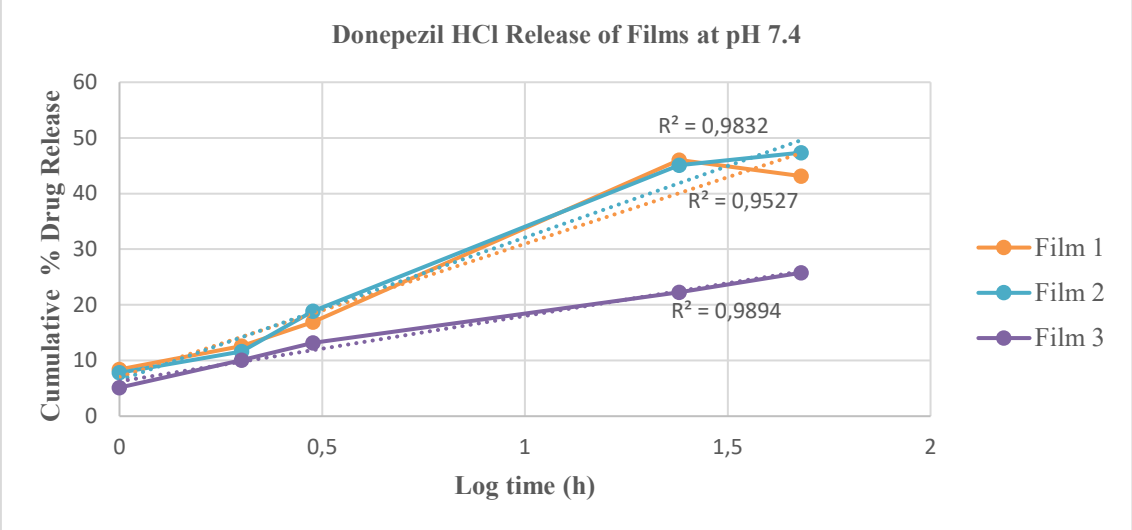

Figure 8. Korsmeyer-Peppas Kinetic Model

Conclusions

In this study, PVP based films were prepared successfully with Na-alginate and gelatine. It has been found that PVP film with Na-alginate has the highest drug release rate with 47.36 %. These results suggest that this type of films may be appropriate for use in the controlled release of drugs. The best fitted model showing the highest determination coefficient (R^2) was Higuchi Kinetic Model which is diffusion controlled transport mechanism of drug permeation.

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