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Development and Characterization of Donepezil Loaded Transdermal Patches for the Effective Treatment of Alzheimer

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ABSTRACT

Donepezil (DNZ) is a centrally acting reversible acetyl cholinesterase inhibitor. The main therapeutic use of donepezil is in the treatment of Alzheimer's disease. The present research work pertains to the preparation of transdermal patches of donepezil with the objective to improve its patient compliance, therapeutic efficacy and to reduce the frequency of dosing and side effects as well as to avoid its extensive first pass metabolism. The recent patents on Rivastigmine (WO2013150542A2), Xanomeline (US5980933A) and Propentofylline (CA2255580A1) helped in selecting the drug and polymers. The transdermal patches were prepared using various polymers in combination with the plasticizer and penetration enhancers. The physicochemical parameters like folding endurance, thickness, drug content, content uniformity, moisture absorption, weight variation, and drug permeation studies of the optimized patches were studied. The system containing Eudragit S -100, Eudragit E -100 and HPMC as matrix forming agent and glycerin as plasticizer was the best formulation. The *in vitro* release data was treated with kinetic equations and it followed zero order release. The diffusion study showed 89% drug was released within 72 hours. Tween-80 (0.83 % w/w) was found to be the best among all penetration enhancers. All the transdermal patches had the desired physical properties like tensile strength, folding endurance, flatness and water vapor transmission rate *etc*. The study concluded that that transdermal patch can extend the release of donepezil for many hours and also ensure enhanced bioavailability, further it also helps in avoiding the first pass effect.

INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems. So, this transdermal drug delivery system has been a great field of interest in the recent time. Many drugs which can be injected directly into the blood stream via skin have been formulated. The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin. A transdermal patch has several components including liners, adherents, drug reservoirs, drug release membrane which play a vital role in the release of the drug via skin. Various types of patches along with various methods of applications have been discovered to deliver the drug from the transdermal patch. Because of its great advantages, it has become one of the highly research field among the various drug delivery system. Transdermal drug delivery system (TDDS) is a controlled drug delivery of drug in to systemic circulation at a predetermined rate and it has advantages compared to the parenteral and oral routes of administration, especially in the elderly [1]. This type of formulation is particularly useful when a chronic neurological disorder is present because it allows for the circumvention of the patient's unwillingness to swallow. It helps in maintaining constant drug blood levels over an extended time period and improves compliance, because there is no need for the patient to remember to take his or her medication or carry pills for further administrations later in the day. When compared to oral route this route has many benefits such as sustaining drug delivery, bypassing first-pass metabolism maintaining a constant and pro- longed drug level in plasma, minimizing patient variability, and making it possible to terminate treatment when necessary [1, 2].

Worldwide TDDS has only 8% market share, while it is still in its infancy in the Indian market. This necessitates the need to develop TDDS to cater to some of the life threatening diseases like asthma, hypertension, diabetes, epilepsy, Alzheimer etc. With respect to the above background a need was found to develop TDDS in one of these areas.

Donepezil (DNZ) is a centrally acting reversible acetyl cholinesterase inhibitor. It is mainly used in the treatment of Alzheimer's disease where it is used to increase cortical acetylcholine [3]. Alzheimer's disease (AD) is the most common type of senile dementia, affecting 6%-8% of people over the age of 65 years and nearly 30% of people older than 85 years [3, 4].

There are some patented transdermal formulations for the treatment of Alzheimer's disease [5-7].

The present study aims at formulating a stable TDDS of donepezil which shall release the drug for a period of 48-72 hours.

MATERIALS AND METHODS

MATERIALS

Donepezil was gifted by Cipla Ltd. Mumbai. Eudragit S 100, Eudragit E 100 (EE 100) and HPMCK100 were purchased from Research-lab Fine Chem. Industries, Mumbai. Other ingredients used are analytical reagent grade [8].

Formulation of Transdermal Patches

In the present study, matrix type transdermal patches of donepezil were prepared by solvent casting techniques. Circular, glass molds coated with aluminum foil having surface area of 75 cm^2 were fabricated for casting the patches.

Selection of Polymers

From the literature review and based on the characteristics of Eudragit S 100 (ES 100), it was selected as parent polymer [8-10]. The further need was to select polymer which can retard the drug release for or near to 48-72 hrs. During the preliminary trial various polymers and their combinations (in 1:1 molar ratio) Table **1** were evaluated for the film forming ability, film separation and appearance. De- pending upon the results of

preliminary trials the T5 batch containing ES 100, EE 100 and HPMC K100 was selected for further study.

Formulation Development

Based on the results obtained from the preliminary trials nine different formulations were made (Table **2**) to study the effect of concentrations of EE100 and HPMCK 100 on the cumulative release. Solvent casting method was used to prepare the drug loaded as well as placebo patches. The casting solutions were prepared by dissolving weighed quantities (Table **3** and **4**) of polymers in various solvents. ES 100 and EE 100 were dissolved in ethanol: acetone mixture (1:1), while HPMCK 100 was dissolved in dichloromethane: methanol (1:1) with aid of a magnetic stirrer in a conical flask with a stopper. The two polymeric solutions were further mixed to form a uniform mixture. 1 ml of Propylene glycol (PG), butylatedhydroxytoulene (BHT) as antioxidant 1%, glycerine as plasticizer (30%w/w of total weight of formulation) was added to the polymer mixture and dissolved. Donepezil solution was made in ethanol (2-5 ml) and it was mixed uniformly with the above polymer solution. The volume was made up to 15 ml with ethanol and was stirred for about 10 min to facilitate uniform mixing. This solution was sonicated using low energy ultrasonicator for 2-3 min in order to remove entrapped air bubbles [11-13].

Preparation of Transdermal Patches

Fifteen milliliter of the prepared solution was cast on a petri plate lined with aluminum foil. The cast film was dried in oven at 38±2°C for first 8 hours and later at 60±1°C for next 40 hours. The patches were removed by peeling and cut into square dimension of 2 cm x 2 cm (4 cm^2). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers [14, 15].

Screening of Formulation

Nine formulations were studied for drug release characteristics by *in vitro* diffusion across dialysis membrane, in order to select the optimum formulation which can retard the drug for desired period of time [16].

Selection and Optimization of Penetration Enhancer Concentration

To achieve the desired release and flux of donepezil across rat skin from the prepared

transdermal patch, 1% w/w concentration of each penetration enhancer was added to the optimized patch (D-3) and the flux achieved was calculated [8]. Considering the flux rate obtained with 1% of different penetration enhancers, further the concentration of each penetration enhancer at which the desired flux can be attained (75 µg/cm^2/hr) was calculated and is shown in table 4.

Evaluation of Transdermal Patches

Drug Content and Content Uniformity

The patch was transferred into a graduated glass stopper flask containing 100 ml of phosphate buffer 7.4. The flask was shaken for 4 hrs in a mechanical shaker. Then the solution was filtered and 1 ml was diluted to 10 ml with phosphate buffer and the absorbance was measured at 270.6 nm(V-630 JASCO, Japan) using a placebo patch solution as blank and the drug content and content uniformity were calculated [19, 20].

Physical Characterization

The following physical evaluation studies were performed on the prepared patches.

Drug Excipients Compatibility Study

The pure drug(DNZ) and a mixture of DNZ with polymers ES 100, EE100 and HPMCK 100 was mixed with IR grade KBr in the ratio of 100:1. This mixture was com- pressed in the form of a pellet by applying 15 tons of pres- sure in a hydraulic press. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in (Shimadzu IR affinity-1) FTIR instrument. The drug and polymers were analyzed individually as well as a physical mixture for study the drug excipients compatibility.

Thickness

The prepared 4 cm^2 patch was divided into four equal quadrants of (1 x 1 cm) using a marker and the thickness was measured in each quadrant and at the center, using Digital Vernier Calliper, (Aerospace-0-150), and the average thickness was reported [21, 22].

Weight Variation

Three patches (4 cm^2) from three different batches were selected randomly, were cut and

weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation [23].

Moisture Content

In order to determine the moisture content of the patches, the patches were weighed accurately. The patches were kept in a desiccators containing calcium chloride ($CaCl_2$) at 40°C until it showed a constant weight. The moisture content was determined by calculating the difference between initial weight taken and the constant weight. The moisture content was reported in terms of percent moisture content [24, 25].

$$\% \text{ Moisture Content} = \frac{(\text{Initial weight of patch}) - (\text{Constant weight of patch})}{(\text{Initial weight of patch})} \times 10$$

Moisture Uptake [26, 27]

The patches were dried at 40°C for 24 h and then weighed accurately up to three decimal points in gram unit and were exposed to two different relative humidity conditions of 75% RH in humidity oven (Thermolab, India) at 27±2°C. Then the weight was measured periodically to constant weight. The moisture uptake by the patches was calculated as a difference between final constant weight and initial dried weight.

$$\% \text{ Moisture uptake} = \frac{(\text{Constant weight of patch}) - (\text{Initial weight of patch})}{(\text{Initial weight of patch})} \times 100$$

Moisture Loss

The patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride ($CaCl_2$). After 72 hours the patches were taken out and weighed. The moisture loss was calculated using the formula.

$$\% \text{ Moisture loss} = \frac{(\text{Final weight}) - (\text{Initial weight})}{(\text{Initial weight})} \times 100$$

Flatness

For the calculation of percent flatness longitudinal strips were cut from the prepared patches and thickness of each strip was measured and the variation in the thickness

(vertical length) due to non-uniformity of flatness was measured. Flatness was calculated by measuring constriction (unevenness) of strips and a zero percent constriction was considered to be equal to 100 percent flatness.

$$\% \text{ Constriction} = \frac{(\text{average thickness}) - (\text{thickness at sampling point})}{(\text{Average thickness})} \times 100$$

Folding Endurance

This was determined by repeatedly folding the patches at the same place until it broke. The number of times the patches can be folded at the same place without breaking or cracking gave the value of folding endurance.

Stability Testing

Accelerated stability testing was conducted for 90 days at different conditions: Room temperature and 40°C and 25% RH. Samples were taken out at predetermined interval of time (day 10, 20, 30, 45, 60, 75, 90) to determine its appearance and texture while drug content and diffusion studies were done at the end of 30, 60 and 90 days. Stability conditions for different patches are depicted in Table **5**.

RESULTS AND DISCUSSION:

Drug Excipients Compatibility Study

IR studies were performed on DNZ, and a physical mixture of DNZ with ES 100, EE 100 and HPMC K100 to understand the interaction between drug and polymers. From these spectras, it was observed that there was no significant change in the original peak of the drug Fig. (**1a)**, when com- pared with the spectra of physical mixture Fig. (**1b**) and this indicates that there is no interaction between drug and polymers selected for film formation.

Evaluation of Trial Batches

The result obtained from preliminary trials Table **6** showed that T5 batch was found to be the best combination with respect to the film forming ability, film separation and appearance of film. Hence it was selected for further study.

Formulation Design

Taking into account all the available pharmacological data for DNZ, the input rate of DNZ in body which will maintain the desired therapeutic level of drug was calculated to be 75 µg/cm^2/hr from a patch of area 4 cm^2 [28, 29]. Nine different formulations (D1-D9) were prepared by varying the concentration of EE100 and HPMCK100. Screening of formulation was done by evaluating for drug release characteristics across dialysis membrane, in order to select the formulation which is able to retard the drug release for 60-72 hours. The result for the % cumulative release and flux (calculated using PCPDISSO V3 software) are shown in Fig. (**2**).

The % CR from matrix type formulations D-1, D-2, D-3, D-5, D-6, D-7, D-8 and D-9 is 79, 80, 85, 75, 73, 68, 70, and 73% respectively while flux obtained from the same was 65, 81, 73, 80, 82, 88, 81 and 65 µg/cm^2/hr respectively. The result of this study showed that the formulation D-4 was unable to control the release of DNZ for desired period of time (60-72 hrs), as about 90 % of drug was released in only 48 hrs. Formulation D-3 was found to be most satisfactory as it was able to control the drug release for 60 hrs with % CR of 85.23%. D-3 batch was further selected for drug release characteristics across rat skin. Therefore there was a need to add penetration enhancer (P.E).

The results of the diffusion study using formulation D-3 and various PE's show all PE's are able to increase the drug penetration to different extent. The release from D-3-1, D-3-2, D-3-3, and D-3-4 was found to be 84.98, 86.87, 86.24 and 89.65%. Their relative efficacy in enhancing penetration of DNZ is as follows.

Tween 80 > Oleic acid >Transcutol>Labrasol

Drug Content and Drug Content Uniformity

The drug content and drug content uniformity of best optimized formulation (D-3-4) is detailed in Table **7**. The % RSD is below 2%, showing that there are no significant changes in drug content of patch.

Physical Characterization of Different Types of Trans- dermal Patches

The results of the physical evaluations are detailed in Table **8**.

Stability Study

The D-3-4 optimized formulation was kept for stability studies in order to get an idea of any possibility of drug degradation during stability testing. The results of stability study of various formulations under different conditions are given in Table **9**.

There was a negligible difference in the drug content observed after stability study. The physical characteristics also remained unchanged suggesting that all the formulations are stable under the given conditions.

CONCLUSION

Currently, the first choice for the treatment of Alzheimer's disease is reducing the cholinergic deficiency in the CNS with reversible acetyl cholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil), which corrects the deficiency of acetylcholine in the CNS. Frequent gastrointestinal symptoms including, nausea, constipation diarrhea, vomiting, abdominal pain, abdominal distention and anorexia were associated with large fluctuation of plasma levels after oral administration of donepezil. A transdermal administration of donepezil offers considerable advantages over conventional delivery methods for patients who have difficulties swallowing liquids or solids. Furthermore, certain unwanted effects may be decreased by this route of administration; for example, plasma level fluctuations could be greatly reduced, first pass effects could be avoided and the dosing schedule can be uncomplicated. Moreover, if adverse side effects occur, termination of drug delivery can be achieved simply patch removal. These compliance profiles and improved tolerability could potentially result in greater treatment adherence, and the patch might be favored over the oral route by the majority of caregivers in the near future.

CURRENT & FUTURE DEVELOPMENTS

The most common type of senile dementia is Alzheimer's disease (AD). The recommended dosage for Donepezil immediate-release IR is 5 mg/day for the first 4 weeks and 10 mg/day thereafter [3, 4]. The transdermal drug delivery route has various advantages as compared to the other routes of administration, especially in the elderly people. Indeed, this type of administration is particularly useful when a chronic neurological disorder is present because it allows for the circumvention of the patient's unwillingness to swallow. It also provides constant drug blood levels over an extended period of time and hence good patient compliance.

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AUTHOR'S CONTRIBUTION

All authors have contributed in the studies performed and in the preparation of manuscripts.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

FINANCIAL DISCLOSURE

No financial supports have been granted by any agency to conduct these studies.

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Table No. 1. Preparation of initial trial batches for polymer selection.

Batch code	Polymers
T1	ES 100
T2	EE 100
T3	ES 100 + EE 100
T4	HPMC
T5	ES 100 + EE 100+ HPMC

Table No. 2. Selection of polymer for D-3 type patch.

Trial Batches	Drug(mg)	EE100 (mg)	HPMC(mg)
D-1	22	125	325
D-2	22	125	225
D-3	22	125	125
D-4	22	225	125
D-5	22	225	225
D-6	22	225	325
D-7	22	325	125
D-8	22	325	225
D-9	22	325	325

Table No. 3. Selection of penetration enhancers for D-3 type patch.

Ingredients	D-3-1	D 3-2	D-3-3	D-3-4
Donepezil (mg)	22	22	22	22
ES-100(mg)	325	325	325	325
EE-100(mg)	125	125	125	125
HPMCK 100 (mg)	125	125	125	125
Glycerine (mg)	239.1	239.1	239.1	239.1
PG-400 (mL)	0.07	0.07	0.07	0.07
Penetration enhancer	1%	1%	1%	1%
BHT* (mg)	6.0	6.0	6.0	6.0

Table No. 4. Optimized concentration of various penetration enhancers.

Penetration enhancer	Concentration (%w/w)
(D3-4) Tween-80	0.83
(D3-3) Oleic acid	1.00
(D3-2) Transcutol	1.04
(D3-1) Labrasol	0.93

Table No. 5. Stability testing conditions for stability study.

Sample	Room Temperature	40°C, RH < 25%
Drug	+	+
Placebo	+	+
Optimized Matrix	+	+

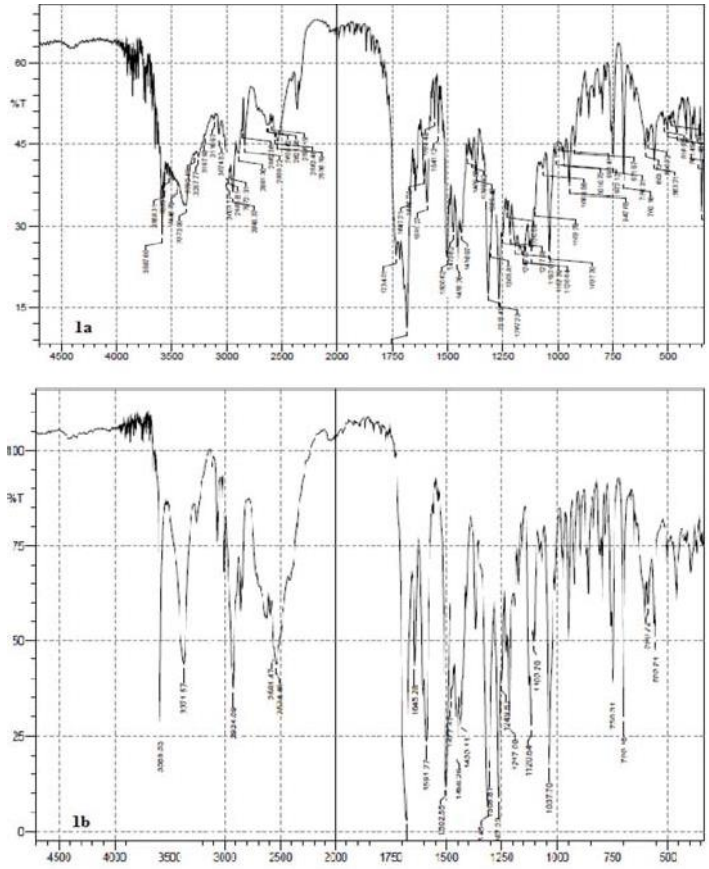

Figure No. (1a). FTIR of Donepezil 1b: FTIR scan of physical mixture.

Table No. 6. Preliminary testing of trial formulations.

Trial Batches	Polymer	Film forming ability	Film separation	Appearance
T1	ES100	Good	Poor (Brittle)	Slightly transparent
T2	EE100	Poor	Poor (More Brittle)	Whitish
T3	HPMC	Good	Good	Opaque
T4	ES100:EE100	Good	Poor (Brittle)	Slightly white
T5	ES100:EE100:HPMC	Excellent	Excellent	Transparent

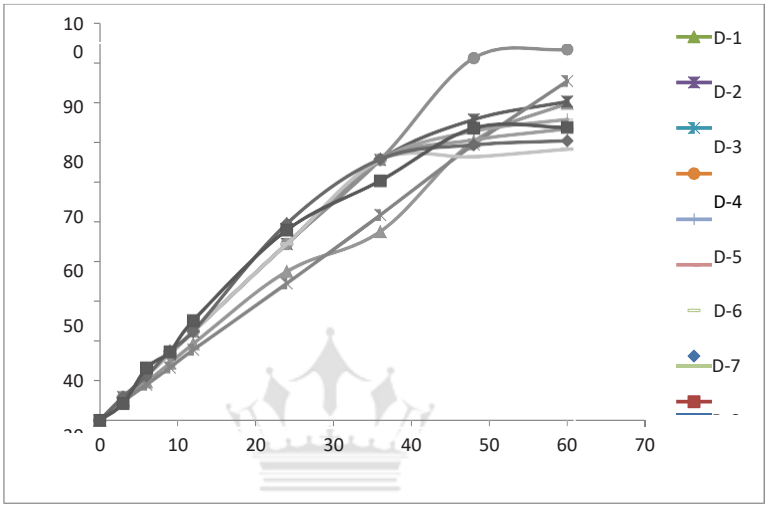

Figure No. (2). Drug release characteristics of formulations across dialysis membrane.

Table No. 7. Drug content and drug content uniformity.

Parameters	Patch (D-3-4)
Drug Content (%)	**99.12±0.54**
Drug Content Uniformity (%)	
1st quadrant	98.4±0.64
2nd quadrant	95.24±0.35
3rd quadrant	95.97±0.61
4th quadrant	97.62±0.25
Mean	96.30
S.D	1.45

Table No. 8. Physical evaluation of prepared transdermal patches.

Parameters	D-3-4
Thickness	0.49 mm
Weight Variation	201 ±14 mg
Moisture Content*	4.21%
Moisture uptakes 75% RH	5.23%
Moisture loss	3.25%
Water vapor transmission rate (gm/m^2/24 hrs)	92.85
% constriction	1.51%
% Flatness	98.49%
Folding endurance	110-115

Table No. 9. Results of TTS analysis after stability testing.

Parameters	R.T	40°C < 25% RH
% Drug content*	99.05	98.02
Appearance*	No Change	No Change

*Results after 90 days studies.