Permeability studies of anti hypertensive drug amlodipine besilate for transdermal delivery

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Amlodipine besilate, an antihypertensive drug has a half–life of 35-50 hours and a bioavailability of 60-65 %. It undergoes extensive first pass metabolism. The Present study aims to evaluate suitability of transdermal drug delivery of amlodipine besilate. The partition coefficient in octanol / water system was studied, the effect of permeation enhancers SLS, β-cyclodextrin, DMSO, tween 20, sodium tauroglycolate and hyaluronidase on the drug release were studied using parchment paper. The flux and enhancement ratio calculations of amlodipine besilate were studied. The results indicated that the hyaluronidase enzyme show higher permeability and steady state flux increased linearly with increasing donor concentration.

Keywords: Amlodipine besilate, Permeability studies, Flux, Enhancement ratio, β-cyclodextrin, Hyaluronidase enzyme.

INTRODUCTION

Transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on the intact skin surface [1]. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutical activity and targeting the delivery of drug to a tissue [1].

Amlodipine besilate, an antihypertensive drug has a half–life of 35-50 hours and a bioavailability of 60-65 %. It undergoes extensive first pass metabolism. The Present study deals with the effect of enhancers on permeation kinetics of amlodipine besilate for transdermal system [2, 3].

The substances that help to promote drug diffusion through the stratum corneum and epidermis have been referred to as skin penetration enhancers [4, 5, 6]. Enhancer can increase the solubility of the drug in the skin and increase drug diffusivity in the stratum corneum by acting as solvents to dissolve the skin lipids or to denature the skin proteins. Enhancer promotes skin permeation and are classified in to three categories, Lyophilic solvents eg. dimethyl sulfoxide, acetone, primary alcohol with small numbers of carbon, polyethylene glycol, azone, oleic acid, PEG, dimethyl formamide. Surface active agents eg. Ionic surfactant a) anionic – sodium lauryl sulphate, b) Cationic – cetyl trimethyl ammonium bromide, c) Nonionic surfactant - decyl methyl sulfoxide and two other components oleic acid and propylene glycol [4,5,6].

Formulation on skin can be classified in to two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneus microvascular network and the other exhibits local effects in the skin. The current study focused the drug release kinetic from the rate limiting membrane by varying the types of solvent used and drug loading in transdermal systems [7].

MATERIALS AND METHODS

Amlodipine Besilate was a gift sample from Dr Reddy's Lab, Hyderabad. Dimethyl sulfoxide (DMSO), Tween-20, Sodium lauryl sulphate (SLS), β-cyclodextrin and Sodium tauroglycolate were obtained from S. D. Fine Chemicals, Mumbai. Hyaluronidase enzyme was

obtained from Charles Pharma. Ltd.

Partition Coefficient of drug in Octanol/Water [8]

The partition coefficient of the drugs was determined by taking equal volumes of n-octanol and water in a separating funnel. A drug solution of 25 µg/ml of amlodipine besilate was prepared in distilled water. 25 ml of this solution was taken in a seperating funnel and shaken with an equal volume of n-octanol / water for 10 minutes and allowed it to stand for 1 hour. Then water phase was seperated, centrifuged for 10 minutes at 2000 rpm. The water phase was assayed before and after partitioning using UV-spectrophotometer to get partition coefficient. Triplicate readings were taken and average was calculated.

Permeability study

The gelatin paper (parchment paper) was washed under 0.1N HCl and soaked in order to remove acidity from the paper. A franz diffusion cell was used (diffusion studies were carried out using different enhancers). The drug solution was prepared as per the dose. The donor compartment contained a suspension of the drug (amlodipine besilate) along with semi permeable membrane (parchment paper) was used as the barrier between donor and receptor compartment. Receptor compartment contain buffer (pH 7.4). Sample was withdrawn every hour till 24 hours. The medium was magnetically stirred for uniform drug distribution and was mentioned at a temperature of $37\pm1°C$. The amount of drug diffused was estimated spectrophotometrically at 238 nm.

The enhancers considered for the study were β-cyclodextrin, DMSO, tween 20, sodium tauroglycolate and hyaluronidase. The donor compartment contained a suspension of drug and 10% w/w concentration of different enhancer.

Permeability coefficient [8, 10] is the velocity of drug passage through the membrane in cm/hr. Permeability coefficient (P) was calculated from the slope graph of % of drug transported v/s time as,

$P = slope \times V_d / S$

Where, V_d = Volume of donor solution, S = Surface area of tissue.

Flux [8, 10] is defined as the amount of material flowing through a unit crosssectional barrier in unit time . It is calculated by,

Flux (J) = P X CD

Where, CD = concentration of donor solution.

Enhancement ratio [8, 10] was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules. It is calculated by -

$$ER = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeability coefficient of drug alone}}$$

RESULTS AND DISCUSSION

Amlodipine besilate, an antihypertensive drug has been selected which has half-life of 35-50 hours, the drug extensively undergoes first pass metabolism. The present study aims to find the permeability studies of amlodipine besilate for transdermal drug delivery. Partition coefficient of amlodipine besilate in octanol/water system shown was found to be 2.66, which is favorable for the transdermal drug delivery system (Table 1).

Table 1. Partition coefficients [9]

| Drug	Practical value	Therotical value
Amlodipine besilate	2.66 in octanol/water	3 in octanol /water

The permeability coefficient, flux and enhancement ratio of drug which performed for the different enhancer like SLS, β-cyclodextrin, DMSO, tween 20, sodium tauroglycolate and hyaluronidase was studied in which hyaluronidase gave higher drug release as compared to the other enhancer. Hyaluronidase was found to be 110.059 cm/hr, 715.6 µg/cm^2/hr and 1.69. It is concluded that the hyaluronidase enzyme show higher permeability and steady state flux increased linearly by increasing donor concentration (Table 2, Figure 1, Figure 2, Figure 3 and Figure 4).

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Table 2. Permeability coefficients, flux and enhancement ratio of amlodipine besilate with different enhancers (10 %w/w)

| Enhancer	Permeability coefficient (cm/hr)	Flux ($\mu g/cm^2/hr$)	% ER
Pure drug	65.1	423.15	1
SLS	85.55	556.07	1.31
β-cyclodextrin	88.65	576.22	1.36
DMSO	97.37	632.93	1.49
Tween 20	88.92	578.01	1.37
Sodium tauroglycolate	78.93	513.04	1.21
Hyaluronidase	110.09	715.6	1.69
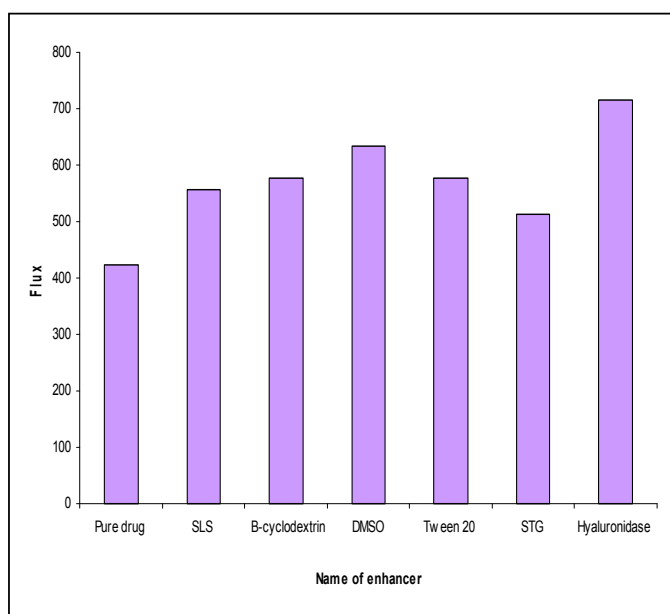
Figure 1. Bar graph showing flux of amlodipine besilate with different enhancers
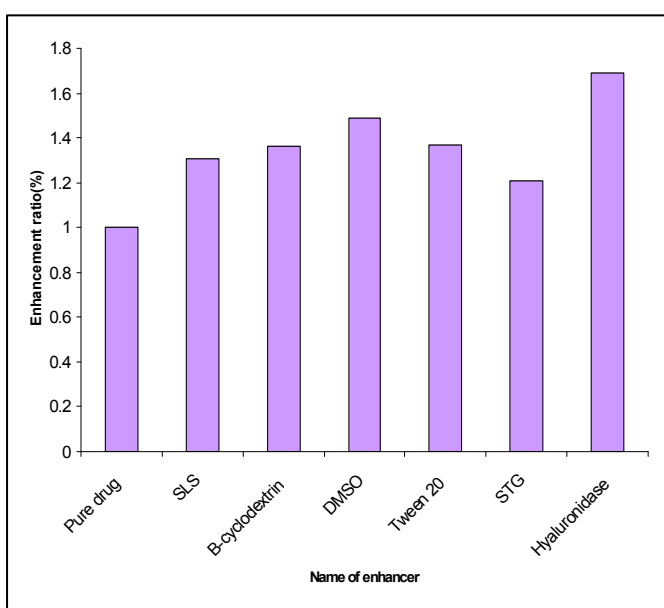
Figure 2. Bar graph showing enhancement ratio of amlodipine besilate with different enhancers
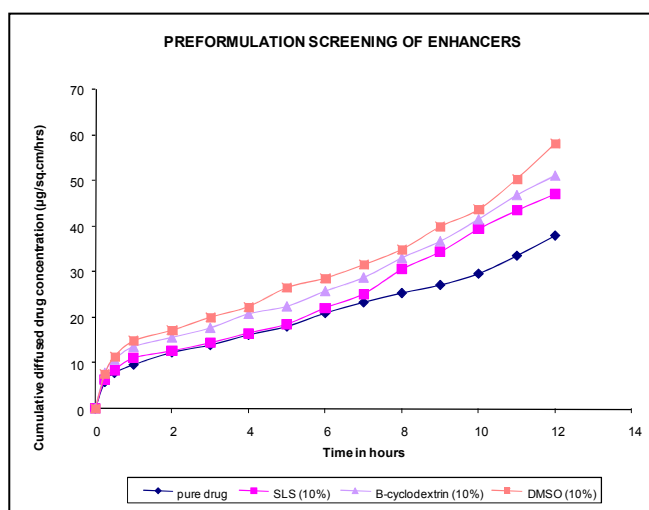
Figure 3. In-vitro diffusion of pure drug with different enhancer (SLS, β-cyclodextrin, DMSO) v/s time in hours, using a franz diffusion cell fitted with parchment paper
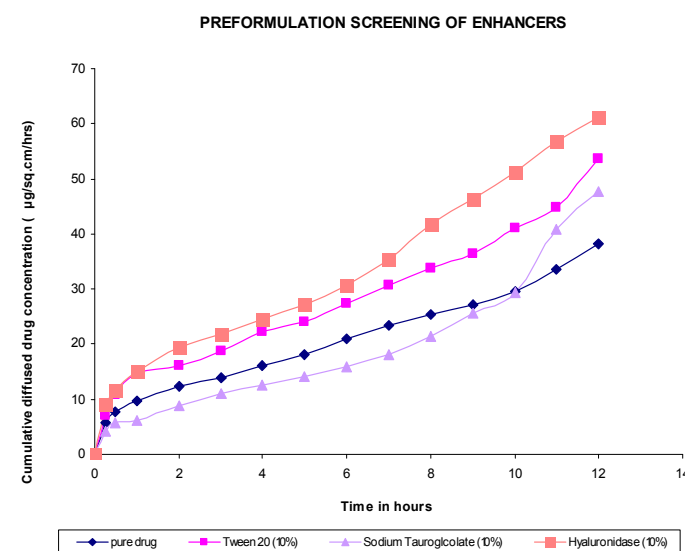
Figure 4. In-vitro diffusion of pure drug with different enhancers (tween 20, sodium tauroglycolate, hyaluronidase) v/s time in hours, using franz diffusion cell fitted with parchment paper

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