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Enhanced Transmembrane Permeation by Molecular Modification

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Verapamil free base and diltiazem free base, were prepared from corresponding salt forms and characterized prior to evaluate their *in vitro* diffusion kinetics from ethylenevinylacetate-vinylacetate 40% copolymer membrane. Base forms of original drug molecules exhibited enhanced trans membrane permeation as compared to corresponding salt forms; facilitating to deliver the drug in a controlled manner, across a convenient small surface area of delivery device.

THE most commonly used membranes for controlled release systems are nonporous, homogenous, polymeric films. Diffusion of a drug molecule from a membrane moderated delivery device is governed by steady state Fick's law diffusion equation :

$$Jss = \frac{D.K.Cd}{h} \qquad \text{equation (1)}$$

Where Jss is steady state flux mg/cm².h, K, drug partition coefficient, D, diffusion coefficient, cm²/h, Cd. concentration difference on either side of membrane which is usually donor phase concentration mg/ml, h, thickness of membrane, cm. So far membrane remaining saturated with drug, a constant amount of drug will diffuse across an unit surface area of membrane. There is linear relationship between magnitude of drug flux and area of drug delivery device[1]. Where a large amount of drug in controlled manner is required to diffuse out, a large surface area hence the big size of delivery device may not be an elegant formulation and also inconvenient to use by a patient. Diffusion of a drug molecule across a membrane is influenced by physico-chemical nature of drug and membrane polymer. In general human skin is considered as hydrophobic and it is reported[2,3] that the salt form of original drug molecule has poor permeability across skin as compared to its base form. Commonly used membranes for controlled release systems are hydrophobic in nature. Here an attempt is being made to test the scope of the above information to get enhanced release of base forms of verapamil hydrochloride and diltiazem hydrochloride across hydrophobic, ethylenevinylacetate-vinylacetate 40% copolymer (EVA) membrane. The aim of present work was to prepare, characterize base forms of above drug molecules from corresponding salt forms and to evaluate their *in vitro* permeation kinetics across EVA membrane .

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EXPERIMENTAL

MATERIALS

Verapamil hydrochloride B. P. (Torrent Pharmaceutical Industries-Ahmedabad), diltiazem hydrochloride (SUN-Pharmaceutical Industries- Baroda), ethylenevinylacetate-vinylacetate 40% copolymer (Aldrich-U. K.), toluene (Burgoyene-Bombay), Hydrochloric acid (E-merck-Bombay), solvent ether IP, were used as received. All other chemicals .used were of analytical grade.

Preparation of verapamil free base : Verapamil hydrochloride 1 g. was dissolved in 20 ml distilled water, pH of

TABLE : 1 Release rates from EVA membrane

Drug	Membrane Thickness $x10^{-4}$cm	Flux, Jss mg/Cm^2.h.10^3	Permeability p cm/h	Permeation rate p^1 mg/cm.h.10^5
Verapamil hydrocloride	97.00	8.00	8.89×10^{-6}	7.76
Verapamil base	97.00	264.00	2.93×10^{-4}	255.62
Diltiazem hydrocloride	35.00	26.00	9.68×10^{-5}	9.18
Diltiazem base	35.00	111.00	4.10×10^{-4}	38.95

N. B.: Cd for verapamil 9.0×10^2 mg/ml and for diltiazem 2.71×10^2 mg/ml.

the solution was adjusted to 11.0 with 0.5 N NaOH. Free base precipitated. The base was extracted and purified using solvent ether.

Preparation of diltiazem free base

Method adopted was as above except pH was adjusted to 9.5 with strong ammonia solution.

Physico-chemical properties of verapamil free base[4, 5], were tested. Similar physico-chemical tests for diltiazem free base were carried out. Infrared spectra of both the bases were taken and U. V. characteristics were also determined. Both the bases were subjected individually to evaluate their *in vitro* permeability across EVA membrane.

Preparation of EVA-rate controlling membrane

Solution casting on a glass substrate technique was used to prepare rate controlling memrane. EVA copolymer solution, 3 to 4 % w/v in toluene was prepared at 85°. The solution was brought to room temperature. Ten ml of this solution was poured in a levelled glass petridish. Solvent was allowed to evaporate overnight at room temperature. Membrane was lifted carefully and dried further at room temperature for 24 h. The thickness of membrane was measured by a micrometer and average thickness recorded.

***In Vitro* Diffusion Studies**

Membrane moderated reservoir type devices were fabricated to evaluate the permeation kinetics of verapamil hydrochloride, verapamil base, diltiazem hydrochloride, and diltiazem base. Low density PVC sheet, 0.22 mm thick was drilled to make a hole of 2 cm diameter. The sheet was affixed on a polyethylene coated aluminium foil backing, thus forming a reservior. Aqueous solution of parent drug and alcoholic solution of base was filled in the reservior. The reservior was covered with EVA membrane. Modified version of Keshary-Chien diffusion cell was used for diffusion study, where volume of diffusion medium was 40 ml. Hcl (0.01 M) and distilled water were used as diffusion media for bases and parent drugs, respectively. Device was clamped on the brim of the cell, membrane facing the diffusion medium. Diffusion medium was stirred with a bar type magnetic stirrer and maintained at 37±0.5°. Periodic samples were withdrawn. Verapamil hydrochloride and it's base (i) diltiazem hydrochloride and it's base, (ii) released from the respective devices were estimated U. V. spectrophotometrically (i) at 279 nm. and (ii) at 234.5 nm. respectively. Cumulative amount of drug released was ploted as function of time. Regression analysis of steady state data was done to calculate the steady state flux Jss. Membrane permeability P cm/h. and membrane thickness, independent permeation rate, P' mg/cm. h. were calculated using equations (2) and (3) respectively.

$$Jss = P.\ Cd. \text{———} \quad \text{equation (2)}$$

$$P' = Jss.\ h. \text{———} \quad \text{equation (3)}$$

RESULTS AND DISCUSSION

Physico-chemical characteristics of verapamil base

tested, were complied[4,5]. Diltiazem base, an amorphous, white powder, M. P. 103° was soluble in most of organic solvents and insoluble in water. The various peaks and finger print region of I. R of diltiazem base were identical to that of IR of diltiazem hydrochloride BP. The UV spectrum of 0.002% solution of diltiazem base in methanol exhibited a maxima at 234.5 nm.

Release of both drugs from the corresponding devices were diffusion under membrane controlled. Enhanced flux and permeabilities (Table-1) were exhibited by base form of drug molecule as compared to corresponding salt forms, across EVA (hydrophobic) membrane.

By modification of salt form of parent drug molecule to free base (i) verapamil base exhibited 33 fold and (ii) diltiazem base exhibited 4.24 fold more permeation rates as compared to their corresponding salt forms across unit surface area of EVA (VA40%) copolymer (hydrophobic) membrane. The results of present approach for hydrophobic membrane were in good agreement with that reported for skin[2,3].

The results indicate a potential to deliver large amount of verapamil base and diltiazem base, in controlled manner, across ethylenevinylacetate-vinylacetate 40% copolymer membrane moderated reservoir type of devices. This approach will definitely decrease the area and size of delivery device, giving an elegant product, which will also be convenient for patients. The present approach may found to be useful for designing controlled release membrane coated unit solid dosage forms also.

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