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Administration of Anti Parkinson's Agent Through Matrix Type Transdermal Systems

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Abstract

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness.

Keywords: Anti Parkinson's Agent; matrix type transdermal systems; conventional dosage forms

Introduction

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness.

A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ, is a controlled drug delivery system.

Definition: Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. 1, 2,3,4

Review Of Literature:

1. Mandal S. C et al.,(1994) fabricated A matrix-dispersion type Transdermal Drug Delivery System (TDS) of Pentazocine (PZ) using combinations of rate controlling polymers, namely E RS100 (RS), E RL100 (RL), Ethylcellulose (EC) and Polyvinyl pyrrolidone (PVP). In vitro drug release and skin-permeation kinetics with three different loads, were studied using male albino mice abdominal skin . .The release of PZ over a 12 hour period followed Higuchi kinetics, while in vitro mice-skin permeation of PZ followed an apparent Zero-order kinetics over a period of 24 hours22.

2. A.Bhattacharya et al.,(2001) prepared matrix type transdermal patches of ketotifen fumarate containing combination of EC/PVP and E RS 100/RL100. Three hydrophobic biocompatible substances, viz, isopropyl myristate, isopropyl palmitate and linoleic acid and also combination of isopropyl myristate and linoleic acid were used as penetration enhancers. Their drug release kinetics and skin permeation profiles were evaluated.It was found that isopropyl myristate and linoleic acid combination and isopropyl myristate alone produced promising results compared to isopropyl palmitate and linoleic acid23.

3. B.S. Dave et al.,(2003) formulated Diclofenac sodium gels containing carbomer as a polymer. Among four different polymers Acrypol 940 was selected as gelling agent and limonene as penetration enhancer. All the formulations were evaluated for cumulative % drug release and permeation. It was concluded that Transdermal permeation of Diclofenac sodium was significantly improved in presence of limonene1.

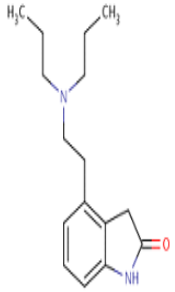
4. Biswajit Mukherjee et al.,(2005) developed matrix type Transdermal drug delivery system of dexamethasone using blends of two different polymeric combinations, povidone and EC and eudragit with PVP. Physical studies including moisture content, moisture uptake, flatness and in vitro dissolution, ex vivo permeation were performed. In vitro dissolution studies showed that the drug distribution in the matrix was homogenous and the SEM photographs further demonstrated this. The formulations of PVP:EC provided slower and more sustained release than the PVP:Eudragit formulations during skin permeation studies24.

5. M. Aqil et al., (2005) formulated matrix type drug delivery systems of Pinacidil Monohydrate by film casting technique on mercury substrate and evaluated in vitro prior to this work. the TDDS was composed of polymers; Eudragit RL 100 and PVP K-30 in different ratios along with 20 % w/w of drug; pinacidil monohydrate, 5% w/w of plasticizer; polyethylene glycol-400 and 5% w/w of penetration enhancer; dimethyl sulfoxide. The films were evaluated in vivo for drug permeation. The results indicate that increasing the quantity of E RL 100 (a freely permeable polymer) up to 60% w/w leads to an increment in the rate and extent of drug absorbed and higher % reduction in BP25.

Drug Profile

Ropinirole

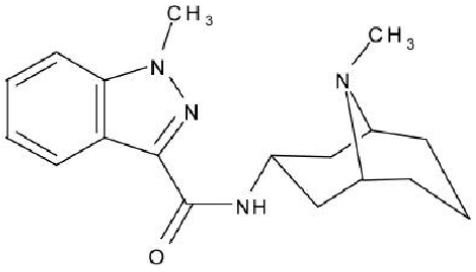
Chemical Structure:



Chemical name : 4-[2-(dipropylamino)ethyl]-1,3-dihydro2H-indol-2-one.
Formula : C16H24N2O
M. Wt. : 260.3746
Description : Ropinirole is a off - white to cream crystalline powder.
M.P : 243-250°C
Solubility : It is soluble in water, methanol and dichloromethane
Log P : 2.3
Bioavailability : reduced to around 50% as a result of first pass metabolism.
Absorption : It is well absorbed through gastrointestinal tract
Metabolism : Ropinirole is extensively metabolized to inactive metabolites via N-despropylation and hydroxylation

Protien Binding : 40%
Half life : 6hrs
Category : Antiparkinson's Agent
Plasma Conc. : 18ng/ml
Adverse effects : Headache, nausea and dizziness

Granisetron:
Chemical Structure:



Granisetron

Chemical name : 1-methyl-N-[(1,R,3r,5S)-9-methyl-9-methyl azabicyle[3.3.1]non-3-yl]-1H-indazole-3-carboxamide.
Formula : C18H24N4O
M.Wt. : 312.4 g/mol.
Description : Granisetron is a white to off-white crystalline powder.
M.P : 219°C
Solubility : It is soluble in water, methanol and dichloromethane
Log P : 2.6
Bioavailability : reduced to around 60% as a result of first pass metabolism.
Absorption : It is well absorbed through gastrointestinal tract
Metabolism : undergoes hepatic metabolism due to N-demethylation

mainly by cytochrome P-450 3A enzyme
Protein Binding : 65%
Half life : 4-6hrs
Category : Antiemetic (in Chemotherapy induced vomiting and nausea)
Dosage : 1mg twice a day /2mg orally once daily
Plasma Conc. : 64ng/ml
Adverse effects : Headache, constipation and dizziness
Methods
Preparation of Phosphate buffer pH7.4: To 6.8gm of potassium dihydrogen ortho phosphate and 1.564gm of sodium hydroxide, sufficient water is added to get 1000 ml of water and the pH was adjusted to 7.4 with ortho phosphoric acid or sodium hydroxide if necessary.
Stock solution of 10µg/ml is prepared from 1mg/ml stock solution. Then serially diluted in phosphate buffer pH 7.4 and water, to get a concentration of 5, 10, 15, 20, 25 and 30µg/ml. The absorbance of solutions is measured at 250nm using UV-Visible spectrophotometer. The standard graph is plotted with concentration on X-axis and absorbance on Y-axis.

Preparation of Rat Abdominal Skin
The male albino rats weighing 150-200gm were sacrificed using anaesthetic ether. The hair of test animals were carefully trimmed short (<2mm) with a trimmer taking extreme precaution not to damage the skin and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique, which involved soaking the entire abdominal skin in water at 60oC for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water, dried in a desiccator, wrapped in aluminium foil and stored at 4±1oC. At the time of use, the epidermis was rehydrated by immersion in water for 1hr at room temperature35.

Effect of D-limonene on permeation of ropinirole through rat abdominal skin

The aim of this study was to investigate the permeability of skin to ropinirole. Method of skin preparation for the experiment is described in section
Procedure
The skin was carefully mounted between the two compartments of a Franz diffusion cell whose ID is 2.1 cm (4.15cm2 area) and a transdermal patch was placed over the skin. A dialysis membrane (Hi-media) with molecular weight cut off of 5000 was placed over the membrane so as to secure the patch tightly from getting dislodged form the skin (the transdermal patch was sandwiched between the skin and the dialysis membrane). The receiver compartment of the diffusion cell was filled with 24 ml of phosphate buffer and the donor compartment contained a transdermal patch. All individual patches in donor compartment were prepared separately with and without penetration enhancers (0%, 4%, 8% and 12%v/w). The entire set up was placed over magnetic stirrer and temperature was maintained at about 37¬±0.5oC by placing the diffusion cell in a water bath. Samples of 5ml were withdrawn and replenished immediately from the receiver compartment at 1,2,3,4,6,8,10,12 and 24 hr. They were stored in refrigerated condition till the analysis was performed. The content of ropinirole in the samples was analyzed using UV-Visible Spectrophotometer at 250nm against phosphate buffer pH 7.4 as reference. All the experiments were performed in three replicates.
Results
Development of Ropinirole Transdermal Films

Studies on the influence of D-limonene for Drug Penetration through the Rat Abdominal Skin
The cumulative amount of ropinirole penetrates through the skin was shown in Table . Thickness of the isolated skin was found to be in between from 844 to1234 microns. The required Flux to maintain therapeutic levels in body were calculated according to formula described in section 2.7.3., was found to be 3.396µg/cm2/hr. The flux obtained without penetration enhancer was found to be 1.46±0.2µg/cm2/hr. In order to meet the required flux there is need to incorporate a penetration enhancer. 3 Different concentrations (4% v/w, 8% v/w and 12% v/w) of penetration enhancer (D-limonene) were studied to enhance the penetration of ropinirole across the rat abdominal skin.

The drug permeation profiles from transdermal patches of ropinirole through the rat skin are presented in Figure. The flux obtained with 8%v/w limonene was 3.52±0.81µg/cm2/hr and more than that of required flux, therefore it was selected as optimum concentration and incorporated in all formulations and studied their permeation kinetics.

Preparation of Transdermal Films of Ropinirole
Films were formulated with E RL 100, E RS 100 and HPMC E15 . Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 1.50gm of polymer and as the polymer concentration increased the patch could accommodate more amount of Ropinirole. Precipitation of the drug was predominant with 1.50gm of polymer and as the polymer concentration was increased to 1.75gm, the precipitation decreased. No precipitation was observed with 2.00gm of the polymer and the films were flexible. Therefore the polymer

amount taken was 2.00gm.In addition, experiments were conducted to know optimal concentration of plasticizer to be used in all kind of films. Plasticizer at concentration of 5%v/w of film former was insufficient to form films. Plasticizer concentration at 5-10% v/w yielded hard and inflexible films. Further, increasing the concentration of plasticizer above 20%v/w resulted in enormous increase in drying time. 8%v/w limonene was incorporated in all formulations and studied their permeation kinetics.

• Different polymeric films containing ropinirole and granisetron were prepared and evaluated for physicochemical, release and permeation characteristics.

• The formulations containing limonene (8% v/w) were found to meet the target flux. As the proportion of HPMC increased in all the formulations, increased drug release and permeation were observed.

The Transdermal patches of ropinirole and granisetron with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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