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Transdermal Delivery of Newer Atypical Antipsychotics

ABSTRACT

Risperidone and olanzapine, newer atypical antipsychotics are highly effective and safer in the treatment of psychosis. A low dose maintenance therapy of these atypical antipsychotics is needed for prolonged treatment of psychosis with lower oral side effects. To develop low dose maintenance therapy of these antipsychotics, which can minimize the risk of major side effects, help in overall cost saving and address to the problems of poor compliance in patients, eudragit containing transdermal films of risperidone and olanzapine were developed. For development of successful transdermal drug delivery system (TDDS), various permeation enhancers belonging to the group of surfactants (cationic surfactant, benzalkonium chloride (BC); anionic surfactant, sodium lauryl sulphate (SLS); non-ionic surfactant, span 20) and vegetable oils (olive oil, jojoba oil and groundnut oil) were also investigated in the present study to find out their effect on the rate of permeation of drug through TDDS.

The whole research work was divided into various parts such as introduction, review of literature, preformulation studies, formulation and evaluation of TDDS of risperidone and olanzapine, in vivo studies, results & discussion and summary & conclusion.

In preformulation studies, drugs were characterized by UV, IR, partition coefficient and solubility studies. FTIR studies were carried out to determine compatibility between drug and excipients. Transdermal patches of risperidone and olanzapine were prepared by solvent casting technique using Eudragit RL 100 (ERL 100) and Eudragit (ERS 100) with and without permeation enhancers (surfactants and vegetable oils in the concentration of 1%, 5% and 10% w/w of polymer weight).

The prepared transdermal patches were evaluated for their physicochemical characterization viz., weight variation, thickness, drug content determination, moisture content and moisture uptake, flatness, folding endurance and tensile strength. Distribution of drug in the film and skin was studied by using scanning electron microscope (SEM).

The in vitro drug release studies were performed by using a modified USP type II dissolution apparatus. A circular patch with an internal diameter of 3.57 cm
was used for the study and a stainless steel ring was employed to sink the patch at bottom. All dissolution studies were performed at 32±0.5°C, at 100 rpm. The in vitro permeation studies were carried out in vertical Franz diffusion cell with a capacity of 35 mL using Wistar rat skin. The present work also involved in vivo pharmacological studies for tranquilizing and sedation activity. Safety and skin toxicity of the developed formulations was determined by skin irritation and histopathological studies. In vivo pharmacokinetic studies were also done to check the efficacy of optimized transdermal formulation in rabbits. Various pharmacokinetic parameters C_{max}, T_{max}, K_{el}, MRT, AUC were determined by Winnonlin version 5.2. The present work incorporated the comparison of fabricated formulation with API and marketed formulation.

Results of preformulation studies confirmed the purity of risperidone and olanzapine. In order to access the partitioning of drug between skin and in vitro study fluid, partition coefficient was determined. The partition coefficient of risperidone and olanzapine in n-octanol: PBS (pH 7.4) was found to be 3.01±0.16 and 2.32±0.36 respectively, which was optimum for transdermal delivery. FTIR study implied that all the excipients are compatible with risperidone and olanzapine.

An attempt was made here to find out whether the media phosphate buffer pH 7.4 was able to maintain sink conditions in release studies as well as in permeation studies. From the data obtained, maximum solubility of risperidone was obtained with 1% w/v Tween 80 in PBS 7.4, while in case of olanzapine maximum solubility was found with 0.75% w/v Tween 80 in PBS 7.4. So buffer containing 1% Tween 80 and buffer with 0.75% Tween 80 was selected as receptor media for in vitro and ex vivo permeation studies of risperidone and olanzapine respectively.

Films containing ERL 100 and ERS 100 were found to be smooth, wrinkle free, transparent and with uniform colour distribution. 20 - 30% of dibutylphthalate were found to be optimum for flexibility and uniformity of transdermal patches. All the formulations of risperidone and olanzapine were found to be acceptable in terms of weight variation, thickness and drug content variations. The results indicated that the process employed to prepare transdermal patches in this study was capable of producing formulations with uniform drug content and minimal patch variability.
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Results of moisture content and moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer (ERL 100) was directly proportional to the increase in moisture content and moisture uptake of the patches. Moisture content and uptake of the formulations was found to be low, which could help the formulations to remain stable for long term storage. The microbial studies confirmed that no films had bacterial growth. Low moisture content and moisture uptake also indicated stability of the formulation. SEM images showed homogenous drug distribution in matrix patches of both the drugs.

Films with acceptable qualities were subjected to in vitro release studies. The release studies are crucial because one needs to maintain the drug concentration on the surface of the stratum corneum consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation. In vitro release studies showed release was less than 50% without permeation enhancers but with the permeation enhancers, the release was improved significantly. Permeation enhancers in case of olanzapine TDDS affected the order of release as: Span 20 > BC > SLS > Olive oil > Groundnut oil > Jojoba oil, while the order of release in risperidone TDDS was found as: Span 20 > Olive oil > BC > SLS > Groundnut oil > Jojoba oil.

On the basis of in vitro release studies, patches from each batch with acceptable release i.e. RB2, RC2, RD3, RE3, RF3, RG3 for risperidone and OB2, OC3, OD3, OE3, OF3, OG3 for olanzapine were selected for in vitro permeation studies and compared with formulation containing no permeation enhancer (RA2 and OA2 respectively). In case of olanzapine, maximum transdermal flux 26.74 µg/cm²/h was obtained with formulation containing non ionic surfactant as permeation enhancer. In case of risperidone, maximum transdermal flux 23.14 µg/cm²/h was obtained with formulation containing olive oil as permeation enhancer respectively. The results of permeation fluxes supported the data for prolongation of drug release characteristics of formulated transdermal films. Non ionic surfactants and vegetable oils are receiving much attention as permeation enhancers. Span 20 is non ionic surfactant and olive oil is vegetable oil and both combines good penetration enhancing abilities along with low skin irritancy and low systemic toxicity. Our
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results showed that non-ionic surfactant and olive oil facilitates the flux of olanzapine to a greater extent than that of ionic surfactants and other vegetable oils.

The microphotographs of SEM showed presence of drug particles on dorsal and ventral side of skin during permeation studies, which confirmed permeation of drug through skin. It can be said that drug released from patches after permeation studies reached into the receptor media through skin and this permeation of olanzapine occurred through skin appendages as indicated in SEM images.

The results of skin irritation studies revealed that neither blank patches nor patch containing risperidone or olanzapine caused any noticeable sign of erythema or edema on rabbit skin throughout the study period.

In clinical situations, therapeutic efficacy of the formulation is important. Rotarod test, grip test and behavioural observations were carried out to find out the tranquillizing efficacy of TDDS comparable to oral marketed formulation in mice. From the results, it can be noted that falling time in case of rotarod test and gripping time in case of grip test was almost similar to marketed oral formulations. So it was concluded that transdermal formulations have sufficient active drug risperidone and olanzapine, which produced muscle relaxant and sedation effect due to effect on muscular strength and neuromuscular function. This was also supported by general behaviour test.

In vivo pharmacokinetic studies of olanzapine TDDS were done to check the efficacy of transdermal formulation in rabbits. Various pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$, $K_{\text{el}}$, MRT, and AUC were determined. Results of in vivo studies showed $C_{\text{max}}$ for test formulation was 129.63 ng/mL as compared to 256.72 ng/mL of marketed formulation. The $C_{\text{max}}$ for TDDS was less but was able to produce therapeutic effect and therefore side effects of drug are supposed to be minimal. The $T_{\text{max}}$ for the marketed product was shorter than that of TDDS and the elimination rates of test formulation were found to be less than that of marketed oral formulation. Upon removal of patch, a mild reservoir effect was observed for 24 h followed by normal elimination, which was again due to the slow depletion of drug accumulated in skin tissues and the long elimination half life of olanzapine. This proves the sustained release potential of prepared transdermal patches for better
therapeutic profiles. Lesser $C_{\text{max}}$, more $T_{\text{max}}$ and less $K_{\text{el}}$ of test formulation reveals that in case of TDDS of olanzapine blood plasma levels are better controlled. The better bioavailability data of transdermal patches also proves advantage of transdermal formulation as compared to conventional formulations. Accelerated stability testing confirmed the stability of formulations for three months, which was done according to ICH guidelines.

From these results, it can be concluded that the prepared and optimized transdermal formulations of risperidone and olanzapine using polymers such as ERL 100 and ERS 100 with olive oil and span 20 as permeation enhancers demonstrated their ability to give sustained release. These studies have shown promising results, hence there is feasibility of delivering risperidone and olanzapine through transdermal route. The developed TDDS of atypical antipsychotics may prove to be a better alternative to conventional dosage forms.