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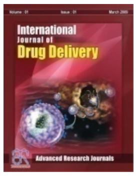

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Development and Evaluation of Transdermal Patches of Quetiapine fumerate for the treatment of psychosis

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Abstract

The aim of the present study was to formulate and evaluate the transdermal patches of an antipsychotic drug Quetiapine fumerate (QF) for the treatment of psychosis and schizophrenia. The transdermal patches was prepared by the solvent evaporation method using hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) in five different ratios 1:0, 2:1, 1:1, 1:2, 0:1. The PEG-400 and DMSO were used as plasticizers and permeation enhancer respectively to enhance the permeability of the drug. The FTIR studies showed no evidence of incompatibility between the drug and the polymers. The prepared patches were evaluated for various parameters like thickness, weight variation, folding endurance, percentage moisture uptake, percentage moisture content, drug content and i*n-vitro* drug release. The results concluded that the formulation F2 (with HPMC and EC in 2:1 ratio) showed 80.89% in drug release during *in-vitro* studies after 24 hours. With the incorporation of PEG-400 and DMSO smooth, transparent and flexible film were produced.

Keywords: Transdermal patches, Quetiapine fumerate, i*n-vitro* drug release.

Introduction

During the past two decades, significant advances have been made in the area of controlled release as evidenced by an increasing number of patents, publications, as well as commercial controlled-release products for the delivery of a variety of bioactive agents ranging from pharmaceutical to agricultural and veterinary compounds. The goal of pharmaceutical research is to find drugs with desirable therapeutic and low risk of undesirable side effects. Recent research and development efforts have been channelized into the development of drug delivery systems for controlled drug administration through various routes (or parts) of administration, for example, the skin, to maximize the bioavailability, to optimize the therapeutic efficacy, and/or minimize the side effects of the drug [1].

Transdermal patches offers various advantages over other type of conventional dosage forms like improved bioavailability, uniform plasma level, reduced dosing interval, user-friendly, avoid first pass metabolism and GI irritation, convenient, painless, offering multi-day dosing, thereby resulting in improved patient compliance [2-4].

Schizophrenia is a neuro-developmental psychiatric disorder with etiology spanning both genetic and environmental factors. According to WHO, schizophrenia affects about 24 million people worldwide. It is a treatable disorder, treatment being more effective in its initial stages. More than 50% of persons with schizophrenia are not receiving appropriate care. 90% of people with untreated schizophrenia are in developing countries [5-6].

Quetiapine fumerate (QF) is a dibenzothiazepine derivative, an atypical antipsychotic with demonstrated efficacy in acute schizophrenia. It is indicated for the treatment of schizophrenia as well as for the treatment of acute manic episodes associated with bipolar I disorder. It has a relatively broad receptor binding profile. It has major affinity to cerebral serotonergic ($5HT_{2A}$), histaminergic (H1), and dopaminergic D1 and D2 receptors, moderate affinity to $_1$- und $_2$-adrenergic receptors, and minor affinity to muscarinergic M1 receptors; it demonstrates a substantial selectivity for the limbic system. It also has an antagonistic effect on the histamine H1 receptor [7].

The aim of present work is to formulate matrix type transdermal patches of Quetiapine fumerate using the hydroxypropyl methylcellulose (HPMC), and ethylcellulose (EC) to enhance its bioavailability and sustain its action.

Materials and Method

Materials

Quetiapine fumerate was obtained as a gift sample from Aurobindo pharmaceuticals, Hyderabad. HPMC was obtained as gift sample from Windlass Biotech Ltd., Dehradun. Polyethylene glycol (PEG-400) was procured from Central Drug House, New Delhi. All other chemicals were of analytical grade and were used as provided.

Method

Identification by FTIR spectroscopy

FTIR spectra of drug, and drug-polymer in formulation was carried out to find any possible interactions between the drug and the polymers during formulation and were obtained in KBr pellets using a Perkin Elmer model spectrum BX-FTIR spectrophotometer in the ranges, 4000- 400 cm^{-1}.

Partition coefficient

The partition coefficient was performed using n-octanol as oil phase and phosphate buffer pH 7.4 as aqueous phase. The two phases were mixed in equal quantity and 10 mg of weighed amount of drug was added. Then, these were saturated on a mechanical shaker for 2 hours. The saturated phases were separated by separating funnel and equal volume of both phases n-octanol and phosphate buffer were taken in a conical flask and then analyzed for respective drug controls. The partition coefficient of drug $P_{o/w}$ was calculated by the following formula [8].

$P_{o/w} = \quad C_{oil} / C_{water}$ (at equilibrium)

Preparation of drug free polymeric film

Matrix type transdermal patches were prepared by solvent casting technique employing glass and aluminum foil as substrate with few modifications [9]. A flat square shaped, aluminum foil coated glass mould were fabricated for casting the patches.

A fixed amount 300 mg of polymers were dissolved in to the 10 ml of solvent system (water: methanol, 7:3) using a magnetic stirrer for 30 minutes. Then, PEG-400 and DMSO as plasticizer and penetration enhancer respectively, were added in the above polymeric solution. A weighed quantity of the drug (300mg) was dissolved in the polymeric solution. And finally volume makes upto 20 ml. The solution was poured into the petridish coated by aluminum foil and dried at room temperature for 24 h for solvent evaporation and an inverted funnel was kept over petridish to control the evaporation of solvent. The patches were removed by peeling and cut in to squares with dimension of 2x 2 cm^2. These patches were kept in desiccators for further evaluations. The composition of transdermal patches is given in Table 1.

Evaluation of transdermal films

Thickness

The thickness of the film was measured at three different points using digital vernier calliper and the average thickness was calculated [10]. The experiment was performed in triplicate (n=3).

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated [11].

Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance [12].

Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films were reweighed and the percentage moisture content was determined by using the given formula [13].

$$\text{Percentage moisture content} = \frac{\text{Initial weight- Final weight}}{\text{Final weight}} \times 100$$

Percentage moisture uptake

The weighed films were kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films were reweighed and the percentage moisture uptake was determined by using the given formula [14].

$$\text{Percentage moisture uptake} = \frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity

The uniformity of drug content of the transdermal film was determined, based on dry weight of drug and polymer used, by means of a UV/VIS spectrophotometer method [15]. A specified area (2.5cm^2) of patch was cut and dissolved in 5 ml of phosphate buffer pH 7.4. Then the solution was transferred in a volumetric flask and the volume made up to 10 ml. Appropriate dilutions were made using phosphate buffer (pH 7.4), filtered and analyzed for drug content at 254 nm by using UV spectrophotometer (Shimadzu Pharmspec UV-1700, Japan). (n=3).

In-vitro drug release

The *in-vitro* permeation study of fabricated transdermal patches of quetiapine fumerate was carried out by using excised rat abdominal skin and franz diffusion cell [9]. The skin was sandwiched between donor and receptor compartments of the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 32 ± 0.5 C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24h, simultaneously replacing equal volume by phosphate buffer (pH 7.4) after each withdrawal. Perfect sink conditions were maintained during the study. The samples were analyzed spectrophotometrically by UV (Shimadzu Pharmspec UV-1700, Japan) at 252nm.

Statistical analysis

The results were expressed in mean ± S.D. One way ANOVA (Analysis of Variance) was performed for studying the statistical significance using Minitab 15 software. Values of $P< 0.05$ were considered to be significant.

Results and Discussion

Identification by FTIR spectroscopy

FTIR spectra of the drug and the formulation predicted that it did not show any type of incompatibility. The major peaks of –CH stretching 2948.63, C-N stretching 1575.56, -OH stretching 3748.68 was also observed in the final formulation (Figure 1-2).

Partition coefficient

Partition coefficient of drug in n-octanol/ phosphate buffer pH 7.4 was found to be 2.7 which indicated that the drug was lipophilic in nature. Compounds with values below these optimum values do not partition readily into the stratum corneum, while compounds with higher values of are so lipophilic that they remain dissolved in the stratum corneum [16].

Evaluation of transdermal films

The physicochemical properties (thickness, weight, folding endurance, drug content, percentage moisture content and percentage moisture uptake) of the transdermal patches are shown in Table 2. Thickness of the patches varied between 0.17± 0.035 to 0.23± 0.027 mm. Low standard deviation values in the film thickness measurement ensure uniformity of the patches. Weight variation of the patches was found to ranging between 193.3±3.9 to 203.7±3.5 mg. Folding endurance was found to be ranging between 10±3.3 to 21±4.4. Results indicated that as the HPMC content decreased, the folding endurance also decreases. Jacob et al., 2012 also indicated an increase in polymer concentration increases the folding endurance [17]. Folding endurance test result indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Drug content (69.62±0.03 to 86.66±0.02 mg) of the patches indicated the uniformity of the patches. A small standard deviation was observed for the drug content. Li et al. (2007) reported that the total amount of drug in a transdermal dosage form did not affect the magnitude of the drug release but only determines the duration of drug delivery [18].

Percentage moisture content of the patches ranged from 2.19±0.04% to 4.82±0.03%. Maximum % moisture content was found in F1 and minimum % moisture content was found in F4 formulation, respectively. Percentage moisture uptake was found to be between 3.40±0.04% to 4.89±0.04%. Maximum % moisture uptake was found in F5 and minimum % moisture uptake was found in F2 formulation, respectively. The results revealed that % moisture content and % moisture uptake was found to increase with increasing concentration of hydrophilic polymer. The small moisture content in formulation helps them to remain stable and form a completely dried and brittle film. Again a low moisture uptake protects the material from microbial contamination and bulkiness of the patches [19]. In most cases, the moisture content and uptake was found to increase with increasing concentration of hydrophilic polymer [20].

In-vitro drug release

The in vitro drug release pattern of QF from formulated transdermal patches is shown in Figure 3. All of these transdermal patches slowly released the drug, incorporated and sustained over a period of 24 h. The drug release from transdermal patches varied with respect to the polymer composition and nature. An increase in drug release from the transdermal patches was found with increasing concentration of polymers that are more hydrophilic in nature. Among all formulations, the maximum in vitro drug release (80.89 %) over a period of 24 h was observed in the case of formulation F2, while the minimum in vitro drug release (58.05 %) over a period of 24 h was found in the case of formulation F5. The formulation F1 with HPMC alone showed drug release of 96.46% in 12 h.

The drug release was found to increase with increase in the concentration of hydrophilic polymer in the polymer matrix. This might be due to the fact that dissolution of aqueous soluble fraction

Table 1: Composition of transdermal patches

Formulation code	Polymers amount (mg)		Drug (mg)	PEG-400	DMSO
	HPMC	EC			
F1	300	0	300	5%	2%
F2	200	100	300	5%	2%
F3	150	150	300	5%	2%
F4	100	200	300	5%	2%
F5	0	300	300	5%	2%

Table 2: Physical characteristics of transdermal patches

Parameter	F1	F2	F3	F4	F5
Thickness(mm)	0.20±0.03	0.17± 0.03	0.18±0.04	0.23± 0.03	0.21±0.04
Weight variation	193.3±3.9	202.7±3.03	198.7±3.8	201.4±2.8	203.7±3.5
Folding endurance	21.0±4.4	17.0±2.5	15.0±2.3	13.0±2.9	10.0±3.3
% Moisture content	4.82±0.03	3.43±0.05	3.18±0.06	2.19±0.04	2.43±0.04
%Moisture uptake	4.62±0.06	3.40±0.04	4.08±0.05	4.79±0.04	4.89±0.04
Drug content	80.63±0.02	84.75±0.03	86.66±0.02	76.98±0.04	69.02±0.03

Values shown are in mean±S.D. (n=3)

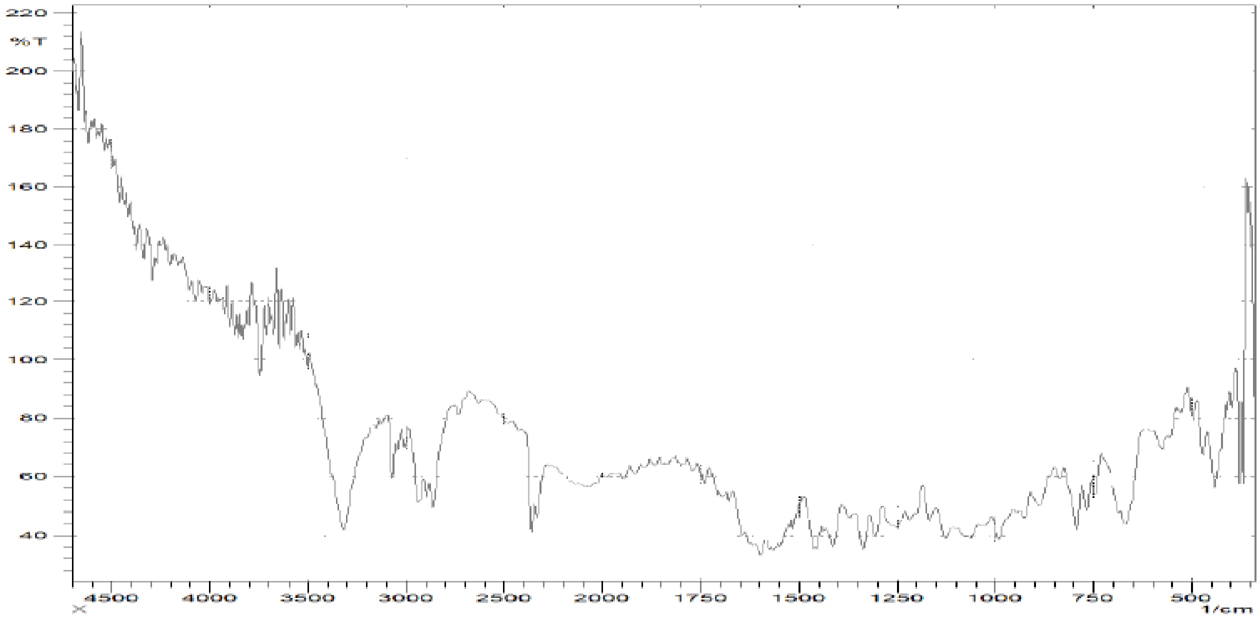

Figure 1: FTIR spectra of Quetiapine fumerate

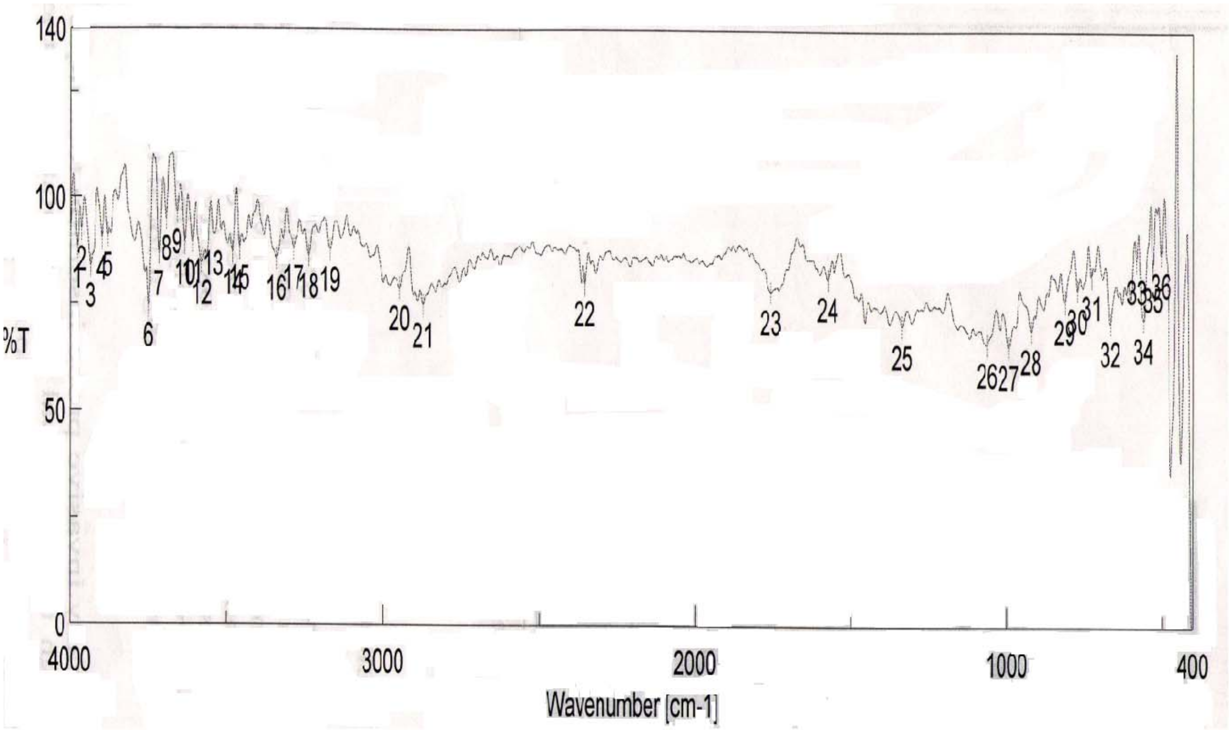

Figure 2: FTIR spectra of formulation

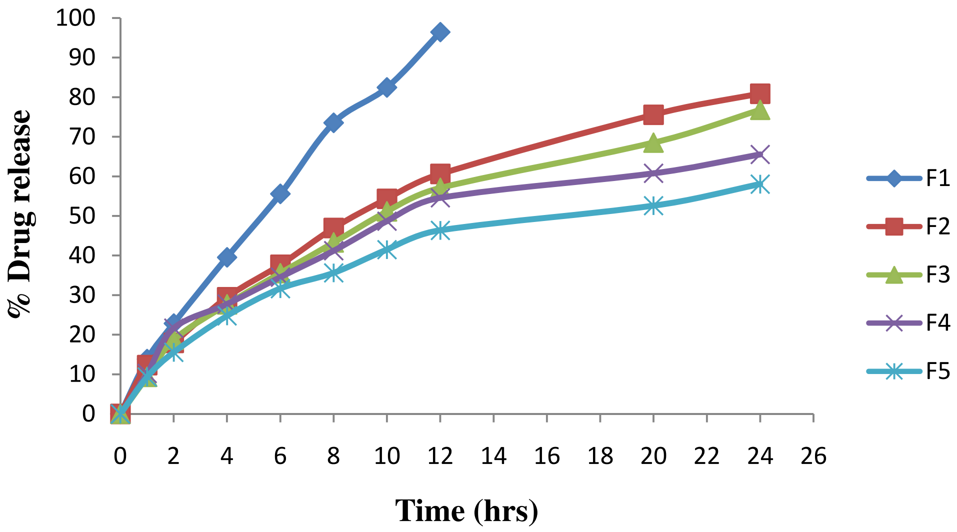

Figure 3: Graph showing drug release from the transdermal patches in phosphate buffer pH 7.4

of the polymer matrix leads to the formation of pores. The formation of such pores leads to decrease in the mean diffusion path length of drug molecules to release into the dissolution medium and hence to increase the release rate [9].

Conclusion

Quetiapine fumerate patches in combination with HPMC, EC and with incorporation of PEG-400 (5%) and DMSO (2%) produced smooth, flexible and transparent film. It can be concluded that Quetiapine fumerate produces sustained effect for prolonged period by transdermal route for the management of psychosis. Transdermal patches of quetiapine fumerate is likely to enhance he patient compliance as it would eliminate the need of repeated dosing, enhance the bioavalability and sustain the action of the drug.

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