PREPARATION AND CHARACTERIZATION OF TRIFLUOPERAZINE LOADED TRANSDERMAL PATCHES FOR SUSTAINED RELEASE

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ABSTRACT

Objective: The purpose of the present study was to formulate and evaluate the polymeric transdermal delivery system of antipsychotic drug Trifluoperazine (TFP) for sustained drug release.

Methods: A transdermal patch loaded with (TFP) was formulated by solvent casting technique. Polyvinyl pyrrolidone (PVP) K-30 and ethyl cellulose (EC) was used as a polymeric matrix with different ratios. Di n-butyl phthalate was used as a plasticizer. The parameters such as thickness, folding endurance and weight variation of the prepared patches were studied. The interaction study by attenuated total reflectance-infrared (ATR-IR) spectroscopy, X-ray diffraction and thermal analysis by differential scanning calorimetry (DSC) were performed. In vitro drug release study was performed by modified paddle over-disc technique.

Results: The infrared spectroscopic study confirmed the absence of any chemical interaction between TFP and selected polymers. All the prepared formulations showed folding endurance values ranging from 130-162 and a satisfactory drug loading of 90-95%. In in vitro drug release study, formulations PE-3 and PE-4 exhibited a sustained and stable cumulative release of 54 % and 48% respectively, at the end of 24 h. The DSC and XRD analysis proved the partial conversion of the drug from crystalline to amorphous form when integrated into the polymeric matrix.

Conclusion: The prepared transdermal formulations using polymers PVP and ethyl cellulose demonstrated their ability to sustain the release of TFP. The developed formulation could be exploited for multiday therapy of TFP for the effective treatment of schizophrenia with a simplified dosing regimen and enhanced patient compliance.

Keywords: Trifluoperazine, Transdermal patches, Psychiatric disorders, Solvent casting, Sustained release

INTRODUCTION

Trifluoperazine (TFP) is an antipsychotic drug; it is widely used to treat psychotic conditions of acute and chronic schizophrenia, since 1950s. TFP is the first generation (typical antipsychotics) medication that has proved to be a potent phenothiazine derivative with a strong affinity to D2 receptors [1, 2]. New generation antipsychotic drugs are available for claiming fewer extrapyramidal side effects. TFP still remains to be an inexpensive and widely used drug in the management of schizophrenia and anxiety. Even though TFP is well absorbed orally, it is reported to undergo extensive first-pass metabolism in the liver. Psychiatric disorders often demand long term drug treatment, and compliance with the prescribed medication is a severe issue for mental illness people. Nonadherence to prescribed medication in psychiatric patients is mainly due to factors like undesirable side effects, dosing regimen, route of administration, nature of illness, belief systems and personal attributes [3]. The transdermal delivery of psychotropics is an under-investigated area of research. The approach of developing antipsychotics in the form of a sustained release transdermal patch is promising as the occurrence of non compliance with medication and relapse is high in patients with mental illness [3].

In comparison with both the parenteral and oral routes, transdermal delivery seems to have several benefits. Transdermal systems offer advantages like controlled drug release, improved bioavailability, minimal side effects, reduced dosing frequency and evasion of first pass metabolism [4–6]. Moreover, non-invasive transdermal devices are self-administered and the drug action can be rapidly terminated by removing the system from the skin. Transdermal drug delivery also provides a long-standing and steady systemic absorption pattern, minimising several side effects caused by the peak valley profile of plasma drug concentrations [7–10] and the fabrication techniques are usually simple and of less cost.
MATERIALS AND METHODS

Materials

Trifluoperazine dihydrochloride was purchased from Tokyo Chemical Industry, Japan. Ethyl cellulose was purchased from the Dow Chemical Company, USA, which has a viscosity of 100 cP. Polyvinyl pyrrolidone (PVP K-30) was obtained from Loba Chemie, Mumbai. Chloroform and Di n-butyl phthalate were obtained from the Merck life sciences Pvt. Ltd., (Bengaluru) and Central drug house (P) Ltd., (New Delhi). The chemicals were employed as obtained without any other purification. All remaining reagents employed in this analysis were of analytical grade.

Methods

Preparation of TFP loaded transdermal patch

TFP loaded transdermal patch comprising varying proportions of PVP K-30 and EC was fabricated by the solvent casting technique. Preliminary studies were done with blank patches to select proper ratios of polymer and concentration of plasticizer to be incorporated. The prerequisite ratios of polymers were weighed and allowed to swell for 4 h in chloroform-methanol (9:1) solvent mixture. The total weight of the polymer in one formulation was kept 400 mg. Plasticizer Di n-butyl phthalate was incorporated at 30% w/w of polymer dry weight. The weighed amount of TFP was incorporated with the polymer blend, and this was stirred using a magnetic stirrer at 300 rpm for 20 min to get a homogeneous mixture. The mixture was ultrasonicated to remove air bubbles and slowly poured into glass moulds (dm-3 cm) formerly dried with 4% v/v PVA solution as backing [21]. A funnel was positioned over the glass mould in an inverted position to regulate the rate of evaporation and was dried at room temperature for 24 h. The matrix films were detached from the mould and folded in aluminium foil and stored in a desiccator until used for further evaluation.

Drug-excipient compatibility study

The interaction of the drug with selected excipients was studied by Infrared spectroscopy. The IR spectra of pure drug TFP, individual polymers (EC and PVP K30) and physical mixture of drug with polymers were recorded by ATR-FT-IR (jasco FT/IR-4700) over the spectral range of 4000–500 cm\(^{-1}\) [22, 23]. The FT-IR spectra of the formulated patches were also recorded and compared with that of pure drug.

Evaluation of the physicochemical properties of the patches

Weight and thickness

Six patches (3 cm\(^2\)) from each batch were randomly chosen for the analysis of weight variation. Weights of the formulations were taken independently, and further, the average weight was measured. The thickness of the patches was evaluated at 3 different points utilizing a digital micrometer and the mean values were tabulated [24, 25].

Folding endurance

The mechanical strength of the patches can be evaluated by determining folding endurance. The analysis of folding endurance was carried out for all patches, and it was calculated manually. A strip of the patch was folded manually at the same position repeatedly until it was broken. The number of folding needed to break the film was tabulated as folding endurance [26].

Drug content analysis

A patch of 3 cm\(^2\) area was randomly taken and dissolved in 5 ml of casting solvent, and the volume was diluted suitably and filtered by using Whatman filter paper. The drug quantity in each solution was also determined spectrophotometrically utilizing UV–Visible spectrophotometer (Shimadzu UV-1800, Japan) at 257 nm. A control was also performed using drug-free films [14]. An average of three readings was tabulated.

In vitro drug release study

The dissolution studies of the formulated patches were carried out in the USP type 2 dissolution apparatus. The patches (3 cm\(^2\) area) were fixed on a small glass plate at the bottom of the vessel. The pH 7.4 phosphate buffer medium 900 ml was used and the temperature was maintained at 37±0.5 °C with paddle rpm of 75. Samples were withdrawn at different time intervals and analysed utilizing a UV-visible spectrophotometer at 257 nm against a blank. Cumulative amounts of TFP released were plotted against time for all the formulations. The drug release pattern from different formulations was compared.

Thermal analysis with differential scanning calorimetry (DSC)

Thermal analysis of TFP, physical mixture (TFP, EC and PVP K30) and the developed patch PE-3 and PE-4 was performed using differential scanning calorimetry (DSC) (Q 20, TA instrument). Specimens were heated from room temperature to 300 °C at a rate of 10 °C per min in a nitrogen purge of 50 ml per min [19].

X-ray diffraction study (XRD)

The X-ray diffraction (XRD) study was mainly utilized to analyze the crystalline and stable dispersive behaviour of the drug TFP when dispersed in the patch. The X-ray diffractogram of TFP and the formulations PE-3 was recorded (Bruker model D8 advance) at 25 °C utilizing monochromatic copper K-alpha radiation at 40 mA and 40 kV.

Scanning electron microscopy (SEM) analysis

Scanning electron microscopy analysis was employed for identifying the surface characteristics of the developed formulations PE-3 and PE-4. The specimens were analysed using SEM (JEOL JSM 6390) with a high vacuum and a high voltage of 15 kV.

RESULTS AND DISCUSSION

Preparation of TFP loaded transdermal patch

The formulations were prepared by solvent casting method varying the ratio of PVP:EC. From the results of preliminary studies carried out, the total content of polymer in each patch was maintained as 400 mg and the plasticizer (Di n-butyl phthalate) concentration was kept constant at 30% of the polymer weight. As the objective of the study is to develop a patch releasing the drug gradually over multiple days, the concentration of the retarding polymer EC was gradually increased in the formulations as shown in table 1.

| Ingredients (PVP: EC ratio) | PE-1 (3:2) | PE-2 (2:3) | PE-3 (1:3) | PE-4 (1:5) | PE-5 (1:7) |
|-----------------------------|------------|------------|------------|------------|------------|
| PVP K-30 (mg)               | 240        | 160        | 100        | 67         | 50         |
| Ethylcellulose (mg)\(\times\) | 160        | 240        | 300        | 333        | 350        |
| Di n-butyl phthalate (ml)\(\times\) | 0.12      | 0.12       | 0.12       | 0.12       | 0.12       |
| Trifluoperazine dihydrochloride (mg) | 20       | 20         | 20         | 20         | 20         |
| Chloroform: methanol (9:1) (ml) | 5          | 5          | 5          | 5          | 5          |

Drug-excipient compatibility study

Interactions of drug with excipients play an important role in controlling the release of drugs from the formulation. ATR-FTIR technique has been used here to study the physical and chemical interactions between the drug and polymers used. The infrared spectra for the TFP, excipients (EC, PVP K30) and physical mixture of TFP, EC and PVP K-30 were recorded. The IR spectra of prepared
formulations PE-3 and PE-4 was also analysed (fig. 1). The IR spectra of TFP exhibited bands of C=O symmetric stretching at 1108, 1143 and 1080 cm⁻¹; C–S stretching at 678 and 754 cm⁻¹; C=N stretching at 1250 cm⁻¹; C=CF₂ stretching at 1316 cm⁻¹ and aromatic C=C stretching at 1600, 1565 and 1470 cm⁻¹ [23, 27]. The spectrum of ethylcellulose shows characteristic absorption bands for C–O–C–stretching vibration at 1052 cm⁻¹ and C–H stretching bands at 2871 cm⁻¹ and 2969 cm⁻¹. The absorption at 1374 cm⁻¹ corresponds to C–H bending. The infrared spectrum of PVP is characterized by a strong C=O absorption peak from the amide group of PVP at 1650 cm⁻¹, C–N group appeared at 1287 cm⁻¹, C–H stretching and bending vibrations were observed at 2800-3000 and 1420-1460 cm⁻¹, respectively.

From the FT-IR spectral analysis, it is evident that the characteristic peaks of the drug were intact in the physical mixture and the formulations (PE-3 and PE-4) with only minor variations. The non-appearance of additional peaks in the formulations indicates the absence of any chemical incompatibilities between the drug and the polymers selected for the formulation development. However, the FTIR spectra for the formulations show overlapping of TFP and excipients bands and there are some very minor changes in the peaks in the range of 1000–1300 cm⁻¹ probably due to some weak physical interactions between polymers and the drug, but this type of interaction did not interfere with the release of drug from the PVP: EC polymer matrix.

Physicochemical characteristics of the transdermal patch

The physicochemical characteristics of all the formulations were analysed. The thickness of the formulations was found to be in the range of 0.529 to 0.568 mm. Moreover, the weight disparity was identified between 0.5098 to 0.5414 g (table 2). From the analysis, it was clear that all the PE formulations were more or less equivalent in weight and thickness.

| Formulation code | Thickness in (mm) (n=3) | Average weight (g) (n=6) | Folding endurance (n=3) | Average drug content (%) (n=2) |
|------------------|-------------------------|--------------------------|-------------------------|-----------------------------|
| PE-1             | 0.537±0.002             | 0.541±0.0010              | 134±4                   | 93.8±2.0870                 |
| PE-2             | 0.546±0.004             | 0.529±0.0062              | 142±2                   | 90.9±7.292                 |
| PE-3             | 0.568±0.005             | 0.522±0.0117              | 156±4                   | 95.2±0.478                 |
| PE-4             | 0.529±0.005             | 0.5098±0.0060             | 152±2                   | 93.2±1.425                 |
| PE-5             | 0.531±0.003             | 0.519±0.0093              | 162±3                   | 92.2±1.243                 |

Data represent mean±SD

The folding endurance properties of all five patches were analysed, and their corresponding results were enlisted in table 2. The folding endurance of all the five patches (PE-1 to PE-5), were found to be in the range of 130 to 162 indicating satisfactory flexibility and mechanical strength of the patch. Drug content was identified to be ranging from 90 to 95%, showing that the drug was satisfactorily loaded and evenly distributed in the polymer matrix.

**In vitro drug release analysis**

The in vitro dissolution analysis was performed for all five patches and the results are plotted as percentage cumulative drug released (% CDR) vs. time (fig. 2). Formulation PE-1 with PVP: EC ratio 3:2 released 89% TFP within 8 h, due to high concentration of PVP K-30. PVP K-30 being a water-soluble polymer dissolves in the dissolution medium easily making the polymeric matrix porous leading to leach out of the drug from the matrix. As the concentration of hydrophobic polymer EC gradually increased, the release rate of TFP from the system was found to be retarding. Formulations PE-3 and PE-4 with PVP: EC ratio 1:3 and 1:5 respectively resulted in a sustained and stable release of TFP from the polymeric matrix over a period of 24 h and was selected for further evaluations. These formulations could be exploited for multiday therapy of TFP which can simplify the dosage regimen and improve patient compliance in psychiatric patients. The matrix patch PE-5 with a PVP: EC ratio of 1:7 was showing a stagnant release of drug from the device after 8 h (only up to 20%), owing to a high concentration of hydrophobic polymer that to retard the drug release from the device once the surface drug was released.

**DSC analysis**

The DSC analysis is an important method to identify the thermal characteristics of the drug when incorporated in a formulation. Fig. 3 shows the DSC thermogram of pure TFP and matrix type transdermal patches (PE-3 and PE-4) containing TFP. From the
obtained thermogram of neat TFP, it is evident that melting of TFP appears to start at approximately 240 °C followed by decomposition at about 250 °C [28, 29]. This observation is in concordance with the previous reports. In the thermogram of the formulations, the endothermic peak of TFP was found to be smaller as compared to pure drug; probably due to the minimal amount of TFP incorporated in the formulation. Moreover, the peaks have shown a small shift and broadening. This could be expected as the drug was dissolved completely in the polymeric solution during formulation development, leading to the formation of a molecular dispersion of the drug in the polymer mixture. However, the presence of endothermic peak of TFP in the formulation suggests that the crystallinity of the drug was not completely lost during the development of the formulations.

Fig. 2: In vitro drug release data of formulation PE-1 to PE-5, data represents mean±SD (n=3)

Fig. 3: DSC thermogram of TFP, formulation PE-3 and PE-4

Fig. 4: XRD patterns of TFP and formulation PE-3
XRD analysis

The crystallinity of neat TFP and TFP, when distributed in the formulation PE-3 was evaluated by XRD analysis and the recorded
patterns are presented in fig. 4. The pure drug TFP shows the presence of sharp intense peaks in the diffraction pattern and the
characteristic peaks of the crystal form of neat TFP was observed at 15.4°, 20.5°, 20.7°, 22°and 26.2°(2θ). In the formulation, even
though two peaks (20.5°, 20.7°) were visible other characteristic peaks of TFP were found to be absent. Such a decrease in
amplitude and broadening of the peaks are characteristic of the presence of amorphous substances. The earlier reports suggest
that the presence of PVP K-30 can inhibit the crystallinity of the

CONCLUSION

The results of the present investigation suggest that a polymeric matrix with PVP: ethyl cellulose in the ratio 1:3 or above can
effectively retard the release of TFP. As the concentration of EC in the polymeric matrix was enhanced, the release of TFP was
identified as retarding. Different characterizations done on the developed formulations confirmed satisfactory drug loading and
mechanical properties. The thermal analysis results suggest a change in crystallinity of the incorporated drug in the formulations.
Formulations PE-3 and PE-4 with PVP-EC proportions of 1:3 and 1:5, respectively, can be subjected to further in vitro and in vivo
evaluations to explore the potential of the developed system for effective transdermal delivery of TFP for multiple days and thereby
increasing the patient compliance and bioavailability.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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comparison between povidone-ethylene and povidone-

drug in the polymeric matrix [19]. Since DSC reports also confirm
this observation, it can be assumed that partial conversion of TFP
to amorphous form has taken place during formulation
development.

SEM analysis

The SEM analysis of formulations PE-3 and PE-4 depicted a smooth
surface with the absence of drug crystals or pores, indicating homogenous dispersion of drug in the patch. The Nonappearance of
drug crystals on the surface also supports the results of DSC and
XRD analysis suggesting molecular dispersion of drug in the
polymeric matrix.
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