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Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers

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ABSTRACT

The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of olanzapine using blends of two different polymeric combinations, polyvinylpyrrolidone (PVP) and ethylcellulose (EC). A total of fourteen matrix patches were prepared by using these polymers, dibutylthalate as plasticizer and vegetable oils (soyabean oil, olive oil, eucalyptus oil) as permeation enhancers in dichloromethane and chloroform (1:1) as a solvent system. The formulations were characterized including uniformity of weight, drug content, moisture content, moisture uptake, flatness, folding endurance and thickness to study the stability of the formulations and in vitro dissolution of the experimental formulations were performed to determine the amount of olanzapine present in the patches and scanning electron microscopy (SEM) of the prepared TDDS were taken to see the drug distribution pattern. Drug–excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. In vitro dissolution studies showed that the drug distribution in the matrix was homogeneous and it was found that the maximum drug release in 24 hrs was 89.5% with formulation C3 (containing olive oil). In vitro skin permeation study was also conducted in a modified Franz's diffusion cell which shows that the maximum permeation was with the formulation C3 and it was 768.64µg/cm^2 after 48 hrs. Optimized formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and polymers used.

Keywords: Transdermal matrix patch, permeation enhancers, olive oil, soyabean oil, eucalyptus oil

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INTRODUCTION

Transdermal delivery constitutes one of the most important routes for new drug delivery system (NDDS). Transdermal delivery of drugs offers several advantages over conventional delivery including oral and injection methods. Transdermal delivery, that traditionally uses a patch

containing drug substance pressed onto the skin, is non-invasive, convenient and painless, and can avoid gastrointestinal toxicity (*e.g.* peptic ulcer disease) and the hepatic first pass metabolism [1].

Schizophrenia has been one of the major diseases afflicting mankind in today's scenario [2]. Olanzapine, an antipsychotic drug, is supposed to be effective in the treatment of chronic schizophrenic patients. Currently olanzapine is adminisdered orally or by injection. It is usually administered as one or two daily oral doses, for an overall dosage of 5–20 mg per day. The drug has also been introduced in Italian market as film-coated, gastro-resistant Zyprexa® tablets [3].

The low-dose olanzapine maintenance therapy is required to control the psychotic symptoms, and long-term prophylactic treatment is needed to prevent relapses. Long-acting modified dosage forms of olanzapine are going to be effective in patients and can help to address the problem of poor patient compliance. The use of this drug in the lowest possible effective dosage is recommended for minimizing the risk of major side effects. Based on these hypotheses, a modified transdermal drug delivery system was developed.

Simple drug-matrix type of transdermal drug delivery system for olanzapine was designed for prolonged period of maintenance therapy instead of convention oral dosage forms. Moreover, the physicochemical characteristics of olanzapine also comply with the general requirement for designing a TDDS to a good extent.

This search and investigation is expected to add extensively to the existing knowledge and information in the field of proper drug regimen and maintenance therapy of schizophrenia with controlled-release TDDS of olanzapine [2]. The major problem of transdermal delivery is with the barrier properties of stratum corneum. Thus, the transport across the skin membrane is a complex phenomenon. It is the cells of stratum corneum which present the primary barrier to absorption of transdermally administered drugs. Relatively recent advances in transdemal drug delivery have enabled effective administration of a variety of drug through the skin. These advances include the development of a number of skin penetration enhancing agents, or ‘permeation enhancers’ to increase the skin permeability. Penetration enhancers such as oils are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. The vegetable oils (soyabean oil, olive oil and eucalyptus oil) were used to study their impact as an enhancer to skin permeation of the drug olanzapine. There are number of chemical agents that enhance the permeability of the skin but we are using vegetable oils as they are easily available, cause no skin irritation and natural in origin [4]. Moreover, electron microscopic studies were also conducted in an effort to understand drug distribution in the patches, drug release from the patches, and the permeation of the drug through skin [5].

MATERIALS AND METHODS

Olanzapine was received as a gift sample from Ranbaxy labortary Ltd, Ponta Sahib. All other chemicals used in the study were of analytical grade. Wistar rats were used for permeation studies ethically with the permission of institutional animal ethical committee.

Development of transdermal system

A polymeric solution (5%w/v) was prepared by dissolving ethyl-cellulose and PVP K-30 with olanzapine (20% w/w of dry weight of polymer), dibutyl phthalate (30%w/w) as a plasticizer and vegetable oils (1%, 5%, 10% w/w of soyabean oil, olive oil, eucalyptus oil) as a permeation enhancer in chloroform:dichloromethane (1:1) as solvent system.

Firstly, the solution was prepared with different ratios of polymeric blend without adding vegetable oil as permeation enhancer. The composition of prepared transdermal patches is given in Table 1. Then again the patches were developed using the procedure mentioned earlier with different concentrations of vegetable oils and stirred for 45 min on magnetic stirrer to accomplish homogeneous mixture. After mixing the drug and polymer, solution was allowed to stand for 15 minutes to remove air bubbles and the resulting solution was poured in a glass ring placed on a petri dish containing mercury pool. The solvent was allowed to evaporate at 40°C for 24hr to achieve drug polymer matrix patch. After 24 h the patch was collected and stored in desiccators until further use.

Drug-Excipient Interaction studies

FTIR spectra of olanzapine, ethylcellulose, PVP K-30 and mixture of drug and polymers were carried out by FT-IR spectrophotometer (Bruker). The powdered sample was placed on the sampling plate of FT-IR spectrophotometer. Then scanning of the sample was started and IR spectra of all the samples were obtained.

Evaluation of transdermal patches

Uniformity of weight

Ten different patches from individual batches were weighed individually and the average weight was calculated; the individual weight should not deviate significantly from the average weight [6].

Table 1: Composition of Transdermal Formulations

Formulation code	PVP:EC	Drug (%w/w)	Dibutyl phthalate (%w/w)	Permeation enhancers (%w/w)	Solvent system (1:1)
A1	1:1	20	30	_	Chloroform:dichloromethane
A2	1:2	20	30	_	Chloroform:dichloromethane
A3	1:3	20	30	_	Chloroform:dichloromethane
A4	1:4	20	30	_	Chloroform:dichloromethane
A5	1:5	20	30	_	Chloroform:dichloromethane
B1	1:3	20	30	Soyabean oil 1%	Chloroform:dichloromethane
B2	1:3	20	30	Soyabean oil 5%	Chloroform:dichloromethane
B3	1:3	20	30	Soyabean oil 10%	Chloroform:dichloromethane
C1	1:3	20	30	Olive oil 1%	Chloroform:dichloromethane
C2	1:3	20	30	Olive oil 5%	Chloroform:dichloromethane
C3	1:3	20	30	Olive oil 10%	Chloroform:dichloromethane
D1	1:3	20	30	Euclyptus oil 1%	Chloroform:dichloromethane
D2	1:3	20	30	Euclyptus oil 5%	Chloroform:dichloromethane
D3	1:3	20	30	Euclyptus oil 10%	Chloroform:dichloromethane

Drug content determination

An accurately weighed portion of film (about 100 mg) was dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution was shaken continuously for 24 h in shaker incubator. Then the whole solution was sonicated. After sonication and subsequent filtration, drug in solution was estimated spectrophotometrically by appropriate dilution [7].

Moisture content

The film was weighed and kept in dessicator with calcium chloride at room temperature for 24 h. The film was weighed again after specified interval until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage moisture content [8].

$$\% \text{ moisture content} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100$$

Moisture uptake

The weighed film was kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride. Finally, the films were measured periodically to constant weights [8].

$$\% \text{ moisture uptake} = \frac{[\text{Final weight} - \text{Initial weight}]}{\text{Initial weight}} \times 100$$

Flatness

Longitudinal strips were cut out from the prepared medicated patches and the lengths of each strip were measured and then the variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness [9].

Constriction (%) = $(l_1-l_2)/l_1 \times 100$

Where l_1= initial length of each strip; l_2= final length.

Folding endurance

The strip of film was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [10].

Thickness of the films

The thickness of the drug-loaded polymeric films was measured at five different points using micrometer. The average and standard deviation of five readings were calculated for each batch of the drug-loaded films [11].

***In vitro* release-dissolution studies**

It is desirable to maintain greater drug concentrations at the surface of stratum corneum than in the body. This is required to achieve a constant rate of permeation. The dissolution study, using modified USP Paddle Type Dissolution Apparatus, was carried out at 32°C±0.5°C at 50 rpm. Phosphate saline buffer (PBS) of pH 7.4 with 0.5 % tween 80 was used as the dissolution media. The patches were fixed on the stainless steel ring and then placed in a jar. Samples were

withdrawn at different time intervals and then analyzed using a UV spectrophotometer at 248 nm against blank [12].

***In vitro* skin permeation study**

The *in vitro* permeation studies were carried out in a Franz diffusion cell with a capacity of 35 mL, using wistar male rat skin. The skin was used after the removal of adhering fat. A section of skin was cut and placed in the donor compartment, keeping the dorsal side upward, and the patch was placed on the skin with the drug matrix side towards the donor side and backing membrane on the upper side. The holder, containing the skin and the formulation, was placed on the receiver compartment of the cell containing the dissolution media PBS 7.4 with 0.5% tween 80. The temperature of the cell was maintained at 32± 5°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar set was run simultaneously without using the patch at the donor compartment as a skin control. The samples were withdrawn at different time intervals and replaced with equal amounts of dissolution media. Samples were analyzed spectrophotometrically at 248 nm and the amount of drug permeated per cm^2 of patch was calculated from the standard curve and plotted against time. The difference between the readings of drug skin permeation and skin control was used as the actual reading in each case [13].

Scanning electron microscopy

The external morphology of the skin and the transdermal patch (with enhancer) was analyzed using a scanning electron microscope. For carrying out SEM of skin sample, the skin was first fixed with the help of a fixative (3%glutaraldehyde). Then the skin was washed with buffer thoroughly and then subjected to dehydration with acetone. The moisture from the skin was removed by using increasing concentrations of acetone. The section of the skin was cut and mounted on stubs using an adhesive tape. The samples placed on the stubs were coated with gold palladium alloy using a fine coat ion sputter (JOEL, fine coat ion sputter JFC-1100). The sections were examined under scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan). The abdominal skin of the rat was excised and the fat layer was removed, carefully keeping the underlying dermal tissues containing capillary network intact, using a sterile scalpel with the help of a high power magnifying glass. The process was conducted very quickly and the tissue was immediately used for experiments [13].

RESULTS AND DISCUSSION

A total of 14 formulations were prepared using PVPK-30 and EC polymers as per formula given in Table 1. All the films were evaluated for their physicochemical parameters, and they were found to be flexible, smooth and transparent. They were also found to be uniform in their weight and thickness with low SD values, as shown in Table 2. The transdermal patches were exposed to 84% relative humidity and the percentage moisture uptake of the formulation was determined (Figure 2). It was observed that with an increasing percentage of hydrophilic polymers (PVP), in the formulations, moisture uptake increased. Interestingly, with the addition of vegetable oils in the patches, little increase of moisture was observed. A similar observation was made in the case of percentage moisture content (Figure 1).

Table 2: Evaluation of transdermal patch for uniformity of weight (mg), drug content, flatness, folding endurance and thickness (mm)

S. No.	Formulation Code	Uniformity of weight	Drug Content (%)	Flatness	Folding Endurance	Thickness
1	A1	187±4.50	85.2	100%	9±0.57	0.210±0.01
2	A2	177±2.08	86.25	100%	8±0.57	0.213±0.001
3	A3	193±2.88	88.9	100%	10±0.57	0.227±0.002
4	A4	210±6.08	87.5	100%	8±0.57	0.230±0.01
5	A5	218±6.02	92.1	100%	8±0.57	0.239±0.001
6	B1	221±14.5	89.1	100%	11±1	0.215±0.002
7	B2	172±0.57	92.5	100%	10±0.57	0.22±0.002
8	B3	214±14.1	90.4	100%	10±1	0.234±0.002
9	C1	205±6	95.2	100%	11±1	0.22±0.001
10	C2	201±8.02	91.4	100%	12±0.57	0.230±0.0005
11	C3	208±6.08	94.58	100%	12±1	0.231±0.001
12	D1	170±1.15	84.46	100%	10±0.57	0.21±0.003
13	D2	193±2.88	92.15	100%	9±0.57	0.219±0.0005
14	D3	186±3.21	94.23	100%	10±1	0.225±0.001

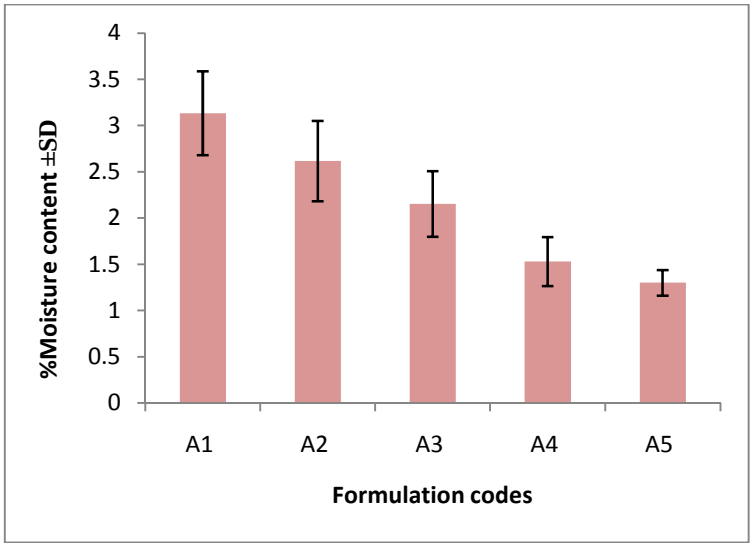

Figure 1: Percentage moisture content of olanzapine containing different matrices films prepared by using different ratios of PVP-30 and ethylcellulose Data shows Mean (n=3) ±SD.

A transdermal patch should possess a smooth surface and should not constrict with time, as the flatness study demonstrated. No constriction was observed in any of the prepared formulations; all of the surfaces were 100% flat (Table2). FTIR was carried out to assess the interaction between the drug and the excipients (Figures 3-6). Graphs of drug and drug-excipients confirmed that there is no interaction between the drug and excipients used.

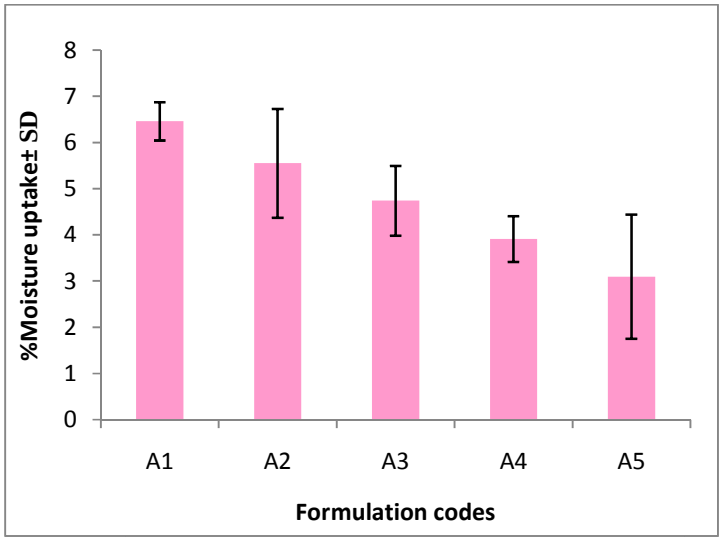

Figure 2: Percentage moisture uptake of olanzapine ontaining different matrices films prepared by using different ratios of PVP-30 and ethylcellulose Data shows Mean (n=3) ±SD

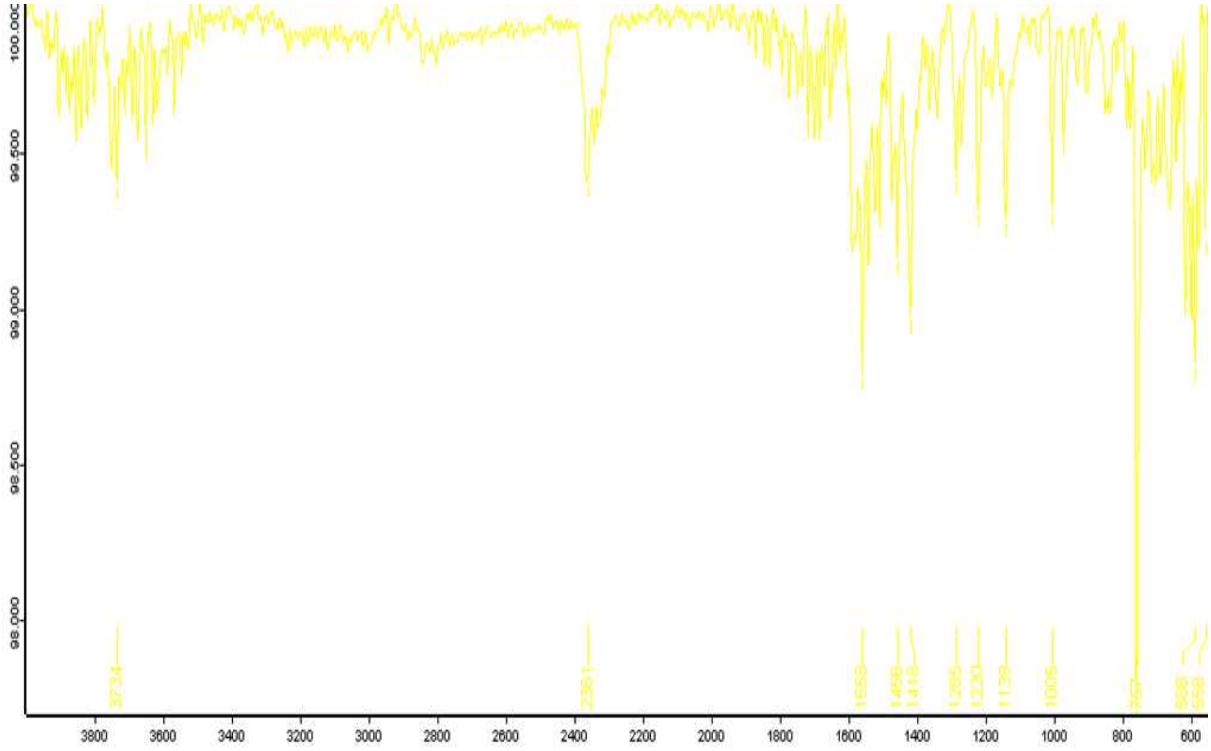

Figure 3: IR spectra of drug olanzapine

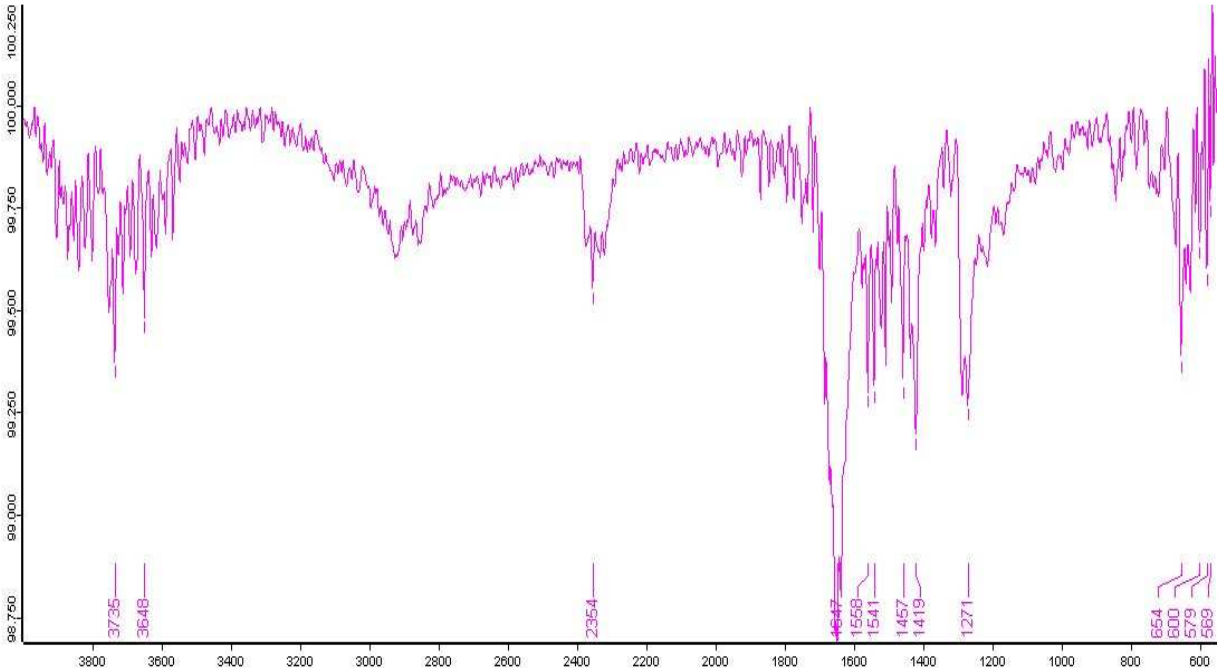

Figure 4: IR spectra of PVPK-30

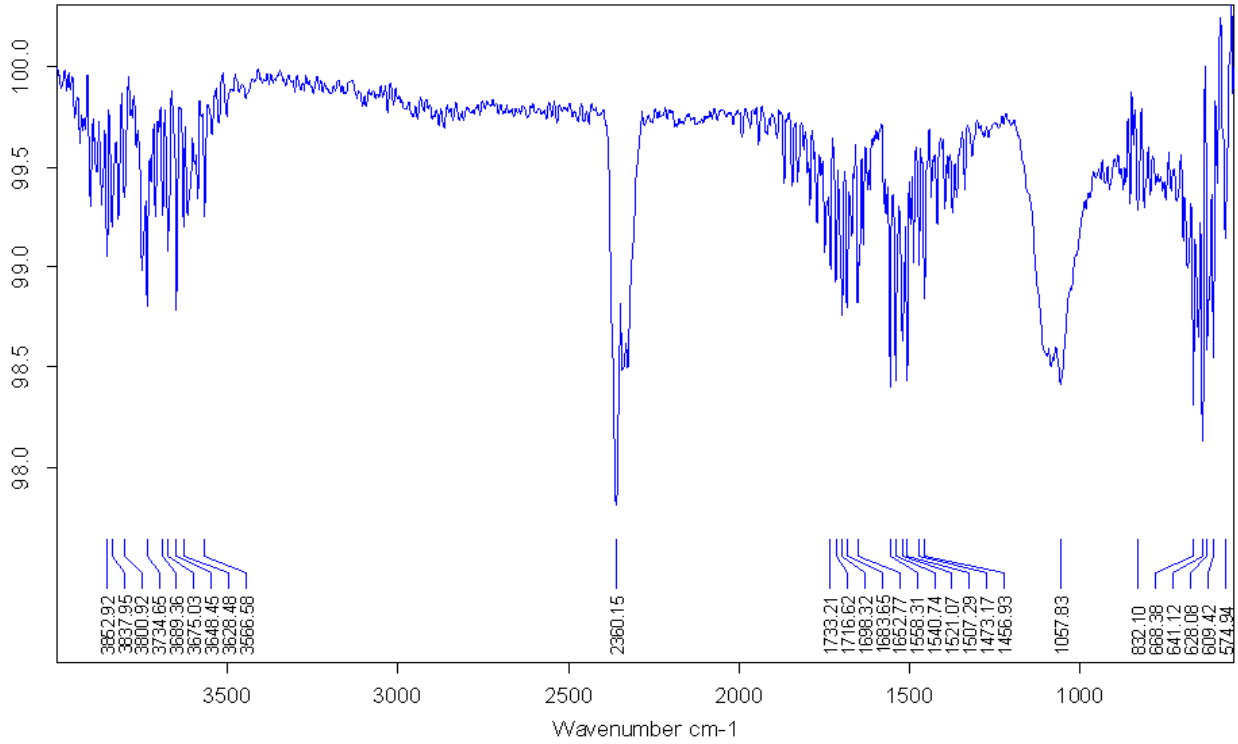

Figure 5: IR spectra of ethylcellulose

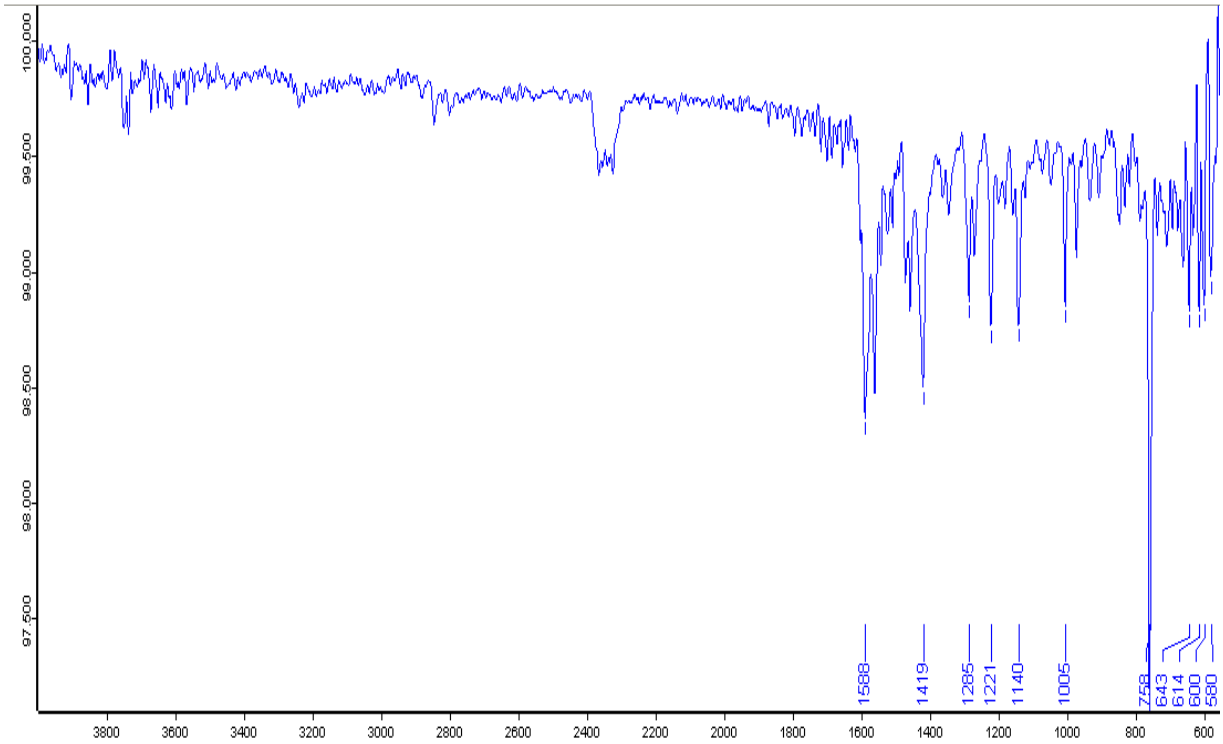

Figure 6: IR spectra of drug, PVPK-30 and ethylcellulose

***In vitro* release and permeation studies**:

Drug release from polymer matrix and drug dissolution ensured sustained reproducibility of rate and duration of drug release. Dissolution studies for different formulations were carried out using modified USP paddle type apparatus using PBS 7.4 with 0.5% tween 80 as dissolution fluid at 32±0.5°C. The in vitro studies of batch A *i.e.* formulations without permeation enhancer showed that the batch A3 (PVP: EC in the ratio of 1:3) showed better release (44.5%) than films containing other combination of polymers without any permeation enhancer. So batch A3 was selected for incorporation of permeation enhancers and batches B, C and D were formulated with soyabean oil, olive oil and eucalyptus oil respectively. Further release studies showed that release was 67.7%, 74.5%, 82.4% from batch B1, B2, B3 and 70.1%, 80.5.%, 89.5% from batch C1, C2, C3 and 68.8%, 74.7%, 82.1% from D1, D2 and D3 as shown in Figure 8-10. From the results it is clear that the best release profile was obtained with batch C3.This may be due to presence of oleic acid present in olive oil. Release studies also indicate that by increasing the concenteration of the olive oil up to 10% showed better release then other concenterations (1% and 5%).

In vitro skin permeation study is predictive of an in vivo performance of a drug. This study was carried out using different formulations in a Franz diffusion cell using rat skin. This study further confirmed the better permeation of drug through skin by using natural oils as permeation enhancers. Mean cumulative amounts of drug released per cm^2 of patch after 48 hours were found to be 188.5µg/cm^2, 452.3µg/cm^2, 768.64µg/cm^2 and 614.3µg/cm^2 from batches A3, B3, C3 and D3. Skin permeation study results are also represented in Figure 11.

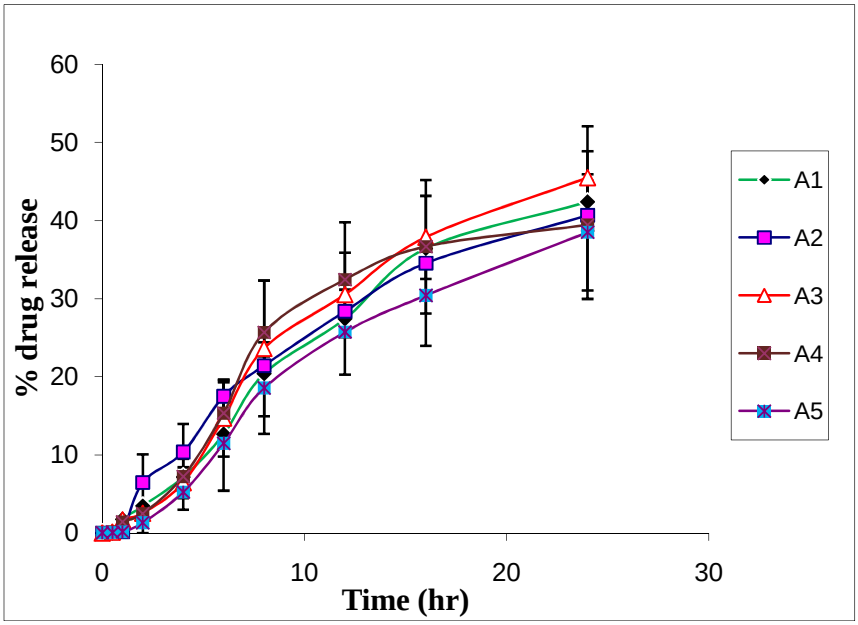

Figure 7: Release profile of batch A (without permeation enhancer) containing different concentrations of polymers

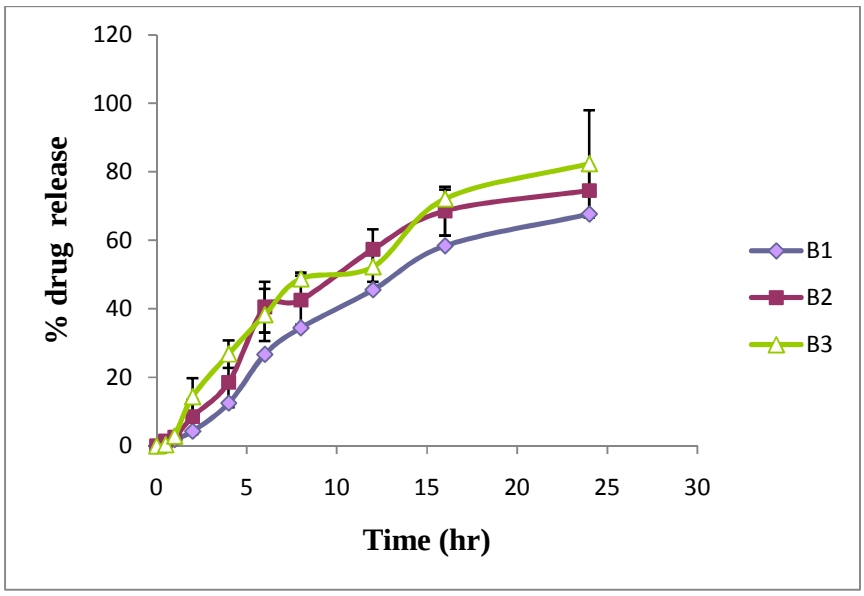

Figure 8: Release profile of batch B (soyabean oil as permeation enhancer)

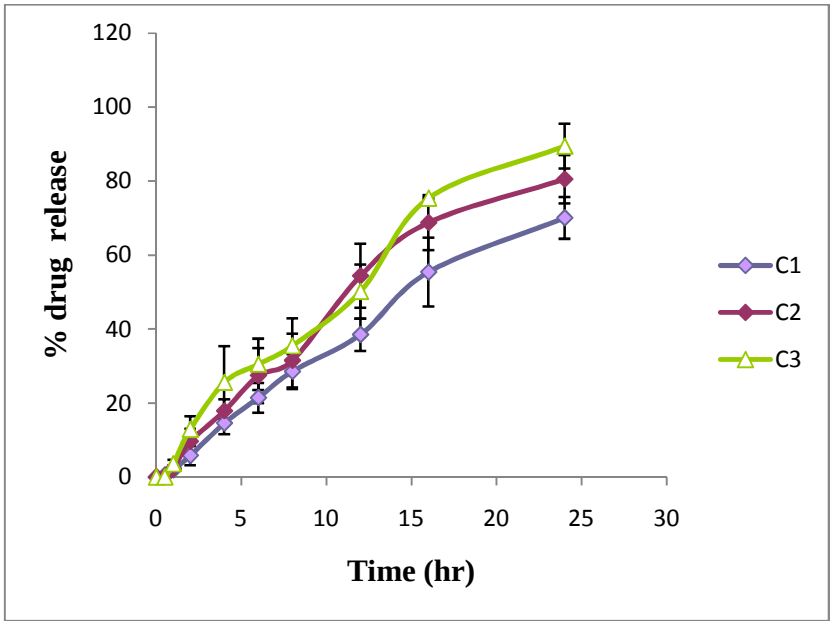

Figure 9: Release profile of batch C (olive oil as permeation enhancer)

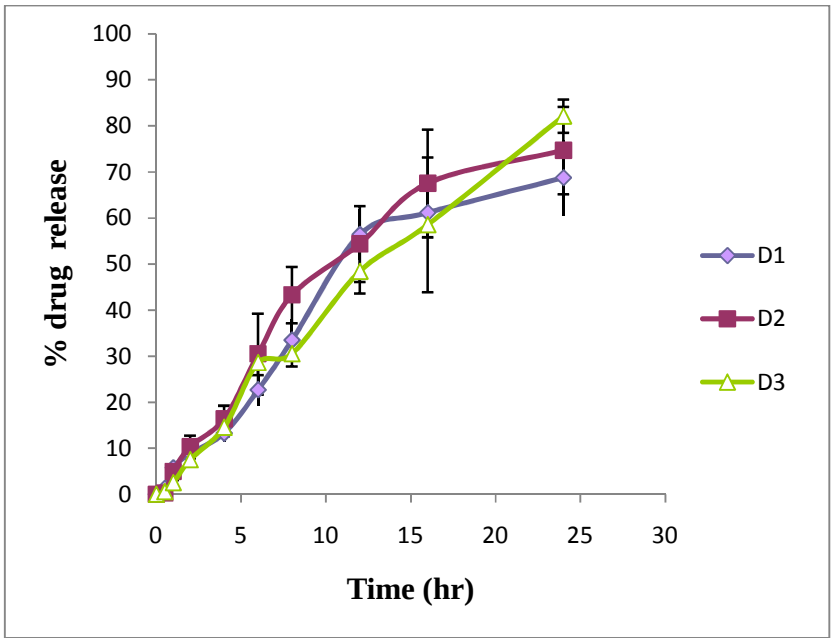

Figure 10: Release profile of batch D with eucalyptus oil as permeation enhancer

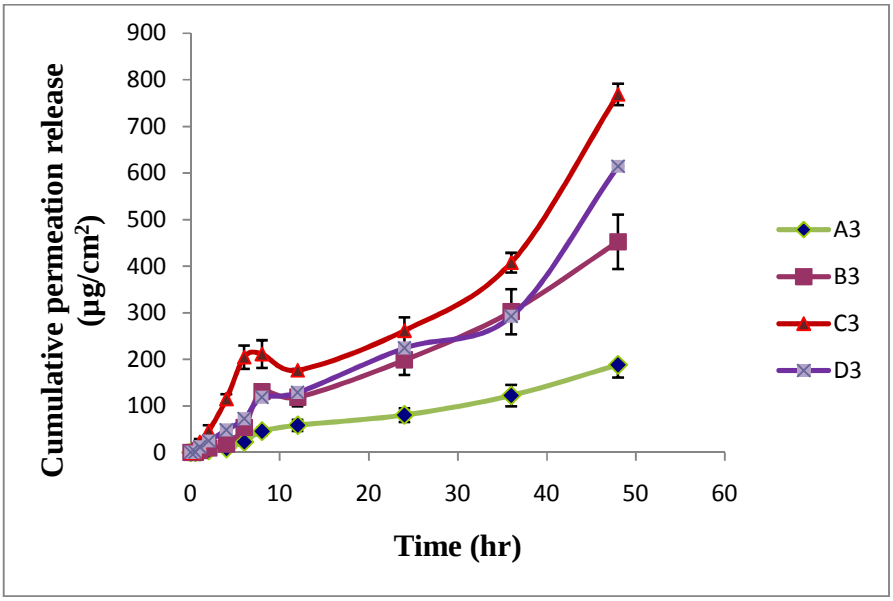

Figure 11: *In-vitro* skin permeation studies of optimized olanzapine TDDS

SEM Result

Electron microscopic studies were conducted to visualize drug penetration through the skin and its distribution in the matrix patches. It was clear from SEM studies that drug distribution in the matrix patches was a particulate distribution (Figure 12). Figure 13 shows drug clusters on the skin surface during its entry through a skin appendage. This result confirms that the drug remains in cluster form when it reaches the surface. Figure 14 and 15 shows a drug cluster is passed through the skin appendages from the dorsal side to the ventral side of the skin and reached the ventral side of the skin. These figures clearly indicate that the drug, in cluster form, was transported from the dorsal side to the ventral side of the skin.

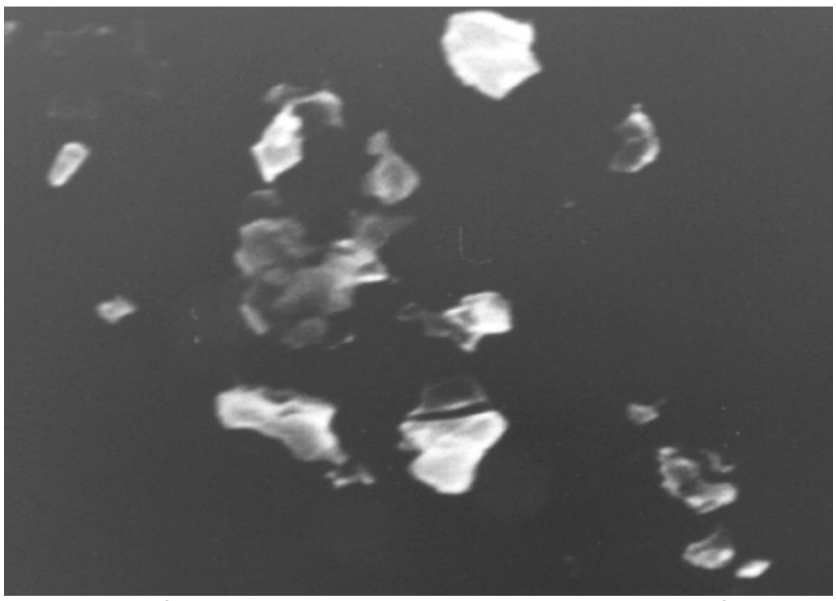

Figure 12: SEM photograph of the transdermal patch showing the distribution of the drug in the matrix as particulate distribution

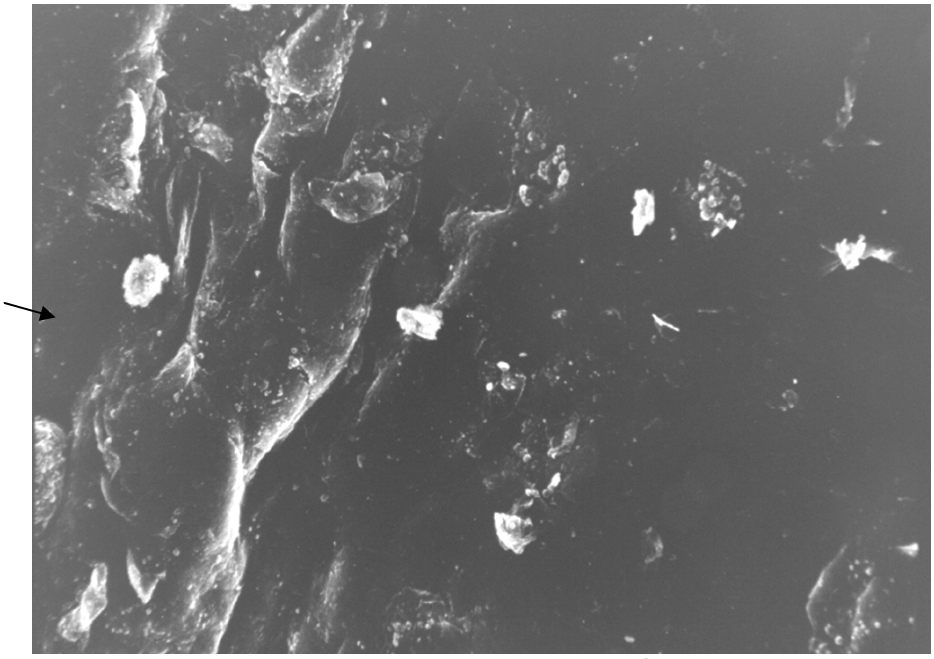

Figure 13: SEM photograph shows drug particles on the skin surface during their entry through skin appendage.

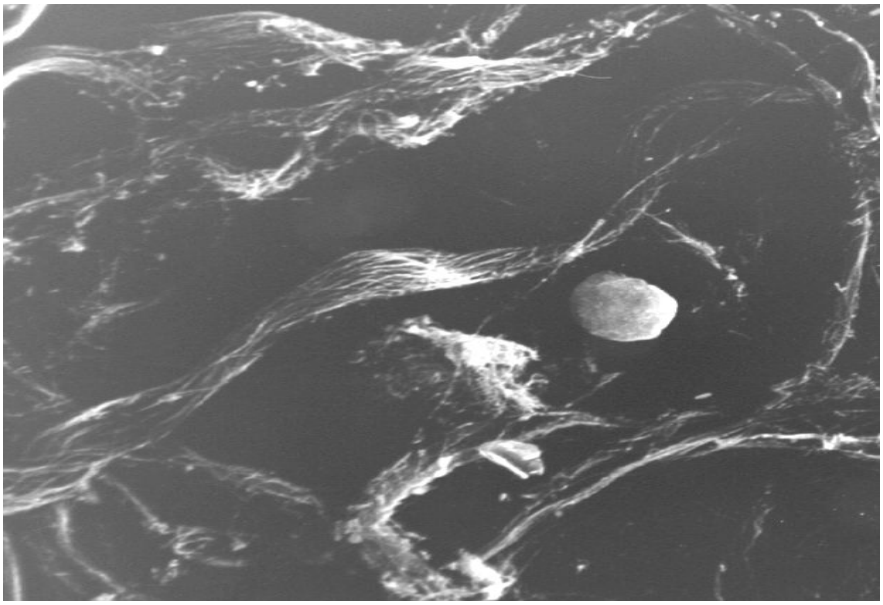

Figure 14: SEM photograph shows a drug cluster as such reached at the ventral side of the skin

In this study the transdermal patches were developed for sustained studies of transdermal drug delivery systems. The patches were subjected to in vitro release and permeation studies through rat skin using a Franz diffusion cell. Physicochemical parameters like uniformity of weight, moisture content, moisture uptake, and flatness studies proved the uniformity and integrity of the prepared transdermal formulations. It is important to detect any possible chemical or physical interactions, since they can affect the bioavailability and stability of the drug [14]. FTIR study implied that all the excipients are compatible with olanzapine. The selection of receptor fluid is an important criterion in the design of in vitro studies for transdermal drug delivery systems.

Biphasic characteristics of the receptor fluid are desirable, since drug molecules are diffused through both aqueous and nonaqueous heterogeneous media. 0.5% tween 80 with PBS (pH 7.4), was chosen because of more solubility and to provide the biphasic characteristics to the receptor fluid [15]. Moreover, tween 80 is considered to be a non-interacting fluid for the receptor media [16].

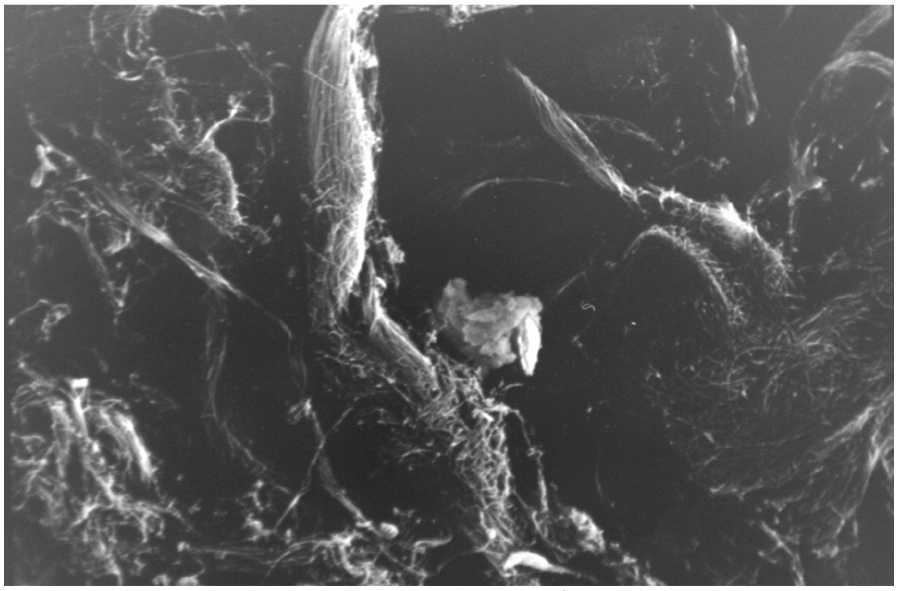

Figure 15: SEM photograph shows how a drug cluster proceeds for absorption at the ventral side of the skin

The mechanism of penetration enhancement effects of the vegetables oil (soyabean oil, olive oil, eucalyptus oil) is primarily believed to be due to the promotion of membrane-vehicle partitioning tendency of the drug with the oils. It is also reviewed that penetration of the vegetables oil into the intracellular lipid phase of the membrane may also increase the degree of fluidity in this phase resulting in a decreased resistance to permeation, which can in turn increase flux [17]. An electron microscopic was used to visualize what actually happens when the drug diffuses through the skin and how it diffuses from the patch formulations. The drug molecules were distributed in the form of small clusters in the patch. Though the drug, polymers, plasticizer, and enhancer are completely soluble in dichloromethane and chloroform, the distribution of the drug in the polymer matrix was in a particulate distribution.

CONCLUSION

Flexible, smooth and transparent films were obtained with PVPK-30 and EC polymers. It was found that the transdermal patch containing polymers PVPK-30:EC (1:3); 20% olanzapine; 30% dibutylthalate and 10% olive oil showed best release and permeation. Again, it was concluded here that the formulation C3 showed better permeability amongst the prepared transdermal matrix type patches for olanzapine and olive oil may be an option amongst the other skin permeation enhancers for permeating the drug steadily through the skin.

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