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Original Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF PSEUDOEPHEDRINE HCL

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ABSTRACT

Objective: This study was conducted to design a transdermal dosage form of pseudoephedrine HCL and to evaluate its release under controlled rates for sustained transdermal delivery of Pseudoephedrine.

Methods: Transdermal patches were prepared by the casting evaporation method. Utilizing eudragit RL100. Patches were characterized by physical appearance, moisture content, thickness, weight variation, folding endurance, tensile strength and stability studies. Fourier transform infrared spectroscopic studies (FTIR), differential scanning calorimetry analysis (SCA) and XRD studies. Four different permeation enhancer (Tween 20, thymus oil, castor oil and eucalyptus oil) was employed. *In vitro* release of drugs was done in the dissolution paddle apparatus. Release studies were performed in distilled water at 37 °C. Scanning electron microscope studies were performed before and after the drug.

Results: Transdermal patches with enhancers were formulated successfully with a concentration of 1% (W/V). The patches indicated stable physicochemical characteristics. FTIR, SCA and XRD Studies showed that there were no physical and chemical interactions between excipients and drugs. Results of *in vitro* permeation studies showed that enhancers used in this study increased drug released. The enhancers showed faster released than no enhancer. This arrangement can be shown as Tween>Eucalyptus oil>Thymus oil and castor oil. Formulation F2 is optimized among all formulations showed an 83.3% release.

Conclusion: Transdermal patches of pseudoephedrine were successfully developed by using pseudo epinephrine HCL. These patches proved to be very useful for therapeutic purposes in the pharmaceutical industry without making the patients unconscious, unlike the trivial methods of treatment.

Keywords: Dissolution, Enhancers, Pseudoepiderine, release, Transdermal patch

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INTRODUCTION

Transdermal Drug Delivery Systems are generally known as TDDS. In this technique, the drug is normally used in the form of patches. These patches are applied on the skin of the patients, which can enter conveniently from the skin into the bloodstream, simply by the process of diffusion and then transported to their target tissues where they display their therapeutic results. These transdermal patches can survive in the blood of the patients for a long time, unlike other techniques of medications. This system of medication is very effective and advantageous; therefore, it has substituted the traditional methods of medications and drug application in the field of pharmaceuticals. It is patient-compliant, sustainable and avoids damages caused by the liver by direct injection of drugs into the body [1].

At present, numerous diseases such as motion diseases, cardiovascular diseases, and hormonal abnormalities are being treated using this technique. The treatment of many other diseases like skin cancer, sexual and menstrual dysfunctions in women, anxiety, stress, etc. are yet to be treated by using this technique in future. The products of the transdermal system generate handsome revenue in the international pharmaceutical markets too [2].

The application of drugs via trivial methods was very common till 1990s. This had many side effects like that of gastrointestinal ulceration, anemia and liver deformities causing hepatitis. The primitive methods of drug administration would most likely cause death in certain cases. In order to minimize the risks in the field of pharmaceutics, the experts were desperately in need of a technique that could overwhelm the side effects of the conventional system of medication. They, therefore, introduced the transdermal application as an alternate source of treatment, which is simple in applying it and patient compliant simultaneously [3].

Polymers, enhancers, plasticizers and solvent systems are given due consideration while fabricating polymers, which are believed to be the key ingredients of the transdermal drug delivery system because the frequency of drug penetration and its release depends upon polymers. Pseudoephedrine hcl is a sympathomimetic drug of the phenethylamine and amphetamine chemical classes. It may be used as a nasal/sinus decongestant and as a stimulant, or as a wakefulness-promoting agent in higher and frequent doses, therefore, to avoid the systemic circulation, so as to overcome the hazardous effects of oral applications of drugs [4].

Pseudoephedrine HCl a short half-life of 4-5 h. Doses of 20 mg are, therefore administered orally 3 to 4 times a day [5]. However, frequent dosing may cause side effects, including tachycardia, hypotension, insomnia, and tremors. The objective of this study was to formulate a pseudoephedrine HCL patch for transdermal administration.

MATERIALS AND METHODS

Chemicals

Pseudoephedrine HCl (SS) was fetched as a gift sample from Merck (Quetta, Pakistan). Eudragit RL 100 and Polyvinyl alcohol that had a Molecular Weight of 72 000 were procured from Sigma-Aldrich, UK. Thymol oil extracted in the lab of UOB. Eucalyptus oil was fetched from George Rennie, France. Tween 20 and Methanol bought from Merck, Germany. Distilled water was obtained from the assembly of water distillation. This facility was available at the laboratory, Faculty of Pharmacy and health services, University of Baluchistan, Quetta, Pakistan.

Backing membrane preparation

Polyvinyl alcohol (PVA) was utilized for the purpose of making the backing membrane of patches. A conical flask was taken in order to prepare a solution (Aqueous 4% w/v) of PVA. During this process stirring in flask continued with hot plate stirrer by keeping Temp at Eighty Degrees Centigrade. Cooling of the solution was done, followed by a deaeration of PVA solution in a sonicator for two minutes. Lastly, a glass petri dish (61 cm^2) was taken in which

fifteen mili liter ml prepared solution was transferred that had dry air for twenty-four hours [6]. Films were dehydrated at room temperature. Furthermore, for the purpose of fabricating transdermal patches; the conditions of the laboratory, particularly that of temperature and humidity, were kept favorable (i.e. 25 ° and 75% RH). A series of membranes were prepared keeping conditions, ambient wherein air-drying of PVA films were applied in this case. It was proposed by Raruf *et al.* that the films, in which Chitosan was blended, had wonderful physical and chemical properties [7].

A waterproof PVA membrane secures the transdermal system from that of the hazards of the outside environment. The process of permeation of drugs via skin [8]. In enhanced because of the obstructive nature of PVA membrane. For the purpose of making of baking membrane, PVA is the commonly used polymer [9, 10].

Preparation of the casting and matrix solution

Variables of formulation/100 ml of matrix dispersion are shown in table 1. A conical flask (250 ml volume) was taken to prepare the solution of patch formulation. For this purpose, 100 mili liter of methanol and 5 g eudragit was added in the conical flask (250 ml volume). 500 rpm magnetic stirrer was used in which the sealed conical flask was stirred for thirty minutes. The solution was mixed completed after that, enhances and related plasticizer was also added, which was further mixed for half an hour. In order to get a standardized dispersion, pseudoephedrine HCl (0.620 g) was added and then also stirred for half an hour. The aforesaid amount of PE is further added in 100 ml of solvent to get 1.5 mg of PE for every patch that has a size of 1.5 cm^2. In order to eliminate the entrapped air, matrix dispersion was sonicated for a further five minutes. The Petri dishes that had PVA backing membrane were taken in which 10 ml of the aforementioned matrix was emptied, which were put horizontally for a period of twenty-four hours at room temperature. In order to avoid quick evaporation of the solvent, the petri dishes in this process were covered using inverted funnels. The patches, containing, antiasthmatic drugs, were dried first and later on detached from Petri dishes cautiously. The patches were then enfolded into aluminum foil and stirred further at 25°.

Table 1: Formulation variables of transdermal patches

Ingredients	F1	F2	F3	F4	F5
Eudragit RL 100 (g)	5	5	5	5	5
Castor oil(g)	5	-	-	-	-
Tween 20 (g)	-	5	-	-	-
Eucalyptus oil (g)	-	-	5	-	-
Thymus oil (g)	-	-	-	5	-
Methanol (ml)	100	100	100	100	100

Patches cuttings

A stainless steel cutter (1.5 cm^2) was used to cut films. The cuts were circular in shape.

Transdermal patches and their physical evaluation

Different physical characteristics of patches were assessed. Properties like smoothness, brittleness and clarity were visually evaluated [11]. From every formulation, 3 patches were randomly taken. An analytical balance (Shimadzu AUX220, Germany) was used to measure uniformity in weight, weight variations of those circular patches. Measurement of thickness was done with an electronic micrometer screw gauge (Sharp fine Type-A, China). Thickness of the circle cut patches was measured three times. Then the mean value was opted as standard.

A manual test was done so as to determine the strength and folding endurance of circularly cut patches by selecting 3 patches for checking the above-mentioned capacity of patches. Finally, averaged of these 3 trials was taken [12].

The property of moisture uptake, integrity and stability of transdermal patches was also assessed. For this purpose, a humid condition was opted to use a saturated solution of KCl and circularly cut (1.5 cm^2) patches were weighed first. Secondly, a desiccator was used to put a film in it at room temperature. The patches were regularly weighed till getting a constant weight. The formula given below was used to calculate moisture uptake (%) [13].

$$\text{Moisture content}(\%) = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{x} 100$$

FTIR spectroscopy analysis

The compatibility study was done with Fourier Transform Infra-Red spectroscopy (FTIR) on prepared transdermal patches in the presence and absence of pseudoephedrine HCl, respectively. A sample holder (Attenuated Total Reflectance (ATR) Bruker FTIR; Tensor 27 series, Germany) was taken in which sample was put. Sample analysis was done with a software (Opus data collection software), with 4000–750 cm^{-1} wavenumber [14].

Microscopy through scanning electron microscopes

SEM was done with an electron microscope (Quanta 250), that had software (Hillsboro, Oregon, USA) [15].

X-ray diffraction (XRD)

For the confirming nature of drug matrix film (i.e., to determine whether it is amorphous or crystalline), X-ray diffraction studies of the drug (PE.), matrix (PE.) were conducted with software PAN analytical (Netherlands). An anode made of Cu-Ka (30 KV and 15 KA current) was used for determining measurement. Then the diffractograms were captured at a rate of 2 min while keeping the temperature at ambient. A step width of 0.02 °and 2Φ between the 2° and that of 60° was used for this purpose [16].

Drug content

This was followed by (Gul *et al.*, Gupta *et al.* and Dandagi *et al.*). The films (1.5 cm^2) from every formulations-in the presence and absence of drug-were cut into small pieces that were placed in a conical flask of one hundred mili liter of H_2O. The Flask was placed on a magnetic stirrer and was stirred consecutively for thirty-six hours. Later on, this solution was put in a sonicator for sonicating in about thirty minutes. After sonication for thirty minutes, the solution was also filtered. Finally, solutions were evaluated via Spectrophotometer (double beam UV/Vis Shimadzu-1601, Germany) by fixing its wavelength at 210 nanometers for PE [17].

***In vitro* release studies**

A dissolution apparatus (PT-DT7 Pharma Test, Germany) was used for this purpose. Patch (1.5 cm^2) that had PE (1.5 mg) was put horizontally with the help of clips (stainless steel mesh). Water was taken as a medium of dissolution by maintaining temp at ambient. For checking solubility, five hundred mili liters of distilled water were poured in vessels whereas the temp was kept at 32±0.5 ° (skin temperature). Paddle blades were placed in such a way that the distance between paddles and surface was 25 mm. Disk assemblies with patch were put at the bottom of the vessels. In vessels, release surfaces were kept in the center and upward and were centered with the help of a glass rod. Fifty rpm was set as stirring speed while the vessels were shielded to lessen evaporation. In order to withdraw five mili liters of release media at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 h, an Autosampler (PTFC II, Pharma Test, Germany) was used. Spectrophotometric analysis of drug release was also calculated. In order to assess *in vitro* release, three patches from that of every formulation was examined. Finally, the average reading was calculated.

Stability test

Stability test was performed by keeping temperature conditions different for every formulation made of the plants so as to note effects of various temperature conditions for the storage of each formulation. Samples were analyzed after 3 mo of storage at 0±1 °C (freezer), 8±0.1 °C (refrigerator), 25±0.1 °C (incubator), and 40±0.1 °C (incubator) [5]. All formulations were tested for changes in appearance, drugs contents, moisture contents, and weight variations

RESULTS AND DISCUSSION

The current study was done with an objective to develop transdermal patches of PE drugs possessing that of a matrix type. In this regard, a method knows as solvent casting or plate casting method was used. Matrix type patches were made by using eudragit RL100 as a polymer. Enhancers were also used in this current study that comprise of tween 20, castor oil, thymus oil and eucalyptus oil. *In vitro* dissolution and physicochemical properties of different enhancers (having various permeability characteristics).

Table 2: Visual appearance of transdermal patches

Formulation	Brittleness	Clarity	Smoothness	Appearance
F1	X	+	+	Satisfied
F2	++	X	++	Satisfied
F3	++	++	++	Satisfied
F4	++	X	++	Satisfied
F5	++	+	++	Satisfied

X=Level of dissatisfaction,+=Level of satisfaction

The patches were visually examined, which demonstrated that patches which had tween 20, eucalyptus oil, castor oil and thymus oil as permeation enhancers had relatively smooth and clear surfaces. Table 2. Properties of permeation enhancers probably were the main reason of smoothness table 3**.** Shows the results of the weight variation test, thickness, folding endurance, moisture content and tensile strength. The standard deviation having lower values demonstrated that the uniforms in terms of weight were because of patches that contained antiasthmatic drugs. For the purpose of ensuring uniformity in terms thickness of these transdermal patches, every patch was assessed at 3 different positions by finally measuring the average table 3. Shows the value of the thickness of the different patch formulation. The Solvent Casting method produced a standard deviation having lower values regarding uniforms in terms of thickness in patches. Many enhancers were basically applied as a plasticizer and an additive and plasticizer for producing transdermal patches. Formulations that had tween 20, castor oil, eucalyptus oil and Thymus oil as a source of permeability enhancers [18]. Displayed suitable physicomechanical characteristics in the absence of plasticizer.

Table 3: Physical properties of pseudoephedrine HCL transdermal patches

Sample No	Weight variations (mg)	Thickness (nm)	Folding endurance	Moisture content (%)	Tensile strength
F1	30.12±0.01	20±0.011	172±1.10	3.1±0.02	0.70±0.01
F2	29.11±0.32	18±0.021	154±1.01	2.9±0.22	0.57±0.32
F3	28.12±0.22	22±0.041	164±1.02	3.2±0.12	0.60±0.22
F4	30.21±0.01	24±0.021	158±1.03	3.4±0.42	0.76±0.02
F5	29.01±0.01	18±0.011	152±1.01	3.2±0.12	0.71±0.12

The values are expressed as a mean of three trials,±SD= Standard Deviation

One of the important factors for transdermal patches are polymer [19]. The Formulated matrix membrane gets softened and extends because of plasticizers, which interpose forces that grip chains of polymers while patches have appropriate folding durability; results of folding durability and moisture uptake are shown in table 3. Lower values of moisture uptake are because of the hydrophobic nature of eudragit RL100, which protects the product from microbial infection too. The properties of suitable strength and elasticity of patches were drawn form tensile strength, which are also shown in table 3.

The difference in terms of uniformity of drug content in different patches was not significant, which are shown in table 4**.** The plate casting method used for production of patches, in this study, has been proved capable of bringing forth uniformity in the distribution of drugs within the patches.

Table 4: Content uniformity of PE in transdermal patches

Formulations	%Contents
F1	98.54±0.008
F2	100.10±0.002
F3	102.10±0.003
F4	100.02±0.006
F5	Blank

The values are expressed as mean±SD= Standard Deviation from the mean, n=3

Fig. 1. Shows the percentage of the cumulative release of both types of drugs after a period of twenty-four hours dissolution experiment. Drug from that of the F2, which had tween 20 as a permeation enhancer, demonstrated the highest percentage of cumulative release for both of the drugs. The swift release of drug form those of the patches significantly in twenty-four hours are because the ammonium group is present in eudragit RL100 which make it hydrophilic. The drug is released from that of the polymeric device after the formulation mixes with the medium because now the water is absorbed by polymer which hydrates and swells patches that smoothens drug release. By adding enhancers, the amount of drug released fastens via patches during dissolution fig. 1. Which also makes the eudragit RL 100 matrix of patches smooth and flexible [20]. The films swell because of the penetration of water molecules quickly in it, which, resultantly, rises the amount of drug release from [21]. Tween 80 has a solubilizing property as well, which causes the highest

release of drug from F2. F1 showed the lowest amount of percent cumulative PE drug release since permeability enhancer in F1 was absent, whereas the formulations that comprised of enhancers displayed comparatively higher cumulative release of drugs.

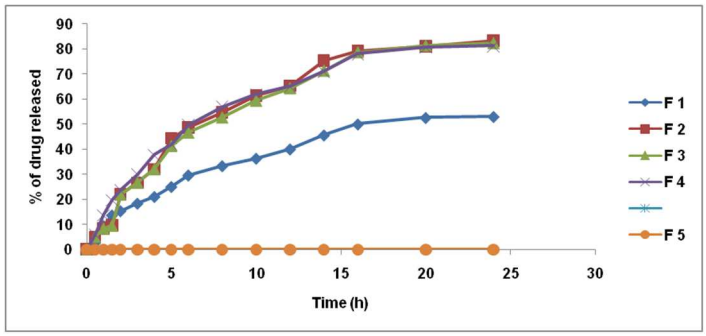

Fig. 1: % of drug released from PE Transdermal patches with different enhancers (mean±SD, n=3)

PE was assessed effectively in transdermal patches in the current study. Formulated patches possessed reasonable physical and chemical properties along with a property of uniformity of drug dispersion. Different permeation enhancers were added in order to optimize the rate of *In vitro* release and ex vivo permeation. F2, that had tween 20 as an enhancer, was the best in terms of performance. F2 demonstrated drug release in large quantity via patches. The results of stability studies were also positive. The patches in which enhancers were not added showed poor permeability. The results of this study offer an inclusive information to developing and optimizing transdermal patches of PE. HCl drugs by using different chemical enhancers.

FTIR spectroscopic analysis

For the purpose of finding out any physicochemical interactions between the polymers, drugs and blends of prepared patches, FTIR spectroscopy was done for PE in [fig. 2a]. Ammonio Methacrylate Copolymer Ph Eur RL 100, as shown in fig. 2. The FTIR spectra of pure PE had characteristic peaks at 3,369 cm1 and 3,288 cm1 corresponding to NH stretching, 1,707 cm1 and 1,674 cm1 due to carbonyl stretching, 1,345 cm1 describing CN stretching, and these characteristic peaks of PE were also found in prepared patches of polymeric blends. The results obtained from FTIR spectroscopic analysis proved that no chemical incompatibility between GPE and the polymers (Ammonio Methacrylate Copolymer Ph Eur RL 100) exists.

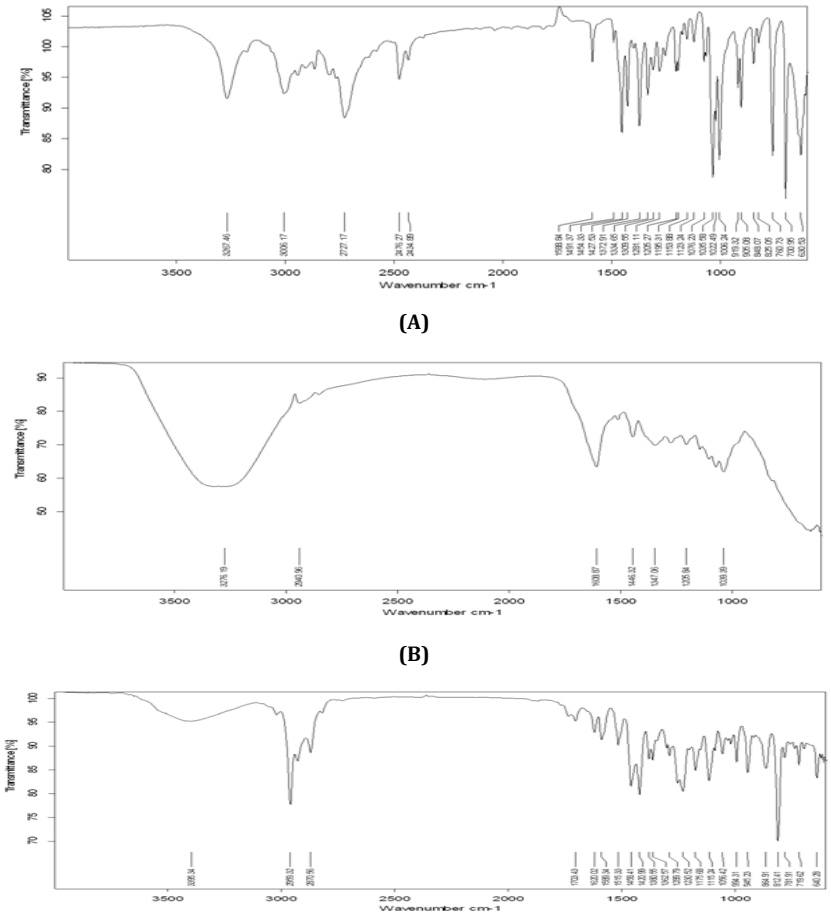

Fig. 2: FTIR spectra of (a) Pseudoephedrine hcl, (b) Blank patch (c) physical mixture of polymers plus drug

SEM

Drug, with its morphology, was studied under an electron microscope after the drug was released. Gapes having irregular shapes were observed under an electron microscope because the polymer used was water-soluble in nature. SEM results showed that the drug indeed had elasticity in its nature because the films did not affect other parts of patches after it was released.

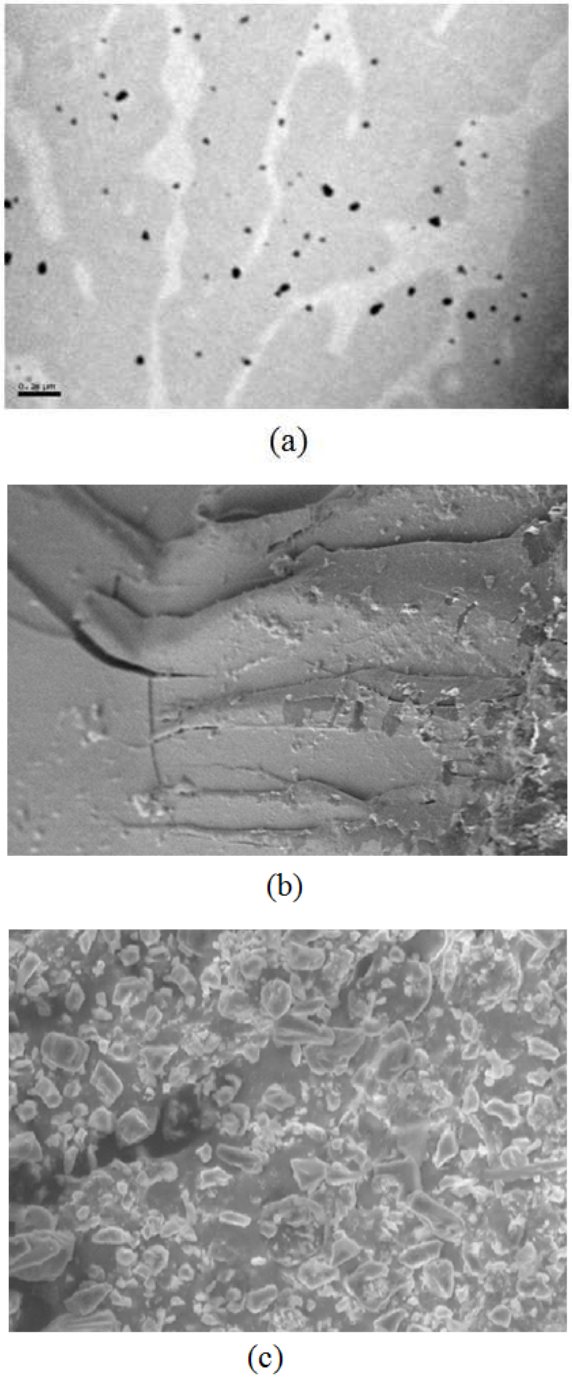

Fig. 3:(a) Illustrates surface morphology of the polymeric films before the drug release, while (b–c) display surface morphology of polymeric patches after the drug release at different magnification powers

XRD studies

X-ray diffraction studies were applied to confirm the physical and chemical properties of PE and polymeric matrix of patches. Pure PE showed sharp peaks of diffraction at an angle of the 2θ value of 13.52 °, 18.23 °, and 21.18 °, etc. X-ray diffractograms are shown in [fig. 4 a]. That shows the crystalline nature of PE, which was reported by Mokale *et al.* previously. PE and Ammonio Methacrylate Copolymer Ph Eur RL, displayed peaks having lesser intensity, while in diffractograms of the PE patch, fused peaks were present.

Irregular peaks of PE demonstrated that drug changed into an amorphous type in polymeric films with a molecularly discrete nature.

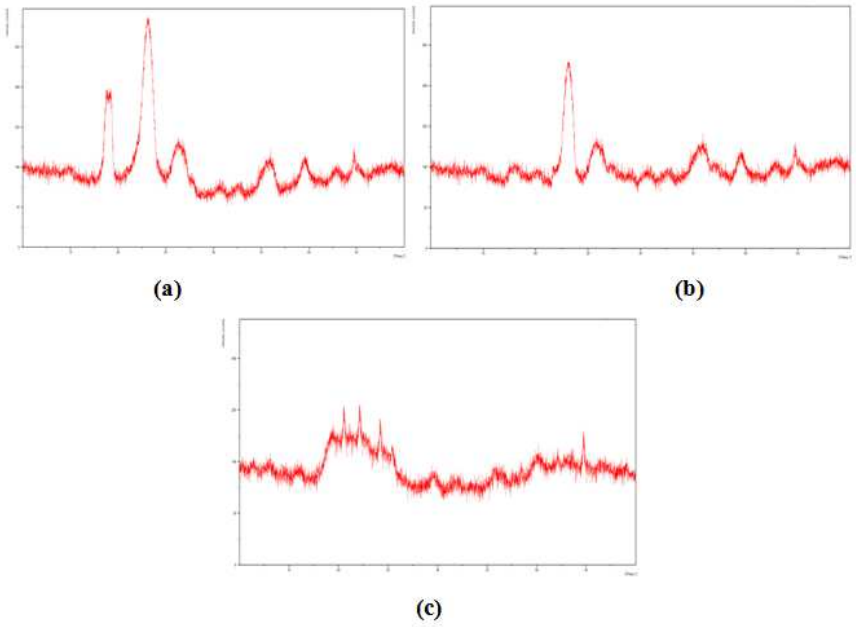

Fig. 4: **X-ray diffractograms of (a) Pseudoephedrine pure (b) loaded Pseudoephedrine hcl polymeric patches, and (c) Blank patch**

CONCLUSION

Pseudoephedrine transdermal patches were successfully formulated with a high *in vitro* release rate. Tween 20, Eucalyptus oil, castor oil and Thyme oil effectively enhanced of pseudoephedrine. Using Pseudoephedrine HCL type of transdermal patches is very useful for therapeutic purposes in the pharmaceutical industry. Further studies are necessary to evaluate the efficacy of the pseudoephedrine patches *in vivo*

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

We have no conflict of interest

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