WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 14, 561-574. Research Article ISSN 2277– 7105

PHYSIOCHEMICAL CHARACTERIZATION OF AN ANTI-INFLAMMATORY TRANSDERMAL PATCHES CONTAINING NOVEL POLYHERBAL FORMULATION ANPG

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Article Received on
25 August 2022,
Revised on 15 Sept. 2022,
Accepted on 05 October 2022
DOI: 10.20959/wjpr202214-25757

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ABSTRACT

A quite a large number of plant components have lipophilic properties, and many attempts have been made to overcome this. The administration of biologically active phytochemical compounds *via* the transdermal route is a possible solution to above mentioned problem. A transdermal patch is used to deliver medication through the skin. An adhesive patch containing medication is placed onto the skin, and a specified dose is then absorbed through the skin and into the bloodstream. Pharmaceutical scientists explore several strategies for the formation and stabilization of transdermal patches in modern medicines and they can be applied to polyherbal formulations too. In this paper, a matrix diffusion transdermal drug delivery system was designed and developed for extended delivery of Ayurgreen Natura Pain Gel ANPG polyherbal formulation using various combinations of polyvinyl pyrrolidine- K30 (PVP) and poly vinyl alcohol (PVA) and to their crosslinked form because of ease of fabrication. The ANPG matrix patches were tested for their physiochemical characterization by Fourier transform infrared spectroscopy (FTIR), UV-Vis spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The characterizations showed the homogeneous patches without the crystal form of the phytochemical constituents in matrix patches. The weight of transdermal patches of ANPG (2 cm^2; 0.4 g/patch) and was found to be 0.235+0.001 gm and its thickness was found to be satisfactory with high drug content.

KEYWORDS: *Transdermal Patch, Polyherbal formulation, Polymers, PVP-K30, PVA.*

1. INTRODUCTION

Traditional medicine is one of the centuries-old traditions that has been helping people fighting disease and live healthy lives for a very long time. It is difficult to give a single description to the wide variety of traditional medicine's traits and components, yet having one in place is essential. This leads to the conclusion that traditional medicines use a variety of health methods, methodologies, understandings, and beliefs, including medications derived from plants, animals, and minerals, spiritual therapies, manual methods, and exercises used singly or in combination to maintain health as well as treat, assess, or cure diseases. In traditional medicine, the use of herbal remedies for the treatment of ailments is often quite common. Herbal medicine has a number of active substances to treat a range of illnesses, but formulations must be made with the right understanding (Formulations, 2014).[1] Due to the presence of active phytochemicals, polyherbal formulations have great efficacy and may even have increased potency as a result of the synergistic interactions between the active components of several plants.[2–4] A novel anti-inflammatory polyherbal formulation named Ayurgreen Natura Pain Gel (ANPG) were reported by Zakariya et.al[2], which was prepared using specified plant parts of dried aloe vera and fresh aloe vera pulp, frankincense, myrrh, ferula asafetida with natural binders like magnesium silicate and a clay mineral. The phytochemistry of ANPG has been evaluated using a liquid chromatography-mass spectrometer and revealed the presence of 40 phytoconstituents contains a variety of chemical compounds including phenolics, flavanones, furans, gallotannin, glucoside, oligosaccharide, acids.[2]

These medications can be administrated through various routes and techniques including oral, inhalation, transdermal etc., Transdermal drug delivery system (TDDS) has been used for the drug administration *via* the skin for both local therapeutic effects as well as for systemic delivery. These include the ability to avoid issues with gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, and reduce the risk of systemic side effects by a minimum of 50%.[5] To administer a particular amount of medication *via* the skin and into the bloodstream, a transdermal patch is employed. Transdermal patches products were first approved in 1981 by FDA.[6] Scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular illness, fentanyl for chronic pain, and nicotine to help smokers quit are all now available in

transdermal administration systems.[6] Transdermal delivery allows for continuous infusion of medications with short biological half-lives, eliminates pulsed entrance into the systemic circulation, and enables regulated, consistent drug administration. On the other hand, certain transdermal drug delivery systems are made for percutaneous drug delivery, which does not use the skin as the target. In this situation, the medication has to penetrate the skin's dermis and epidermis, namely the stratum corneum barrier that contains sweat glands, sebaceous glands, and hair follicles and and pass into deeper dermal layers to reach the systemic blood circulation. Drug in matrix systems or drug in adhesive systems are two different types of delivery methods. The medication is bonded to an adhesive layer that comes in touch with the skin and is disseminated or dissolved in a polymer matrix. The polymer matrix may occasionally act as the adhering layer due to controlling drug release, delivering active pharmaceutical ingredients (APIs) site-specifically, and enhancing drug stability. A control of the rate of distribution is provided by polymer matrix layers and/or an additional adhesive layer.[7] Despite the usefulness of many of the polymers that are already on the market, there is a need for materials with enhanced properties and performance. The introduction and usage of novel polymers is severely constrained because to the substantial safety testing necessary for new excipient licencing. The limits of individual polymers can be solved by the blending of existing approved polymers, which is a beneficial option. When two or more polymers are combined, the features and functionality are enhanced, added to, or tailored. This can have a substantial positive impact on drug delivery applications.[8]

In this work, a matrix diffusion transdermal drug delivery system was designed and developed for extended delivery of ANPG polyherbal formulation using various combinations of polyvinyl pyrrolidine- K30 (PVP) and poly vinyl alcohol (PVA) because of ease of fabrication. The choice of polymers used to fabricate the polymer matrix for drug loading in the transdermal patch has a significant impact on swelling, elasticity, and mechanical properties, as well as skin permeation of the drug. According to earlier reports, poly(vinyl alcohol) (PVA) and poly (vinyl pyrrolidone) (PVP) may be readily cross-linked and mixed to create desired matrix with enhanced elasticity and flexibility due to the addition of cosolvent. Additionally, the interaction between the hydroxyl group of PVA and the carbonyl group of PVP will result in interchain hydrogen bonds, which strengthen the network stability. This network of polymers will incorporate the phytochemical constituents in the polyherbal formulation of ANPG.[9] As we now, ANPG polyherbal formulation is abundant with small and large phytochemicals with desired anti-inflammatory activities. The

ANPG matrix patches were tested for their physiochemical characterization by Fourier transform infrared spectroscopy (FTIR), UV-Vis spectroscopy and X-ray diffraction (XRD).

2. MATERIALS AND METHODS

2.1. Materials

The polyherbal formulation (Ayurgreen Natura Pain Gel-ANPG) was collected from the manufacturing unit of Ayurgreen Ayurveda hospital, Edappal, India. Polymers including poly(vinyl pyrrolidine)- K30 and poly(vinyl alcohol) were purchased from Sigma Aldrich with 99.9 % purity. All other chemicals and solvents used were of analytical grade.

2.2. Preparation of Ayurgreen Natura Pain Gel (ANPG)

A mixture of frankincense and dried aloe vera is boiled with juice of aloe vera to form a melt. All other ingredients including myrrh, magnesium silicate, ferula asafetida, fuller's earth and aloe vera were grinded to form fine powder and added to the melt while stirring to form a homogeneous mixture as shown in **Figure 1**. The stirring will be continued for 2 -3 days without having fermentation and contamination.

Fig. 1: Graphical representation of ingredients in the prepared polyherbal formulation of Ayurgreen Natura Pain Gel.

2.3. Preparation of ANPG extract

The extract of polyherbal formulation (Ayurgreen Natura Pain Gel) was prepared by standard solvent extraction procedure to attain the therapeutically desired portion and to eliminate the inert material. About 20 gm of ANPG was mixed with 200 ml ethanol and stirred using a magnetic stirrer for overnight without temperature. The extract was dried in a hot air oven as shown in **Figure 2**.

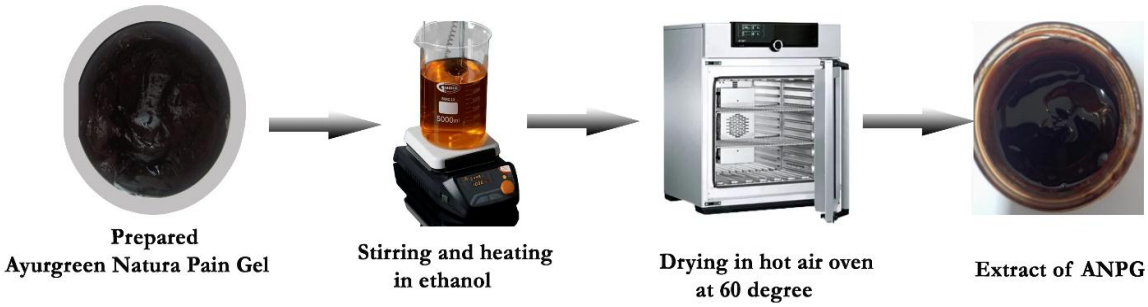

Fig. 2: The sketch of preparation of ethanol extract of ANPG polyherbal formulation.

2.4. Preparation of films with polymer blend and drug

The polymers like polyvinyl pyrrolidine- K30 (PVP) and poly vinyl alcohol (PVA) were used to make the polymer blend. The polymers were taken in 1:1 ratio and dissolved in water separately and stirred for 2 hrs using a magnetic stirrer. The different concentration of ANPG extract (0.1gm, 0.2gm, 0.3gm, and 0.4gm) was also dissolved in water and added to the polymer blend solution. Then the whole mix were stirred for another 3 hrs until a homogenous mixture was formed. The solution casting technique was employed to develop films with varying concentrations (0.1gm, 0.2gm, 0.3gm, and 0.4gm) of extract as depicted in **Figure 3**.

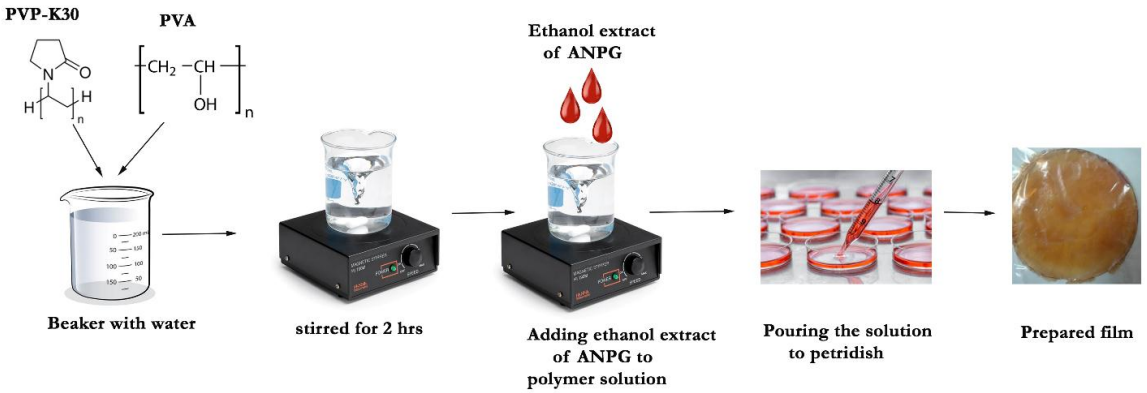

Fig. 3: The graphical representation of preparation of films with polymer blend and drug evaluation parameters of transdermal patches.

Weight Variation Test

An analytical weighing balance (Shimadzu) was used to determine the weight of each patch. The film's mean weight and departure from the mean were determined, and the data was recorded.

Folding Endurance

The folding endurance was measured manually for the prepared patches. The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gives the accurate value of folding endurance.

Thickness

The thickness of patches was determined using Screw Gauge (Lab world, Scientific Utilities). The mean thickness was measured at five different points of film.

Patch Test

In this, the tiny piece of the prepare films were plastered on the surface of the hand and the effects have been observed for irritancy and itchiness caused by formulation.

Stability Test

The prepare films were stored for some time under different temperatures (30^{o}C and 37^{o}C) and humidity conditions, and the change in the physical properties were observed.

Spectroscopic Characterization

Fourier Transform Infrared Spectroscopy

The attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectra of the prepared patches were recorded by JASCO spectrometer at room temperature in the range of 4000 to 500 cm^{-1}.[10–13]

UV-Visible Spectroscopy

The electronic spectrum of the prepared patches was recorded on a model JascoV-550 UV-Vis spectrometer at a wavelength ranging from 200 to 800 nm with films dimension approximately 1×1 cm^2.

XRD analysis

XRD patterns of the prepared patches were recorded using X-ray diffractometer (Rigaku powder diffractometer) with CuKα radiation (λ=1.5418 Å) in the Bragg angle (2θ) range from10 to 60°.

RESULT AND DISCUSSION

Transdermal patches of varying concentrations (0.1gm, 0.2gm, 0.3gm, and 0.4gm) of ANPG extract were prepared using PVP-K30 and PVA polymer blends as shown in **Figure 4**. The polymers were selected on the basis of their significant impact on swelling, elasticity, and mechanical properties, as well as skin permeation of the drug. It was already reported that PVP and PVA are easily blended and cross-linked by strong interaction between carbonyl group of PVP and hydroxyl group of PVA leading to the formation of interchain of hydrogen bonding and enhances the network stability. The polyherbal formulation extract will be loaded across this polymer network with enhanced elasticity and flexibility of film. Though PVA-PVP blend have improved water uptake capacity, possess high elasticity and soft consistency that led to enhanced mechanical strength.[9]

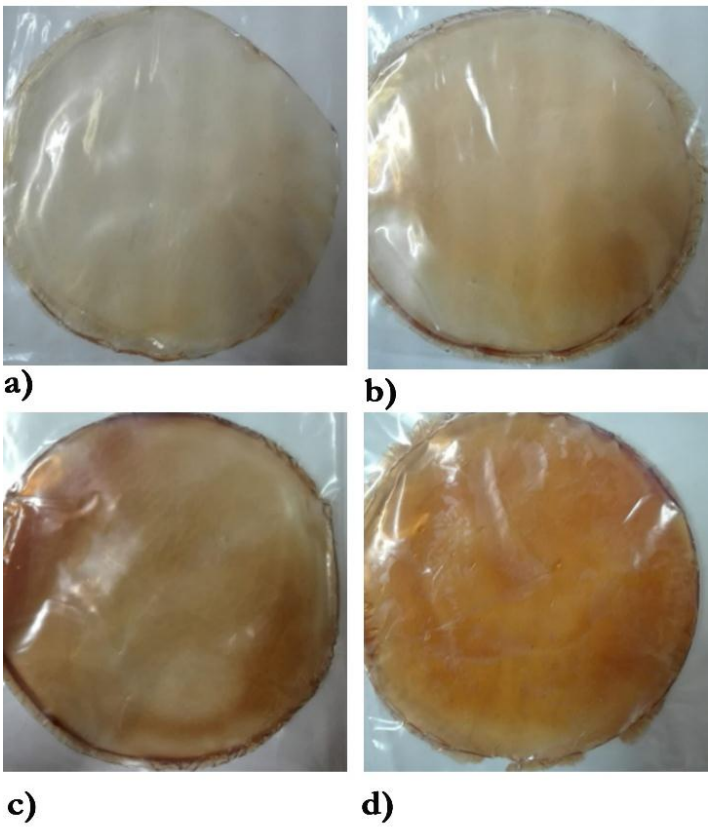

Fig. 4: Images of prepared films with varying concentrations (0.1gm, 0.2gm, 0.3gm, and 0.4gm) of ANPG extract.

Physicochemical Characterization

The physical characteristics of the films were evaluated by means of weight variation, folding endurance, thickness, drug content study, patch and stability analysis. All the parameters were tabulated in **Table 1** and found that all the parameters were within the limit.

Tab. 1: Physiochemical properties of transdermal patches of ANPG.

Parameters	**Transdermal patches of ANPG ($2\ cm^2$, 10 mg/patch)**			
	0.1 gm	**0.2 gm**	**0.3 gm**	**0.4 gm**
Weight variation test	0.173+0.001gm	0.249+0.001gm	0.215+0.001gm	0.235+0.001gm
Folding endurance	>50,000	>50,000	>50,000	>50,000
Thickness	0.1gm-0.44 mm	0.2gm- 0.43 mm	0.3gm- 0.39 mm	0.4gm-0.36 mm
Drug content	67%	78%	86%	97%
Patch Test				
Swelling	Nil	Nil	Nil	Nil
Redness	Nil	Nil	Nil	Nil
Irritation	Nil	Nil	Nil	Nil
Stability Test				
Change in Colour	Nil	Nil	Nil	Nil
Change in Odour	Nil	Nil	Nil	Nil
Change in Texture	Nil	Nil	Nil	Nil
Change in Smoothness	Nil	Nil	Nil	Nil

The films were evaluated for their physical characteristics, such as weight variation, folding endurance, thickness, drug content study, patch and stability analysis. The physicochemical properties viz. Weight variation test, folding endurance, thickness, and drug content of transdermal patches were palpable [Table 1].

FTIR Spectroscopy

From the FTIR spectra of all developed transdermal patches, it was clearly evident that there were no interactions of the extract of ANPG with the polymers. The spectra of ANPG and all developed films were depicted in **Figure 5** and their wave numbers corresponding to their characteristic peaks were tabulated in **Table 2**. The characteristic peaks in the spectrum of ethanol fraction of ANPG were retained in the all developed transdermal patches without showing any substantial difference when ANPG fraction was combined with polymers of PVP-K30, PVA and the blend of PVP-PVA.

Tab. 2: Harmonic vibrations of prepared transdermal patches with varying concentrations (0.1gm, 0.2gm, 0.3gm, and 0.4gm) of ANPG extract obtained from ATR-FTIR and their assignments.

Wavenumbers(cm^{-1})					Bond Assigned[14][15][16]	Functional groups
ANPG	PVP+PVA+ ANPG (0.1 gm)	PVP+PVA+ ANPG (0.2 gm)	PVP+PVA+ ANPG (0.3 gm)	PVP+PVA+ ANPG (0.4 gm)		
3391	3315	3264	3286	3317	O-H(v)	Polysaccharide
2927	2911	2932	2917	2940	C-H(S) O-H(S) CH_2(sv)	Carboxylic acid, alkane and aldehyde
			2350	2362		
1638	1642	1644	1649	1642	O-H(S) N-H(V) C=O(S)	Aromatic ring
1551						
	1430	1429	1429	1427	CH_2(b)	
1392						
1254	1281	1287	1287	1286	C-O-C(S) CH(deformation)	Alcohol and ether
1087	1082	1082	1075	1085	C-O(S), C-C	Carbohydrate, Alcohol
914	919	919	905	930	O-H(S) P-OR esters	Alcohol, ether
826	835	824	834	829	C-C-O C-O-C	
	727	727		735	C-C skeleton vibration	
624	622	629	657	647	C-H wagging vibration	

FT-IR spectrum of ANPG extract and ANPG polymer formulation were depicted in the figure2. The important peaks of ANPG were 3391 cm^{-1}, 2927 cm^{-1}, 1638 cm^{-1}, 1254 cm^{-1}, 1087 cm^{-1}, 914 cm^{-1}, 826 cm^{-1} and 624 cm^{-1}. Blending of ANPG extract with PVA-PVP blend resulted a shift in harmonic vibrations; O-H vibration from 3264 cm-1 to lower wavenumbers 3264 cm^{-1} - 3317cm^{-1} and C-H stretching vibrations shifted from 2927 cm^{-1} into 2911 cm^{-1} – 2940 cm^{-1}. Interestingly, two peaks were merged at 1551 cm^{-1} and 1392 cm^{-1}, this may indicate a functional group sharing of extract and polymers and a new peak were aroused at 1429cm^{-1} due to due to CH_2 bending. Regardless of this there were no new bands observed in drug polymer matrices, which confirms that no new chemical bonds were formed between extracts and polymers.

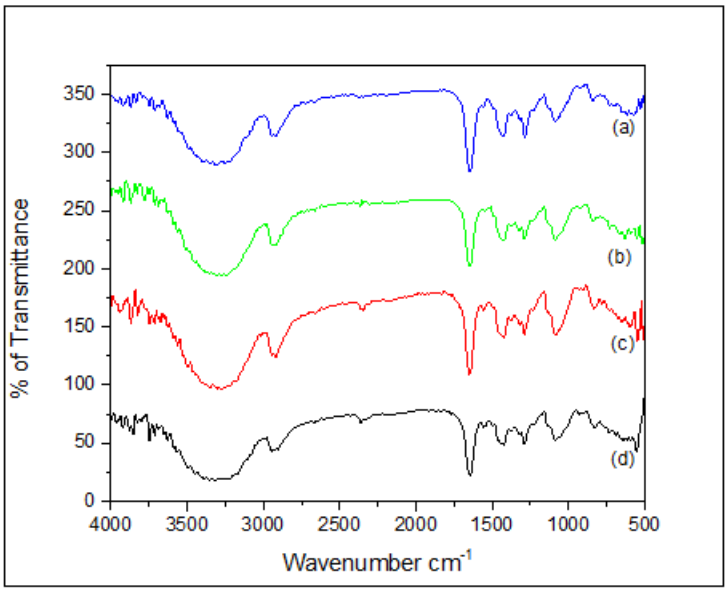

Fig. 5: FTIR spectra of a) PVA+PVP+0.1gm extract b) PVA+PVP+0.2gm extract c) PVA+PVP+0.3gm extract d) PVA+PVP+0.4gm extract.

UV-Visible Spectroscopy

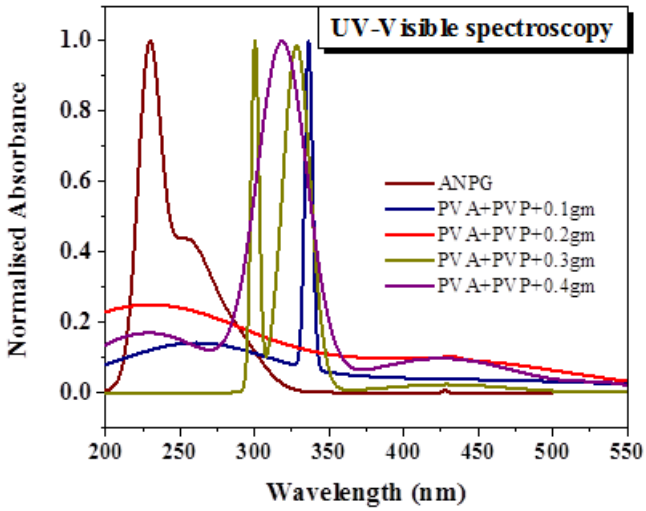

Fig. 6: UV- Visible spectra of a) PVA+PVP+0.1 gm extract b) PVA+PVP+0.2 gm extract c) PVA+PVP+0.3 gm extract d) PVA+PVP+0.4 gm extract.

The absorption spectra of various concentrations of (0.1, 0.2, 0.3 and 0.4) ANPG: PVA/PVP blend polymer films were shown in **Figure 6**. It was observed that maximum absorption peaks of ANPG were found in the region of 232 nm and 268 nm. The absorption at 232 nm may be ascribed to the primary oxidation products like conjugated dienes with Rich p orbitals primed for electronic transition in the formulation and 218nm may be due to double bonds C=C, C=O and N=N of the aromatic or unsaturated components of humic substances present

in the ANPG . Coming to the blend films, the empirical optical absorption edge at 218 nm in 0.1, 0.2 concentrations of ANPG is due to the semi crystalline nature of the polymers, which is well evidently confirmed from XRD. and also reported for pure PVA/PVP blend polymer by Salma et.al.[17] Interestingly, it was observed that the absorptions due to ANPG were unveiled on increasing concentration of the sample with a shift towards lower frequency side (higher wavelength). This shift of absorption peas towards 230nm to 350nm indicates less demand of energy for drug (active chemical compounds) release.

XRD

The **Figure 7** explains the XRD of pure PVA, pure PVP, PVA/PVP blend and PVA/PVP blend with ANPG in different concentrations. The diffraction pattern of PVA shows a diffraction peak at 19.4◦. This band can be apportioned to the partially crystalline nature of PVA polymer molecules. The pure PVP scan shows very broad diffraction peaks around 22◦ and 11◦ which confirm the amorphous nature of the prepared polymer film. For PVA/PVP blend the three peaks that were observed at 2θ = 20°, 23° and 42° which confirms the polymer blend formation and the intensity of the peaks decreased and became broader. This indicates that the addition of PVP to PVA increases its amorphous fraction and the PVA/PVP blend has semi-crystalline nature.

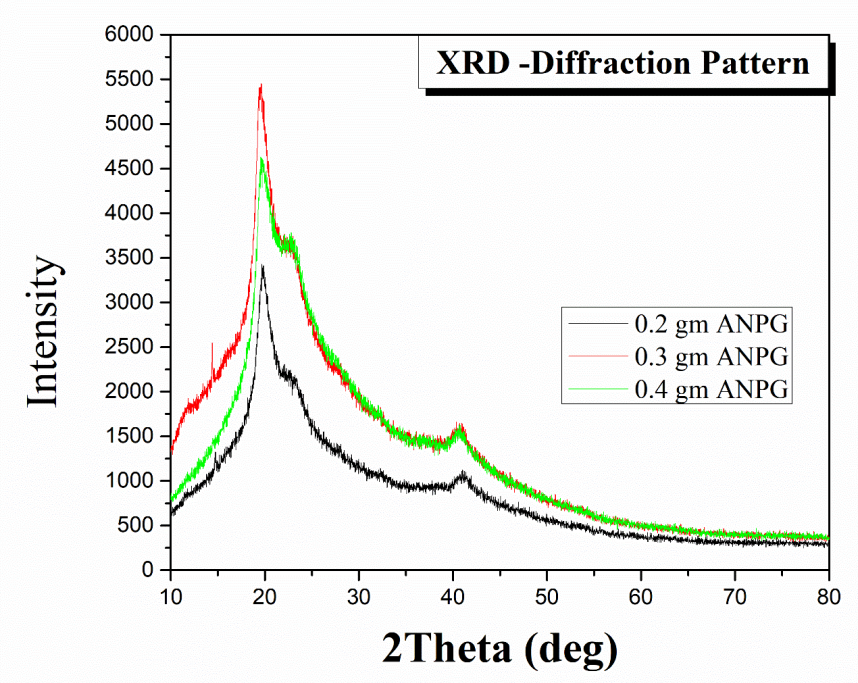

Fig. 7: UV- Visible spectra of a) PVA+PVP+0.1 gm extract b) PVA+PVP+0.2 gm extract c) PVA+PVP+0.3 gm extract d) PVA+PVP+0.4 gm extract.

Biochemical Evaluation

Anti-inflammatory

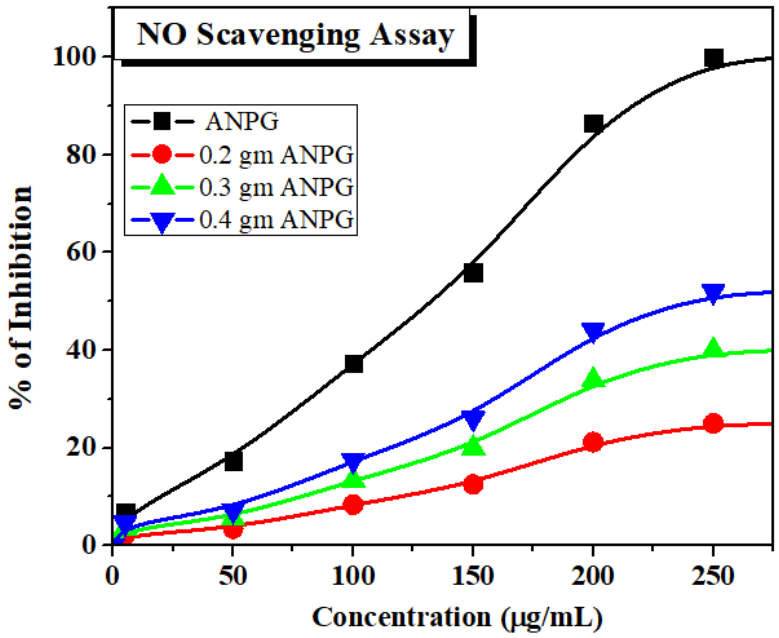

Fig. 8: NO scavenging assay of a) PVA+PVP+0.2 gm extract b) PVA+PVP+0.3 gm extract c) PVA+PVP+0.4 gm extract.

Nitric oxide is a free radical produced in mammalian cells, involved in the regulation of various physiological process including neurotransmission, vascular homeostasis, antimicrobial and antitumor activities. However, excess production of NO is associated with several diseases. It would be interesting to develop potent and selective inhibitors of NO for potential therapeutic use. The toxicity of NO increases greatly when it reacts with superoxide radical, forming the highly reactive peroxynitrite anion (ONOO-). The nitric oxide generated from sodium nitroprusside reacts with oxygen to form nitrite. The poly herbal extract inhibits nitrite formation by directly competing with oxygen.[13] The present study proved that the extract and its patches studied have a potent nitric oxide scavenging activity and the graph (Figure8) showed that the scavenging activity was linearly correlate with the concentration of poly herbal extract.

CONCLUSION

A transdermal drug delivery system was designed and developed for extended delivery of an anti-inflammatory polyherbal formulation Ayurgreen Natura Pain Gel ANPG using various combinations of two biocompatible polymers namely, polyvinyl pyrrolidine- K30 (PVP) and poly vinyl alcohol (PVA) and to their crosslinked form because of ease of fabrication. The

ANPG matrix patches were tested for their physiochemical characterization by Fourier transform infrared spectroscopy (FTIR), UV-Vis spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The characterizations showed the homogeneous patches without the crystal form of the phytochemical constituents in matrix patches. The weight of transdermal patches of ANPG (2 cm^2; 0.4 gm/patch) and was found to be 0.235+0.001 gm. and its thickness was found to be satisfactory with high drug content.

REFERENCES

1. S.P. Gupta, S.K. Jain, Development of matrix-membrane transdermal drug delivery system for Atenolol, Drug Deliv. J. Deliv. Target. Ther. Agents, 2004; 11: 281–286. https://doi.org/10.1080/10717540490493943.
2. S. Kannoth Nadat Pullayil House, H. M.V, J. Dev, J. T.V, H. NK, M.K. P.V, Chemical Profiling, Spectroscopic Characterization and Biological Evaluation of a Novel Polyherbal Formulation with Natural Binders -Ayurgreen Natura Pain Gel, SSRN Electron. J., 2022; 8: 72–84. https://doi.org/10.2139/ssrn.4139051.
3. Prashant Yadav, Mahour Kanhiya, Ashok Kumar, Standardisation and Evaluation of Herbal Drug Formulations, J. Adv. Lab. Res. Biol. 2014; 2: 1–7.
4. R. Petchi, C. Vijaya, S. Parasuraman, Antidiabetic activity of polyherbal formulation in streptozotocin- Nicotinamide induced diabetic wistar rats, J. Tradit. Complement. Med., 2014; 4: 108–117. https://doi.org/10.4103/2225-4110.126174.
5. P. Maji, A. Gandhi, S. Jana, N. Maji, Preparation and Characterization of Maleic Anhydride Cross-Linked Chitosan-Polyvinyl Alcohol Hydrogel Matrix Transdermal Patch, 2013; 22313788: 62–67.
6. S. Dhiman, T.G. Singh, A.K. Rehni, Transdermal patches: A recent approch to new drug delivery system, Int. J. Pharm. Pharm. Sci., 2011; 3: 26–34.
7. J. Suksaeree, L. Charoenchai, F. Madaka, ScienceDirect Zingiber cassumunar blended patches for skin application : Formulation, physicochemical properties, and in vitro studies, Asian J. Pharm. Sci., 2015; 10: 341–349. https://doi.org/10.1016/j.ajps.2015.03.001.
8. N.N. Nyamweya, Applications of polymer blends in drug delivery, Futur. J. Pharm. Sci., 2021; 7. https://doi.org/10.1186/s43094-020-00167-2.
9. C. Monton, W. Pichayakorn, J. Suksaeree, Design and optimization of process parameters of polyvinyl alcohol- graft -lactic acid fi lms for transdermal drug delivery, 2021; 93: 1–15. https://doi.org/10.1590/0001-3765202120210721.

10. K.P. Safna Hussan, T. Mohamed Shahin, T. V Jinitha, K. Jayant, Development of an ionogel membrane PVA /[EMIM] [SCN] with enhanced thermal stability and ionic conductivity for electrochemical application, J. Mol. Liq., 2019; 274: 402–413. https://doi.org/10.1016/j.molliq.2018.10.128.
11. K.P. Safna Hussan, T. Mohamed Shahin, S.K. Deshpande, T. V Jinitha, J. Kolte, Development of ion conducting ionic liquid-based gel polymer electrolyte membrane PMMA / BMPyr . TFSI - With improved electrical , optical , thermal and structural properties, Solid State Ionics, 2017; 310: 166–175. https://doi.org/10.1016/j.ssi.2017.08.012.
12. Safna Hussan K P, Mohamed Shahin Thayyil, Vijisha K Rajan, Anu Antony, The Interplay between Charge Transport and CO2 Capturing Mechanism in [EMIM][SCN] Ionic Liquid: A Broadband Dielectric Study, J. Phys. Chem. B., 2019; 123: 6618–6626. https://doi.org/10.1021/acs.jpcb.9b03929.
13. Safna Hussan K. P, M Shahin Thayyil, Deshpande S K, Jinitha TV, Vijisha K Rajan, K.L. Ngai, Synthesis and molecular dynamics of double active pharmaceutical ingredient-benzalkonium ibuprofenate, J. Mol. Liq., 2016; 223: 1333–1339. https://doi.org/10.1016/j.molliq.2016.09.054.
14. S.A. Soud, B.A. Hasoon, A.I. Abdulwahab, N.N. Hussein, R.K. Maeh, Synthesis and characterization of plant extracts loaded PVA / PVP blend films and evaluate their biological activities, 2020; 2931: 2921–2931.
15. P. Prabhakara, M. Koland, K. Vijaynarayana, N.M. Harish, G. Shankar, M.G. Ahmed, C.R. Narayana, D. Satyanarayana, Preparation and evaluation of transdermal patches of papaverine hydrochloride, Int. J. Res. Pharm. Sci., 2010; 1: 259–266.
16. N. Jaipakdee, T. Pongjanyakul, E. Limpongsa, Preparation and characterization of poly (vinyl alcohol)-poly (vinyl pyrrolidone) mucoadhesive buccal patches for delivery of lidocaine HCL, Int. J. Appl. Pharm., 2018; 10: 115–123. https://doi.org/10.22159/ijap.2018v10i1.23208.
17. C. Salma, B.H. Rudramadevi, Spectroscopic properties of Ho 3 + : PVA / PVP blend polymer films, 2020; 12: 35–44. https://doi.org/10.9790/4861-1206023544.