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FORMULATION AND EVALUATION OF MATRIX DIFFUSION CONTROLLED TRANSDERMAL DRUG DELIVERY OF HYDRALAZINE HYDROCHLORIDE FOR THE TREATMENT OF HYPERTENSION

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Keywords:

Hydralazine hydrochloride, TDDS, *In-vitro*, Ethylcellulose

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ABSTRACT: In the present study novel matrix diffusion controlled transdermal patches of Hydralazine hydrochloride, a hypertensive drug to ensure satisfactory drug release were successfully prepared by solvent casting method with optimization of suitable polymeric blend of Eudragit L100 (EL-100), ethyl cellulose (EC), polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), carbopol, hydroxypropyl cellulose (HPC) to achieve sustained release pattern within the therapeutic range. N-dibutyl phthalate (n-DB) used as a plasticizer and oleic acid used as a permeation enhancer. Different batches of transdermal patches were prepared by varying different polymers with the difference in ratio. Prepared transdermal patches from each batch, gave release profile for over 12 h. Fourier Transform Infrared analysis shows no interaction between drugs and polymers. Cumulative amount of drug release in 12 h from all the prepared formulation were found to be in following order: F1> F2> F3> F4> F9> F8> F7> F10> F5.F6. Combination of Eudragit L100 and PVP (F1 and F2) and Ethylcellulose and PVP (F3 and F4) exhibited good characteristics for sustained release action.

INTRODUCTION: Recently, the transdermal route has veid with oral treatment as the most successful innovative research area in drug delivery. The transdermal drug delivery has gained importance in recent years, as it has potential advantages of avoiding hepatic first-pass metabolism, maintaining constant blood levels for a longer period resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occurs due to local contact with gastric mucosa and improved patient compliance [1-5].

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The most exciting opportunities in polymer-based drug delivery in the arena of responsive delivery systems, with which it will be possible to deliver a drug in responses to a measured blood level or to deliver a drug precisely to a targeted site. It comprises a list of advantages over conventional routes such as: [6-9]

- Drug input can be stopped at any point after removal of the patch from the site,
- Increases compliance and reduce medical costs,
- Improves bioavailability,
- Suitable route for unconscious or vomiting patient.

Mortality from heart disease increases dramatically with age. Heart disease deaths that occur before the age of 65 are generally considered premature,

preventable deaths and are, therefore, of particular public health significance. Hypertension is one of the main causes of heart disease death rates have been increasing. Consequently, the prevention and treatment of hypertension is a major social significance.

Hydralazine hydrochloride is a drug candidate used to treat pulmonary arterial hypertension, and it acts as a vasodilator by relaxing smooth muscles of the pulmonary artery, and the treatment lasts for a long time. Extreme variability in oral dosing of HZH, the bioavailability of 31% and variable half-life of 3-7 h has made the dosage regimen complicated for oral usage. Low bioavailability, variable and short half-life may not be suitable to meet the therapeutic need for an alternative to an oral route where hepatic first-pass metabolism can be excluded and which can improve the therapeutic activity and quality of life of the patient [10-13].

MATERIALS AND METHODS:

Materials: Hydralazine hydrochloride was a gift sample received from D. K. Pharma Chem. Pvt. Ltd., Maharashtra. Dibutyl phthalate and oleic acid (Loba Chemie, Mumbai, India). All polymers were provided by Merck Specialties Pvt. Ltd., Mumbai. All the chemicals were used for analytical reagent grade.

Pre-formulation Studies: Pre-formulation studies such as physical appearance, solubility, melting point, drug excipient compatibility were performed to confirm the suitability and stability of drug and excipients for the formulation of transdermal patches.

Preparation of Transdermal Patches: Transdermal matrix patches of HZH were prepared by solvent casting technique. PVA transparent film as the backing membrane was prepared by pouring PVA (4%w/v) solution into Petri dish and drying in a hot air oven at 40 °C. Then the polymers, Eudragit L100, Sodium alginate, Ethylcellulose, PVP, carbopol, were taken in required quantity and dissolved in 20 ml of solvent. Then drug HZH were added in the polymeric dispersion then PEG400 (plasticizer) and oleic acid (permeation enhancer) were added into it. Then above mixture was poured in Petri dish. The rate of evaporation was controlled by inverting a funnel over the Petri dish for 48 h after drying patches were taken out of the Petri dish, wrapped with aluminum foil and stored separately in desiccators at room temperature for further analysis.

Evaluations of Patches:

Physical Examination of Patches: All the formulated patches of Hydralazine hydrochloride were evaluated visually for appearance in terms of surface smoothness, brittleness, transparency, flexibility.

Thickness: The thickness of the patches was measured by digital vernier calipers with least count 0.001 mm. The thickness uniformity was measured at five different sites, and an average of five readings was taken with standard deviation.

Drug Content and Content Uniformity: A specified area of patch is to be dissolved in 5ml of dichloromethane, and the volume was made up to 10 ml with phosphate buffer pH 7.4, dichloromethane was evaporated. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45 um membrane, diluted suitably, and absorbance was read at 260 nm in a double beam UV is a spectrometer.

Weight Variation: Weight variation was tested by selecting three patches randomly out of each formulation, and weight uniformity of dried and cut patches was checked on digital weight balance. The average weight of three patches of 1.5cm square from each formulation provided information regarding weight variation among different formulations.

Drug Excipients Compatibility Study: The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc pellet method was employed instrument used was Shimadzu FTIR 8400 spectrophotometer. In this study, potassium bromide disc method was employed. IR studies of pure drug and physical mixture were done. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into the transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using a sample holder, and the spectrum was recorded.

TABLE 1: COMPOSITION OF HYDRALAZINE HYDROCHLORIDE TRANSDERMAL PATCHES

Formulation code	Ingredients									
	HZH	Eudragit RL 100	Ethylcellulose	Sodium alginate	Carbopol	HPC	PVA	PVP	Dibutyl phthalate	Oleic acid
	(Mg)								(ml)	
F1(9:1)	100	90	-	-	-	-	-	10	0.5	0.2
F1(8:2)	100	80	-	-	-	-	-	20	0.5	0.2
F3(9:1)	100	-	90	-	-	-	-	10	0.5	0.2
F4(8:1)	100	-	80	-	-	-	-	20	0.5	0.2
F5(9:1)	100	-	-	90	-	-	-	10	0.5	0.2
F6(8.2)	100	-	-	80	-	-	-	20	0.5	0.2
F7(9:1)	100	-	-	-	90	-	-	10	0.5	0.2
F8(8:2)	100	-	-	-	80	-	-	20	0.5	0.2
F9(9:1)	100	-	-	-	-	90	-	10	0.5	0.2
F10(8:2)	100	-	-	-	-	80	-	20	0.5	0.2
F11(9:1)	100	-	-	-	-	-	90	10	0.5	0.2
F12(8:2)	100	-	-	-	-	-	80	20	0.5	0.2

Folding Endurance: The folding endurance of patches was evaluated by folding repeatedly polymeric patches 2×2 at the same point until it broke. The 2×2 cm of the patch was taken from the center as well as from the edge of the patch. The test was conducted on three randomly selected patches from each formulation.

Percentage Moisture Content: The percentage of moisture content was determined for each formulation. Patches of 1×1 cm were taken from each patch. These patches were weighed individually using a digital weight balance. These polymeric patches were then placed in labeled Petri dishes and stored in a desiccator containing silica beads at 25 °C. The films were weighed for 5 days or until the invariable weight was achieved. Then calculated by using the following formula.

Percentage moisture content = Initial weight – Final weight/ Final weight

Percentage Moisture Uptake: The percentage of moisture uptake was determined for each formulation. Transdermal patches of 1 × 1 cm were cut from each patch. Patches were weighed individually by using a digital weighing balance. These patches were then placed in labeled Petri dishes and stored at 25 °C in a desiccator containing 200 ml saturated solution of potassium chloride for 84% relative humidity (RH). The patches were continuously weighed for 5 days of storage or until a constant weight was achieved. The calculated by using the following formula:

Percentage moisture uptake = Final weight – Initial weight / Final weight

***In-vitro* Skin Permeation Studies:** *In-vitro* drug release studies were performed by a Franz diffusion cell with a receptor compartment capacity of 7 ml. cellophane membrane having pore size 0.45 µm and dialysis membrane having pore size 2.4 nm was employed for the determination of drug from plain HZH transdermal patches. The receptor compartment of the diffusion cell wall filled with saline phosphate buffer pH 7.4.

The whole assembly was fixed on the three stations in the receptor compartment was constantly and continuously stirred at 1000 rpm using magnetic beads, and the temperature was maintained at 37 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically.

RESULTS AND DISCUSSION: Transdermal patches of Hydralazine hydrochloride were prepared by solvent casting method. The different formulation containing Hydralazine hydrochloride were prepared to achieve the sustain release pattern within the therapeutic range.

Pre-formulation Studies:

Description: HZH is a white odorless crystalline powder.

Melting Point:

TABLE 2: MELTING POINT OF HYDRALAZINE HYDROCHLORIDE

Drug	Melting point	Normal range
Hydralazine hydrochloride	172 ± 0.145	172-173^{o}C

Solubility:

TABLE 3: SOLUBILITY PROFILE OF HYDRALAZINE HYDROCHLORIDE

S. no.	Solvent	Solubility
1	Water	Soluble
2	Ethanol	Slightly soluble
3	Methanol	Slightly soluble
4	pH 7.4 phosphate buffer	Soluble
5	Ether	Insoluble
6	Chloroform	Insoluble

Observation: The sharp peak observed at 260 nm, the further measurement was taken at 260 nm.

TABLE 4: ABSORPTION MAXIMA OF HYDRALAZINE HYDROCHLORIDE IN PHOSPHATE BUFFER 7.4

S. no.	Concentration (ug/ml)	Absorbance
1	0	0.000A
2	0.5	0.224A
3	1.0	0.422A
4	1.5	0.581A
6	2.0	0.834A
7	2.5	0.978A

Standard Curve for Hydralazine Hydrochloride: The standard plot has good regression coefficient and it shows the linearity.

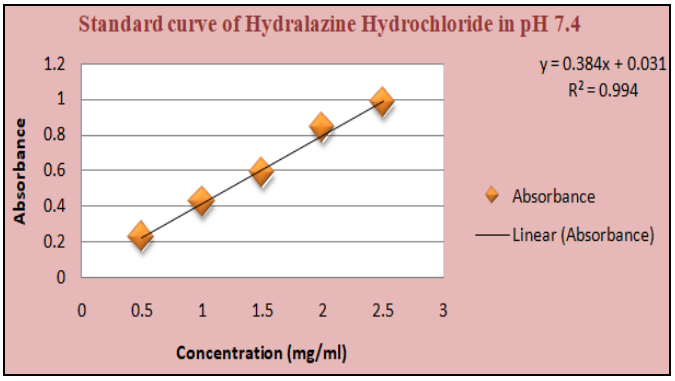

FIG. 1: STANDARD PLOT OF HYDRALAZINE HYDROCHLORIDE

Drug Excipients Compatibility Study: Drug-polymer compatibility was checked by comparing the IR spectra of formulations with that of the pure drug. No significant changes in the functional groups between the two spectra were observed. This ensured the compatibility of the polymer with the drug.

Transparency: Transdermal patches from Eudragit-PVP and ethyl cellulose- PVP had maximum transparency.

Physicochemical Evaluation of Transdermal Patches: The results of the physicochemical evaluation of transdermal patches are described in **Table 5** and **6**. The weight variation of all the formulation varied in between 0.592 ± 0.028 and 0.566 ± 0.001. The variation in the thickness of all the formulation was range in between 0.5634 to 0.6002. The moisture content of these patches was found to vary from 3.31 ± 0.18 to 5.14 ± 0.03. Moisture uptake of these patches was found in between 10.12 ± 0.006 to 2.64 ± 0.002. Folding endurance was found to be in between 8-5. The % elongation break test was found to be from 40.2 ± 0.012 to 34.09 ± 0.14. Folding endurance and % elongation break were found maximum in a formulation containing Ethylcellulose –PVP and Eudragit L 10- PVP. The % drug content and % *in-vitro* cumulative drug release were found maximum in formulation F1-F4, F7, F8.

***In-vitro* Drug Diffusion Studies:** *In-vitro* drug release studies for all the prepared patches were carried out for 24 hours. % cumulative drug release after 24 h were taken and compared for all the prepared patches. F1, F2, F3, F4 exhibited maximum drug release at the end of 24 h.

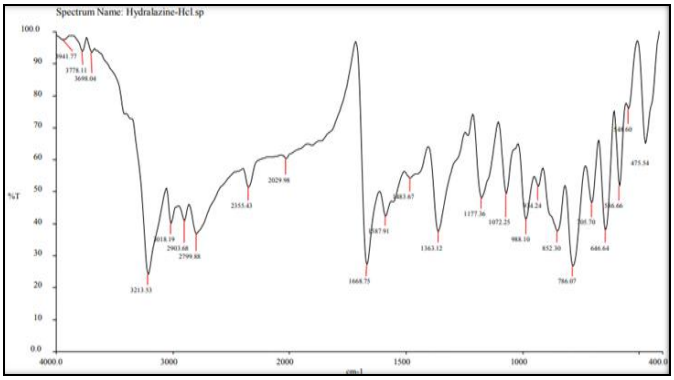

FIG. 2: FTIR SPECTRUM OF HYDRALAZINE HYDROCHLORIDE

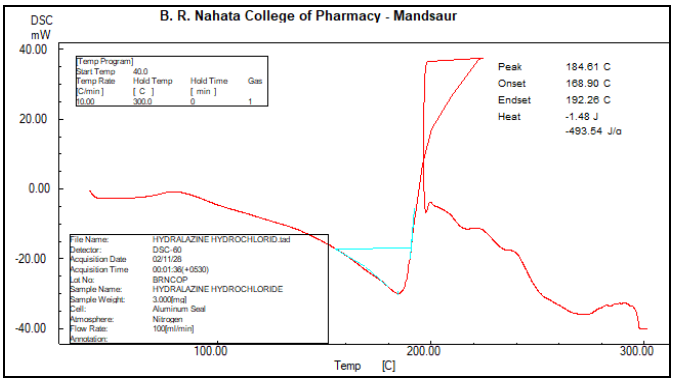

FIG. 3: DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS OF PURE DRUG (HYDRALAZINE HYDROCHLORIDE

TABLE 5: PHYSIOCHEMICAL EVALUATION OF THE PREPARED TRANSDERMAL PATCHES

Batch code	Parameters				
	Physical appearance			Thickness (Mean (mm) ± SD)	Weight variation (Mean (mg) ± SD)
F1	Transparent	Smooth	Flexible	0.15 ± 0.021	10.40 ± 0.37
F2	Transparent	Smooth	Flexible	0.14 ± 0.029	11.12 ± 0.38
F3	Transparent	Smooth	Flexible	0.20 ± 0.031	10.23 ± 0.35
F4	Transparent	Smooth	Flexible	0.17 ± 0.020	11.20 ± 0.39
F5	Transparent	Smooth	Flexible	0.15 ± 0.015	10.73 ± 0.47
F6	Transparent	Smooth	Flexible	0.19 ± 0.018	10.97 ± 0.38
F7	Translucent	Smooth	Flexible	0.16 ± 0.040	11.21 ± 0.38
F8	Translucent	Smooth	Flexible	0.18 ± 0.025	10.87 ± 0.38
F9	Translucent	Smooth	Flexible	0.15 ± 0.013	11.52 ± 0.40
F10	Translucent	Smooth	Flexible	0.19 ± 0.025	10.67 ± 0.42
F11	Transparent	Smooth	Flexible	0.20 ± 0.023	11.24 ± 0.43
F12	Transparent	Smooth	Flexible	0.18 ± 0.019	11.45 ± 0.49

TABLE 6: PHYSIOCHEMICAL EVALUATION OF THE PREPARED TRANSDERMAL PATCHES

Batch code	Parameters					
	% Moisture content ± SD	% Moisture uptake ± SD	% Drug content ± SD	% Elongation break test	Folding Endurance (No. of folds) ± SD	% Drug diffusion in 24 h
F1	3.31 ± 0.18	10.12 ± 0.006	98.01 ± 0.0432	18.01 ± 0.24	19 ± 1.0	87.77±0.38
F2	2.77 ± 0.16	9.88 ± 0.009	96.88 ± 0.0371	17.08 ± 0.26	16 ± 0.9	85.56±0.45
F3	2.59 ± 0.43	8.98 ± 0.013	98.12 ± 0.0083	17.10 ± 0.48	16 ± 1.0	80.80±0.86
F4	2.48 ± 0.90	8.17 ± 0.016	95.70 ± 0.0043	16.21 ± 0.41	16 ± 1.0	79.78±0.67
F5	2.43 ± 0.66	7.76 ± 0.035	93.83 ± 0.0332	15.26 ± 0.32	15±0.5	68.90±0.86
F6	2.09 ± 0.49	6.85 ± 0.048	96.82 ± 3.0043	14.22 ± 0.30	14±0.4	66.72±0.65
F7	8.75 ± 0.015	5.43 ± 0.01	97.12 ± 0.0064	17.12 ± 0.22	16±0.5	72.71±0.65
F8	7.55± 0.007	4.97 ± 0.004	90.55 ± 0.0045	14.88 ± 0.31	13±1.0	70.86±0.86
F9	7.09 ± 0.017	4.05 ± 0.001	92.64 ± 0.0075	15.23 ± 0.04	15±0.9	71.08±0.87
F10	6.63± 0.002	3.77 ± 0.009	88.54 ± 0.0022	13.21 ± 0.12	13±1.0	69.92±0.86
F11	5.88 ± 0.01	3.15 ± 0.001	86.23 ± 0.0032	16.21 ± 0.05	16±0.4	67.54±0.45
F12	5.14 ± 0.03	2.64 ± 0.002	89.79 ± 0.0029	15.21 ± 0.16	15±0.3	65.22±0.75

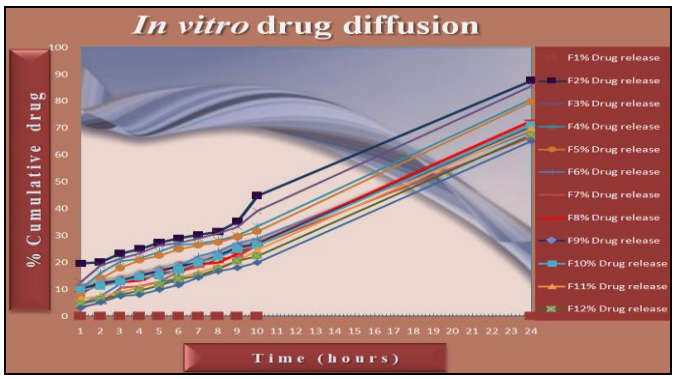

FIG. 4: *IN-VITRO* DRUG RELEASE PROFILE FOR BATCH F1-F12

CONCLUSION: It was concluded that the transdermal patches of HZH were successfully made by using the different concentration of polymers.

Combination of ethylcellulose- PVP and Eudragit L 100-PVP are useful in formulating sustained release matrix diffusion transdermal patches. Moreover, these patches (F1, F2, F3, F4) Exhibited better in vitro drug release time profile. Also amongst the plasticizer (n-Dibutyl phthalate) produced patches that exhibited high folding endurance and good manageable characteristics.

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CONFLICTS OF INTEREST: Nil

REFERENCES:

1. World Health Organization: "A global brief on hypertension" silent killer. Global public health crises 2013; 1-39.
2. Hanumanaik: Design, evaluation and recent trends in transdermal drug delivery system. International Journal of Pharmaceutical Sciences and Research; 2012; 2393-2406.
3. Cherukuri S and Batch R: Formulation and evaluation of transdermal patch of topiramate. International Journal of Pharmaceutical Investigation 2018; 10-17.

4. Gupta V and Ravi G: Development of matrix diffusion transdermal patch. Journal of Pharmacy Research 2017; II(6): 686-689.
5. Revathi S and Dhanaraju MD: Formulation of matrix diffusion controlled transdermal patch of zidovudine. Scholars Research Library 2016; 37- 42.
6. Ahad A and Aqil M: Transdermal delivery of angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and others for management of hypertension. Taylor & francis Informa Healthcare USA; 2016; 579-90.
7. Basavraj K and Nanjwade: Formulation and characterization of hydralazine hydrochloride biodegraded microspheres. Bioanalysis and Biomedicine 2011; 32-37.
8. Muthukumar S: Design and evaluation of hydralazine hydrochloride mouth dissolving tablet for the management of hypertension. International Journal Recent Science Research 2017; 1723-28.
9. Kumar M and Sunrendra R: Formulation and evaluation of hydralazine hydrochloride mouth dissolving tablet. International Journal of Pharmaceutical Sciences and Research 2018; 1068-76.
10. Baviskar D and Venkantesh B: Design and evaluation of patches for transdermal patches for transdermal delivery of losartan potassium. Journal of Pharmaceutical Science and Technology 2015; 126-34.
11. Korsmeyer RW, Gurny R and Doelker E: Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics 1983; 15(1): 25-35.
12. Coasta P, Manuel J and Labao S: Modelling and comparison of dissolution profiles. The European Journal of Pharmaceutical Sciences. 2002; 13: 123-33.
13. Siepmann J and Peppas NA: Modeling of drug release from delivery systems based on hydroxypropyl methyl-cellulose. Advanced Drug Delivery 1931; 23: 923-31.

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