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FORMULATION AND EVALUATION OF HYDRALAZINE HYDROCHLORIDE BUCCAL FILMS BY SOLVENT CASTING METHOD USING DIFFERENT POLYMERS FOR THE MANAGEMENT OF HYPERTENSION

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Keywords:

Buccal Films, Hydralazine Hydrochloride, HPMC, Sodium Alginate, Pectin, *In-vitro* release studies, Zero order release

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ABSTRACT: The main aim of the study was to formulate the buccal films of most satisfactory formulation by *in-vitro* evaluation. The present investigation was done to formulate Hydralazine hydrochloride with an objective to improve therapeutic efficacy, Patient compliance. Hydralazine hydrochloride buccal films were developed by solvent casting method. Formulation H_2, P_4, S_8, was best fitted to the *in-vitro* release studies and zero order release was observed.

INTRODUCTION: A fast-dissolving buccal film drug delivery system is a film containing active ingredient that fastly dissolves or fastly disintegrates in the saliva, within a few seconds without the need for water or chewing [1]. Fast dissolving films for oral administration was a novel approach, for the patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric and dysphasic patients associated with many medical conditions face a problem of difficulty in swallowing the solid dosage forms.

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One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets [2]. Oral fast-dissolving drug-delivery systems were developed in the late 1970's to overcome the problem of difficulty in swallowing solid dosage forms [3]. These systems consist of oral dispersible tablets (ODT) that disintegrate and dissolve quickly in the oral cavity. Oral strips and oral films which rapidly dissolves under the tongue or buccal cavity, could also improve the dissolution of poorly soluble drug. It gives the residence time of the dosage form at the site of absorption, hence increase the bioavailability. It gives ease of administration to paediatric, geriatric patients and also to the patients who are mentally retarded, disabled or non-cooperative [4].

Hydralazine hydrochloride is a medication used to treat high blood pressure and heart failure. This includes high blood pressure in pregnancy.

Hydralazine hydrochloride acts as a vasodilator. The drug undergoes extensive first - pass metabolism with a plasma half-life of 2 - 8 h. Hydralazine hydrochloride has low bio-availability of 50% and efficacy of protein binding is 90% [5].

In this current study, the films were prepared by solvent casting technique, using good bio adhesive polymers like HPMC (Hydroxy propyl methyl cellulose), Sodium Alginate, Pectin as major polymer were used for the studied. The *in-vitro* release studies and further physical characteristics of the films were evaluated. The selected formulations were kept for stability as per ICH guidelines.

MATERIALS AND METHODS: The materials used was Hydralazine hydrochloride (Octopus pharmaceuticals, Chennai), hydroxyl propyl methylcellulose (Hi Media Laboratories Limited, Mumbai.), Pectin (Hi Media Laboratories Limited, Mumbai), Sodium Alginate (Merck Limited, Mumbai), Dimethyl sulfoxide (Merck Limited, Mumbai), Glycerine (Microfine Chemicals, New Delhi), Sodium Lauryl Sulfate (Microfine Chemicals, New Delhi).

Preformulation Studies: Preformulation studies such as physical appearance, solubility, melting point, hygroscopicity and drug excipient compatibility were performed to confirm the suitability and stability of drug and excipient for the formulation of Buccal films [6, 7].

Preparation of Buccal Films: Nine batches of drug loaded buccal films were prepared using drug with different polymer (HPMC, pectin, sodium alginate) in different Drug: Polymer ratio (1:1, 1:3, and 1:5). Weighed quantity of polymer was dissolved in calculated quantity of water and heated on a water bath. Calculated amount of drug was added to the above mixture and stirred well until a homogenous mixture was formed. Then calculated amount of permeation enhancer and Glycerin were added.

The resultant mixture was poured into a petridish and air dried at room temperature for 24 h. The films were then peeled off from the petridish with the help of a knife and kept in desiccator. Formula shown below

Calculation:

Diameter of glass plate = X cm
Radius of glass plate = Y cm
Area of glass plate = πr^2 (π=3.14)
= 3.14 × (y)
= Z cm^2
Z/X= Area/diameter = capacity (ml)

Evaluation Parameters:

Physicochemical Evaluation of Hydralazine Hydrochloride in Buccal Films: [8]

Thickness of the film:

The thickness of the film was assessed by using digital verniercaliper at different points of the film. From each formulation three randomly selected films were used. The average value for thickness of a single film was determined. The result is shown in **Table 6**.

Folding Endurance: This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The result is shown in **Table 6**.

Percentage Moisture Content: The film was weighed and kept in desiccator containing calcium chloride. After 24 h the film were taken out and weighed. The percentage moisture content was calculated using the following formula. The result is shown in **Table 6**.

Percentage moisture content = (Initial weight - Final weight / Initial weight) × 100

Percentage Moisture Uptake: The film was weighed accurately and placed in desiccator containing aluminium chloride. After 24 h, the film was taken out and weighed. The percentage moisture uptake was calculated the difference between final and initial weight. With respect to initial weight. It is calculated by using following formula. The result is shown in **Table 6**.

Percentage moisture content = (Final weight - Initial weight / Initial weight) × 100

Determination of Surface pH: The films was allowed to swell by keeping them in contact with 1ml of distilled water for 2 h at room temperature and pH was noted down by bringing the electrode in contact with the surface of the film, allowing it

to equilibrate for 1 min. The result is shown in **Table 6**.

Tensile Strength: Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below. The result is shown in **Table 6**.

Percentage elongation = (Load at failure / Film thickness × Film width) × 100

Uniformity of Weight: This was done by weighing five different patches of individual batch taking the uniform size at random and calculating the average weight of three. The tests were performed on strip which was dried at 60 °C for 4 h prior to testing. The result is shown in **Table 6**.

Drug Content Determination: The film was taken and added to a beaker containing 100 ml of Phosphate buffer saline pH 6.8. The medium was stirred by magnetic bead for 60 min. The solution was later filtered and analyzed for drug content with proper dilution at 260 nm spectro-photometrically. The result is shown in **Table 6**.

Percentage Elongation: When stress is applied, a strip sample stretches, and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally, elongation of strip increases as the plasticizer content increases. It is calculated by using following formula. The result is shown in **Table 6**.

Percentage elongation = (Increase in length of strip / Initial length of strip) × 100

***In-vitro* Drug Release:** The *in-vitro* release rate of Hydralazine Hydrocloride buccal film were evaluated by open ended tube through using PBS pH 6.8 as diffusion medium up to 60 seconds studies. The cellophane membrane is tied in one end of the tube and then immersed in the receptor compartment containing 400ml of PBS pH 6.8 which was stirred at medium speed and maintained at 37°C ± 2°C. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh diffusion medium. The samples were analysed using UV - visible spectrophotometer (Shimadzu (DM) UV1700) set at 260 nm.

RESULTS AND DISCUSSIONS:

Preformulation Studies:

1. Description: White, Odourless, Crystalline powder

2. Melting Point:

TABLE 1: MELTING POINT OF HYDRALAZINE HYDROCHLORIDE

Drug	*Melting Poin(°C)	Normal Range (°C)
Hydralazine.HCl	172 ± 0.145	172-173

3. Solubility: The solubility of drug in various solvents was shown as follows,

TABLE 2: SOLUBILITY PROFILE OF HYDRALAZINE HYDROCHLORIDE

S. no.	Solvent	Solubility
1	Water	Soluble
2	Ethanol	Slightly soluble
3	Methanol	Slightly Soluble
4	pH 6.8 Phosphate buffer	Soluble
5	Ether	Insoluble
6	Chloroform	Insoluble

4. Hygroscopic Nature:

TABLE 3: HYGROSCOPIC NATURE OF HYDRALAZINE HYDROCHLORIDE

At Room Temperature	75% RH at 40 °C
Sample No-1 Weight gain observed-Nil	Sample No-2 Weight gain observed-Nil

Hydralazine Hydrochloride is non-hygroscopic in nature

Observation: The sharp peak observed at 260 nm, further measurements were taken at 260 nm.

TABLE 4: ABSORPTION MAXIMA OF HYDRALAZINE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 6.8

S.no.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.091
3	10	0.182
4	15	0.273
5	20	0.363
6	25	0.459

5. Identification of Drug Sample:

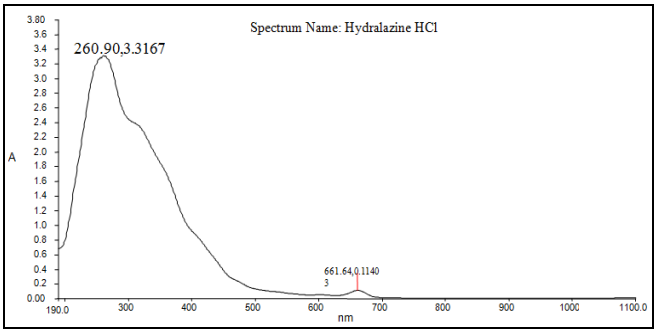

FIG. 1: UV SPECTRUM OF HYDRALAZINE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 6.8

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

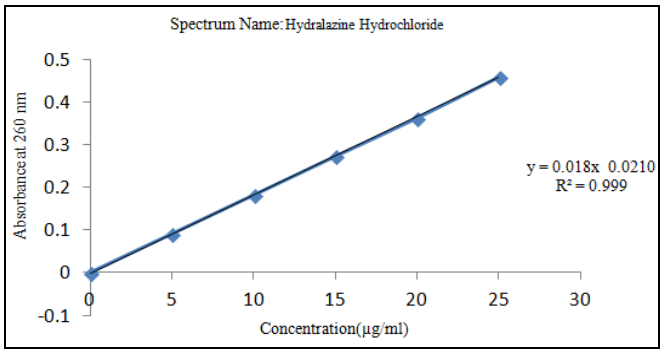

FIG. 2: STANDARD PLOT OF HYDRALAZINE HYDROCHLORIDE

6. Compatibility Study:

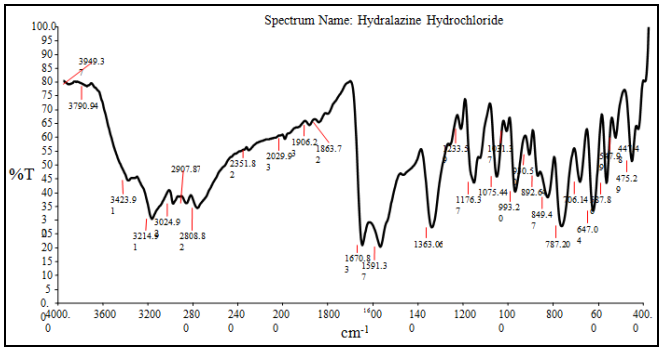

FIG. 3: FTIR SPECTRUM OF HYDRALAZINE HYDROCHLORIDE

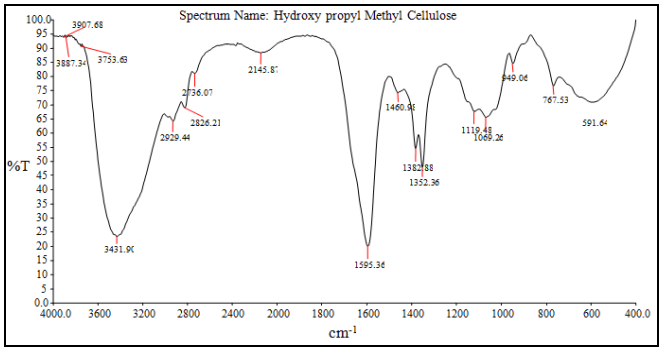

FIG. 4: FTIR SPECTRUM OF HYDROXY PROPYL METHYL CELLULOSE

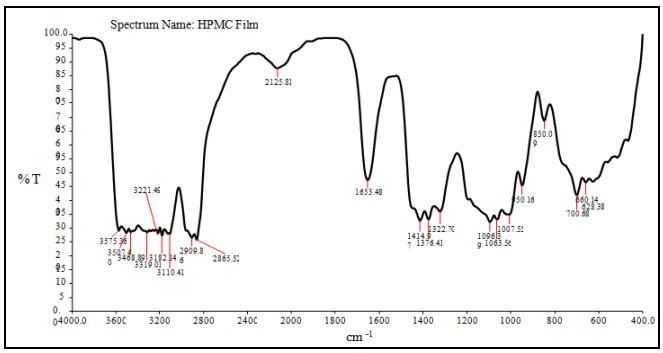

FIG. 5: FTIR SPECTRUM OF HPMC FILM

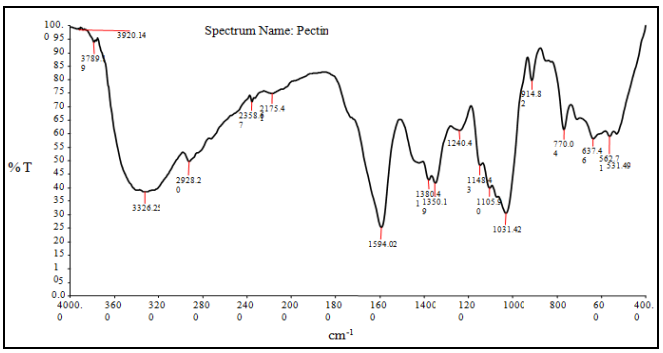

FIG. 6: FTIR SPECTRUM OF PECTIN

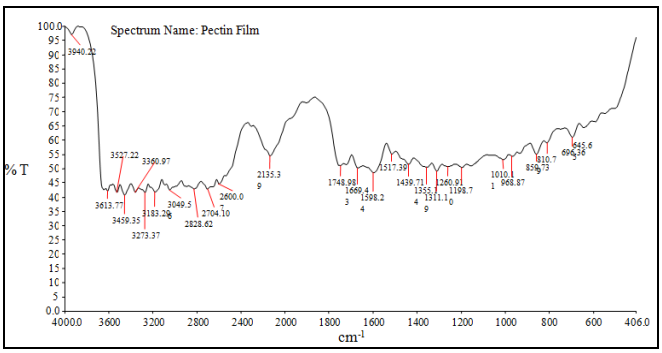

FIG. 7: FTIR SPECTRUM OF PECTIN FILM

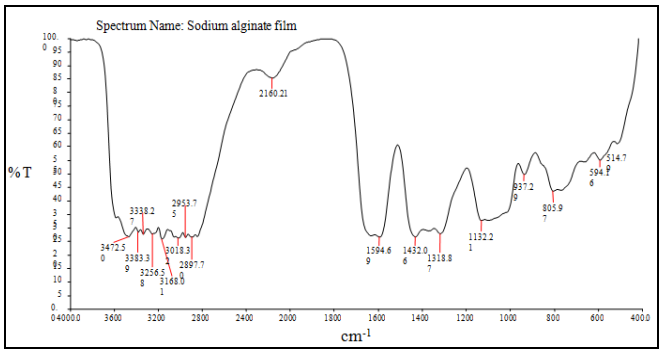

FIG. 8: FTIR SPECTRUM OF SODIUM ALGINATE FILM

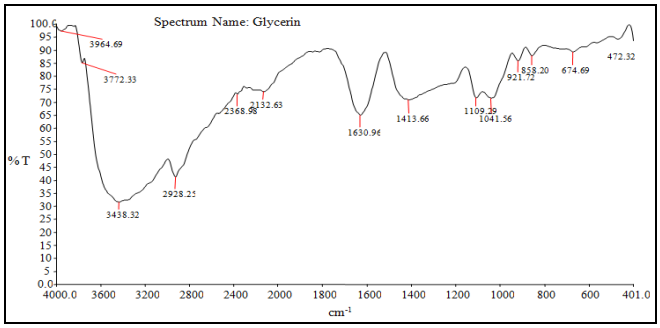

FIG. 9: FTIR SPECTRUM OF GLYCERIN

The FTIR graphs of drug, excipients and formulations showed **(Fig. 3, 4, 5, 6, 7, 8** and **9)** that there is no extra peak (or) broadening of peaks were observed and thus it indicates that there is no incompatibility between drug and excipients.

TABLE 5: FORMULA FOR HYDRALAZINE HYDROCHLORIDE BUCCAL FILMS BY SOLVENT CASTING METHOD

S. no.	Ingredients	HPMC(H)			Pectin(P)			Sodium alginate(S)		
		H1	H2	H3	P4	P5	P6	S7	S8	S9
1	Hydralazine Hydrochloride (mg)	50	50	50	50	50	50	50	50	50
2	Polymer (mg)	150	250	350	150	250	350	150	250	350
3	DMSO (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.7
4	Glycerin (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.3
5	Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation Parameters: The nine (H1, H2, H3, P4, P5, P6, S7, S8, S9) Batch of drug loaded buccal Films were Subjected to various physicochemical evaluations **Table 6**. Based on the Thickness, folding endurance, moisture content, moisture uptake, surface pH, tensile strength, Uniformity of Weight, Drug content and Elongation, the Formulation H2,P4, S8 were selected for further studies.

TABLE 6: PHYSICOCHEMICAL EVALUATION OF HYDRALAZINE HYDROCHLORIDE BUCCAL FILMS

Formulation Code		Thickness (mm)	Folding Endurance (no's)	Moisture Content (%)	Moisture Uptake (%)	Surface pH	Tensile Strength (Kg /mm^2)	Uniformity of weight (g)	Drug Content (%)	%Elongation (mm)
HPMC(H)	H1	0.16±0.52	260±0.06	0.572±0.60	2.06±0.54	6.4±0.05	3.410±0.05	0.23±0.73	94.47±0.05	66±0.52
	H2	0.25±0.47	270±0.57	1.925±0.4	2.14±0.08	7.2±0.10	5.400±0.65	0.37±0.1	98.82±0.65	85±0.43
	H3	0.28±0.61	240±0.82	1.624±0.05	1.97±1.03	6.2±0.72	6.461±0.83	0.41±0.45	95.70±0.68	78±1.21
Pectin(P)	P4	0.26±0.15	265±0.57	1.271±0.4	2.07±0.07	7.4±0.11	6.660±0.21	0.37±0.01	95.24±0.65	130±0.21
	P5	0.31±0.83	259±0.41	1.067±0.03	2.16±0.67	7.2±0.43	6.461±0.46	0.26±0.20	94.07±0.29	125±0.72
	P6	0.36±0.59	245±0.64	1.131±0.62	2.05±0.34	7.2±0.9	5.410±0.72	0.17±0.25	93.93±0.81	118±0.92
Sodium alginate(S)	S7	0.11±0.51	237±0.38	1.481±0.45	0.96±0.41	7±0.65	3.800±0.20	0.25±0.2	94.00±1.04	113±0.89
	S8	0.20±0.32	267±1.0	1.192±0.08	1.88±0.19	6.6±0.30	4.660±0.89	0.28±0.61	96.01±0.47	98±0.06
	S9	0.19.±0.45	245 0.92	1.193±0.01	1.89±0.02	6.6±0.27	6.410±1.63	0.31±1.26	97.76±0.70	86±0.79

Mean ± S. D: n = 3

TABLE 7: *IN-VITRO* DIFFUSION PROFILE

Time (sec)	% of Drug Diffused								
	HPMC			Pectin			Sodium alginate		
	H1	H2	H3	P4	P5	P6	S7	S8	S9
0	0	0	0	0	0	0	0	0	0
10	12.24±0.08	14.04±0.26	14.17±0.24	9.90±0.09	12.54±0.063	14.97±0.072	9.73±0.071	12.06±0.076	12.78±0.072
20	27.76±0.12	28.13±0.43	27.52±0.07	25.72±0.06	27.09±0.072	22.82±0.074	25.98±0.071	27.98±0.072	26.33±0.071
30	42.75±0.09	45.68±0.21	47.90±0.31	41.09±0.42	42.85±0.074	44.72±0.072	40.99±0.076	43.09±0.071	44.77±0.073
40	68.99±0.7	69.09±0.09	65.09±0.27	66.93±0.13	67.98±0.073	62.01±0.071	60.08±0.073	64.01±0.073	66.87±0.074
50	88.05±0.12	87.45±0.72	84.76±0.48	85.87±0.05	84.73±0.073	82.53±0.075	85.82±0.071	84.73±0.072	80.87±0.072
60	95.76±0.16	98.76±0.11	96.05±0.37	95.64±0.08	93.07±0.071	90.43±0.074	93.98±0.075	94.87± 0.073	91.98±0.072

Among the nine batches H2, P4 and S8 showed **Table 7** and **Fig. 10, 11, 12** and **13** maximum amount of drug release as 98.76%, 95.64% and 94.87% respectively at the end of 60 sec. So these three batches were selected for further studies.

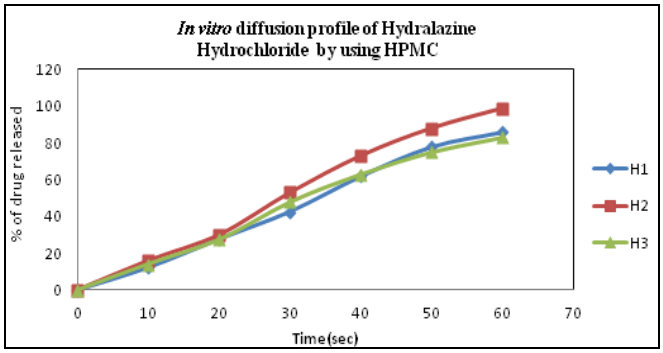

FIG. 10: *IN- VITRO* DIFFUSION PROFILE OF HYDRALAZINE HYDROCHLORIDE BY USING HPMC

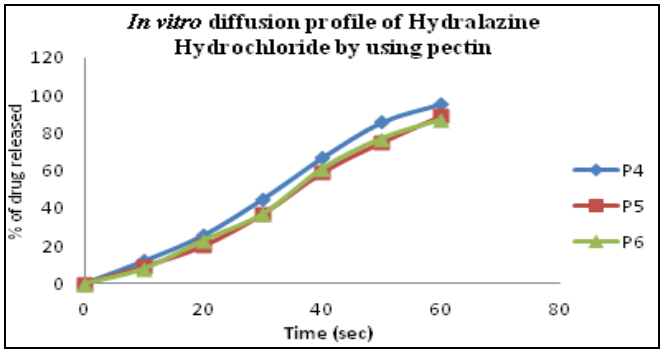

FIG. 11: *IN-VITRO* DIFFUSION PROFILE OF HYDRALAZINE HYDROCHLORIDE BY USING PECTIN

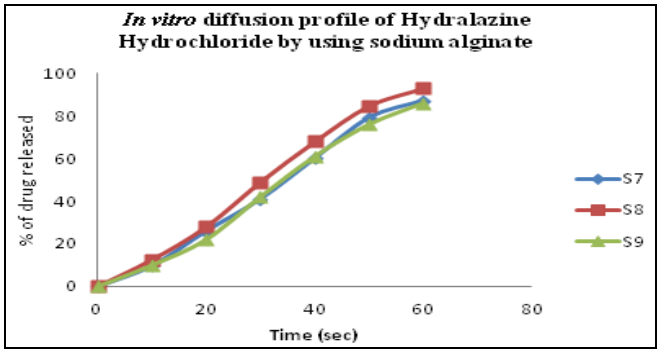

FIG. 12: *IN- VITRO* DIFFUSION PROFILE OF HYDRALAZINE HYDROCHLORIDE BY USING SODIUM ALGINATE

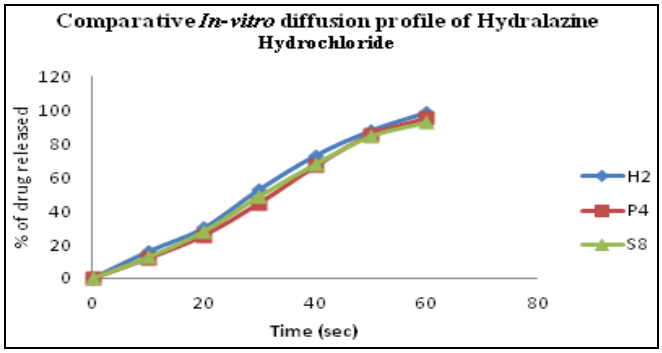

FIG. 13: COMPARATIVE *IN-VITRO* DIFFUSION PROFILE OF HYDRALAZINE HYDROCHLORIDE

CONCLUSION: From this study H2, P4 and S8 concluded as optimized and stable formulations from the results of physiochemical evaluation of Hydralazine hydrochloride buccal films with an effective percentage of drug release at 60 sec indicating faster and maximum absorption at the site of administration.

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CONFLICT OF INTEREST: The authors state that there is no conflict of interest in the present manuscript.

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