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DESIGN AND DEVELOPMENT OF ORODISPERSIBLE FILM OF MIDODRINE HYDROCHLORIDE

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Keywords:

Midodrine Hydrochloride, Orodispersible film, Solvent Casting Method, HPMC E15LV, PEG 400

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ABSTRACT: This work aimed to develop and evaluate fast dissolving strip of Midodrine hydrochloride to overcome the conventional dosage form's limitations and enhance dissolution rate, fast onset of action and improved patient compliance. Various batches of the mouth-dissolving film were prepared by using various grades of hydroxypropyl methylcellulose (HPMC) polymer and plasticizers such as Polyethylene Glycol 200, Polyethylene Glycol 400, Polyethylene Glycol 600 and Glycerin, used for the preparation of film by solvent casting method. The estimation was carried out using phosphate buffer pH 6.8 as a solvent using a double-beam spectrophotometer at 289nm. FTIR and DSC studies showed no interaction between drugs, polymers, or other additives. The prepared film was evaluated for transparency and surface texture, thickness, tensile strength, folding endurance, disintegration time, drug content, uniformity and *in-vitro* drug release study. Midodrine hydrochloride mouth dissolving film was prepared successfully by solvent casting method and that might be an alternative route of drug delivery system of conventional dosage forms with many advantages.

INTRODUCTION: The oral route is the most preferred route for drug delivery and has more advantages over the other route of drug administration. The oral drug delivery system is very advanced or novel because of some problems regarding to various class of patients which including geriatric, pediatric, and dysphasic patients associated with many medical conditions or problems as they have difficulty swallowing or chewing solid dosage forms. Even with the fast-dissolving tablets (FDT) there is a fear of choking due to the type of tablets appearance [1].

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ODFs are kind of formulations that are commonly prepared using Hydrophilic polymers that are rapidly dissolving with saliva. Typical ODFs are commonly equal to the size of a postage stamp. Oral disintegrating tablets (ODFs) and oral disintegrating films (ODFs) are typical examples of orally disintegrating drug delivery systems [2]. Orally fast dissolving drug delivery system was developed in late 1970 to serve several problems with swallowing conventional dosage forms for geriatrics and pediatrics patients.

Orodispersible films (ODFs) are the most advanced oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minutes in the oral cavity after contact with saliva without chewing, and no need for water for administration. It gives quick absorption and instant bioavailability of drugs due

to high blood flow and the permeability of oral mucosa is 4- 4000 times greater than skin's. ODFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active lifestyle. It is also useful whether local action is desired, such as local anesthetic for toothaches, oral ulcers, cold sores or teething [3]. The ODFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets/capsules. Oral thin-film technology is still in the beginning stages and has a bright future ahead because it fulfils all the needs of patients.

Eventually, film formulations having drug/s will be commercially launched using ODF technology [4]. The introduction of orally fast-dissolving films in market was accompanied by educating the mass about the proper way to administer the product, like "do not swallow" or "do not chew". ODFs dissolves in the mouth like cotton candy [5].

Some patients have difficulties swallowing or chewing solid dosage, which forms risk or fear of choking, so this is a major problem in using tablets. orodispersible film (ODF) is a new drug delivery system for oral drug delivery. Is a type of film used in acute conditions such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, asthma, *etc*. Orodispersible film has gained popularity due to its availability in various size and shape. orodispersible films are intended to disintegrate or dissolve within seconds [6, 7]. From the patient's point of view, ODF offers ease of administration and improved compliance. The manufacturing of this dosage form is cost-effective with affordable end-products. From a clinical aspect, the improved bioavailability can be advantageous in reducing the formulation dose. This would lead to a product with minimized side effects [8].

Ideal Characteristics of a Suitable Drug Candidate [9]:

- The drug should have a pleasant taste.
- The drug to be incorporated should have a low dose up to 40 mg.
- Drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water and saliva.
- It should be partially unionized at the pH of oral cavity.

Special Future of Oral Thin Film [10]:

- Thin elegant film.
- Available in various sizes and shapes.
- Unconstructive
- Fast disintegrating and rapid release

Formulation Consideration [8, 11]: A typical composition of the film is given in **Table 1.**

TABLE 1: A TYPICAL COMPOSITION OF FILM

Sr. no.	Ingredients	Amount (% w/w)
1	Drug (API)	1-30%
2	Water soluble polymers	40-50%
3	Plasticizer	0-20%
4	Surfactant	q.s.
5	Saliva stimulating agent	2-6%
6	Sweetening agent	3-6%
7	Flavoring agent	0-10%
8	Coloring agent	q.s.

MATERIALS AND METHODS: Midodrine Hydrochloride was obtained from Xylopia Labs., Ahmedabad, Gujarat, India. Various grades of HPMC were obtained from *Zydus cadila* Healthcare Ltd., Ahmedabad, Gujarat, India, Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600, Glycerine was obtained from Finar Chemicals Ltd., Ahmedabad, Gujarat, India was used as a film base material. Sodium saccharin, Mannitol, Dextrose were obtained from Yarrow Chem. Products, Mumbai, India as a sweetener. Citric acid, Tartaric acid, Malic acid got from Rudra International Co., Haryana, India as a Saliva stimulating agent. Poloxamer 188, Poloxamer 407, Spam 80 was obtained from Yarrow Chem. Products, Mumbai, India as a surfactant.

Drug Excipient Compatibility Study [12]:

FTIR Study: Drug-excipient interactions are vital in drug release from formulation. Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drugs and excipients. FTIR spectra of pure drug, polymer, and mixture of drug and polymer were recorded on FTIR instrument (FTIR 1700, Brukre, Kyoto, Japan).

Differential Scanning Calorimetry Study: The DSC study of Midodrine HCL was performed using DSC instrument (DSC TA-60, Shimadzu). The DSC study was conducted on the pure drug (Midodrine hydrochloride), HPMC E15LV, Poloxamer 407, and a drug mixture with excipients. Midodrine Hydrochloride, oral film thermogram, was obtained by Differential scanning calorimeter (DSC). A small amount was taken in an aluminium cell and scanned at 0-400^{0}C, at 100 ml/min nitrogen flow rate against a blank DSC aluminium cell as a reference.

Preparation of Stock Solution: Accurately weighed 100 mg of Midodrine Hydrochloride added into 100 ml volumetric flask and dissolved in water, 0.1 N HCL, and Phosphate Buffer pH 6.8. The volume was 100 ml with water, 0.1 N HCL and Phosphate Buffer pH 6.8 to get the final concentration of 1000 µg/ml.

Preparation of Calibration Curve: A Shimadzu UV/Vis double-beam spectrophotometer scanned the above stock solutions for maximum absorbance. The λmax for Midodrine Hydrochloride was found to be 289 nm in water, 0.1 N HCL and Phosphate Buffer pH 6.8.

The above stock solution (1000 µg/ml) was further diluted by withdrawing 10 ml of the above stock solution and diluted up to 100 ml with water, 0.1 N HCL, and Phosphate Buffer pH 6.8 to get the concentration of 100 µg/ml then further dilution was prepared by taking aliquots of 1 to 9 ml and diluted up to 10 ml with water, 0.1 N HCL and Phosphate Buffer pH 6.8 to get concentration range of 10-90 µg/ml.

Dose Calculation of Midodrine Hydrochloride: Oral dose of Midodrine hydrochloride is 2.5 mg. For the preparation of oral film, dose 2.5 mg was selected. The desired dimension of the film was 2cm × 2cm (4cm^2) and it should contain 2.5 mg of Midodrine hydrochloride, the area of the casting plate was 62.17 cm^2.

If 4 cm^2 area of the film should contain 2.5 mg of drug, then 62.172 cm^2 film area will contain 38.85 mg of the drug. Therefore, total amount of drug required to be added in the film-casting solution is 38.85 mg. The prepared film was separated from plate and cut in to 2cm × 2cm (4cm^2) which contain required quantity of drug 2.5 mg.

According to surface area of petriplate, Midodrine Hydrochloride dose is calculated.

$$A = \pi r^2$$

Where, A = Surface Area of Petriplate, r = Radius of Petriplate

$$A = 3.14 \times (4.45)^2 = 62.172 \text{ cm}^2$$

Film Area = 4 cm^2, If 4 cm^2 of film area contain = 2.5 mg of Midodrine Hydrochloride 62.172 cm^2 of film area contain = 38.85 mg of Midodrine Hydrochloride, So, total amount of Midodrine Hydrochloride required to be added in film casting solution is 38.85 mg.

Preparation of Film: Accurately weighed polymer was dissolved in 6 ml water. Then accurately, weighed drug and other excipients were dissolved in 4 ml water. Mix both prepared solutions and stir them; then add the required quantity of plasticizer in the above-prepared solution, sonicate it for half an hour, then cast the solution in a lubricated petriplate and dry it at room temperature for 24 hours. Cut the dry film in desired size and shape and store in aluminum foil. The prepared optimized formula is shown in **Table 2.**

Preliminary Trials:

Selection of Polymer: Various polymers were selected, and trails were done. HPMC E15LV was observed with the best transparency, smooth surface texture, moderate tensile strength, low brittleness and less disintegration time. HPMC E15LV was selected as a film-forming polymer.

Selection of Plasticizer: Various plasticizers were selected, and trials were done. PEG 400 observed smooth surface texture, very low brittleness, good folding endurance and moderate tensile strength. PEG 400 was selected as a plasticizer.

Selection of Sweetener: Various sweeteners were selected, and trials were done. Sodium saccharin has shown the best appearance, smooth surface texture, and sweet taste. Sodium saccharin was selected as a sweetener.

Selection of Saliva Stimulating Agent: Various saliva-stimulating agents were selected and trials were done. Tartaric acid had shown good required properties. Tartaric acid was selected as a saliva-stimulating agent.

Selection of Surfactant: Various surfactants were selected, and trials were done. Poloxamer 407 had given best folding endurance, brittleness, surface texture, and transparency. Poloxamer 407 was selected as a surfactant. On the basis of preliminary trials, the optimized formulation has been finalized, shown in **Table 2.**

TABLE 2: OPTIMIZED FORMULA

Ingredients	(Quantity in mg/62.17cm^2)
Midodrine Hydrochloride*	38.85
HPMC E15LV*	360
PEG 400 (ml)	2
Sodium saccharin*	30
Tartaric acid*	100
Poloxamer 407*	10
Water (ml)	10

*****Indicates weight in mg

Evaluation of Film [13-16]:

Folding Endurance: Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Thickness: The thickness of the film can be measured by a micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film

Tensile Strength: The film's tensile strength was evaluated using the tensilometer (Erection and Instrumentation, Ahmedabad). It consists of two load cell grips. The lower one is fixed and upper one is movable.

Film with dimensions of 2×2 cm^2 was fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

Percent Elongation: The percentage elongation break was determined by noting the length just before the break point, the percentage elongation was determined from the below-mentioned formula.

$$\text{Elongation \%} = [(L_1-L_2)/L_2] \times 100$$

Where, L_1 is the final length of each film and L_2 is the initial length of each film.

Disintegration Time: The six films of 2×2 cm^2 put in the disintegration tester (USP) ED-2L at room temperature in tubes in the water environment until they disintegrated, and that time was measured.

Assay/Drug Content and Content Uniformity: A specified area of film (2cm×2cm) was dissolved in 100ml Phosphate buffer pH 6.8 in a volumetric flask and shaken continuously for 10 min.

After filtration, 1 ml was withdrawn from the solution and diluted to 10 ml with Phosphate buffer pH 6.8. The absorbance of the solution was taken at 289nm and concentration was calculated and determined the drug content.

***In-vitro* Drug Release Study:** The *in-vitro* dissolution study of Midodrine Hydrochloride film was performed using USP apparatus (model TDT-08T, Electrolab, Mumbai, India) fitted with paddle (100 rpm) at 37 ± 0.5°C. Dissolution media was 250ml of Phosphate Buffer pH 6.8 used.

At the predetermined time intervals, 10 ml samples were withdrawn, filtered through a 0.45µm membrane filter, diluted with the dissolution media and accessed at 289 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan).

A 10 ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal. The cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

RESULTS AND DISCUSSION:

Drug Excipient Compatibility Study:

FTIR Study for Compatibility: Fourier transforms infrared (FTIR) technique was used to study the physical and chemical interaction between drugs and excipients. FTIR spectra of pure drug and a mixture of drug and polymer were recorded on FTIR instrument at our institute (FTIR 1700, Brukre, Kyoto, Japan). IR study shows that the drug and polymer were compatible with each other. Results of FTIR study are shown in **Table 3,** and spectra are depicted in **Fig. 1** & **2.**

TABLE 3: RESULTS OF FTIR STUDY

Vibrations	Range (cm^{-1})	Midodrine HCL (cm^{-1})	Midodrine HCL and Excipients (cm^{-1})	Inference
N - H	3400 - 3300	3327.13	3326.96	No change
C – O	1275 - 1200	1267.12	1265.34	No change

Differential Scanning Calorimetry Study: The DSC thermogram of Midodrine Hydrochloride and mixture of Midodrine Hydrochloride with excipients are shown in **Fig. 3-4**. The thermogram of pure Midodrine Hydrochloride and mixture of Midodrine Hydrochloride with excipients shows melting endotherm at 221.17°C and 211.11°C respectively. DSC study indicates no significant changes in the melting endoderm of Midodrine Hydrochloride.

Spectrophotometric Method for Estimation of Midodrine Hydrochloride: The data of standard plot of Midodrine Hydrochloride in Water, 0.1 N HCL and pH 6.8 phosphate buffer are shown in table 4, 5 and 6, respectively. The calibration curve of Midodrine Hydrochloride in Water, 0.1 N HCL and pH 6.8 phosphate buffer are shown in **Fig. 5, 6** and **7,** respectively.

TABLE 4: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN WATER

Sr. no.	Concentration µg/ml	Absorbance			Avg. Absorbance ± SD
		I	II	III	
1	10	0.088	0.086	0.091	0.0883 ± 0.002
2	20	0.180	0.175	0.181	0.1787± 0.003
3	30	0.275	0.270	0.273	0.2703±0.002
4	40	0.365	0.365	0.364	0.3647±0.001
5	50	0.445	0.441	0.449	0.4477±0.004
6	60	0.529	0.525	0.527	0.5260±0.002
7	70	0.621	0.619	0.618	0.6203±0.001
8	80	0.710	0.712	0.711	0.7123±0.001
9	90	0.791	0.789	0.793	0.7910±0.002
Absorbance (y) = 0.0088*concentration(x) + 0.005					
Correlation Coefficient (R^2) = 0.9996					

TABLE 5: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN 0.1 N HCL

Sr. no.	Concentration µg/ml	Absorbance			Avg. Absorbance ± SD
		I	II	III	
1	10	0.080	0.077	0.085	0.0807 ± 0.004
2	20	0.145	0.148	0.151	0.1480 ± 0.003
3	30	0.216	0.219	0.222	0.2190 ± 0.003
4	40	0.281	0.284	0.286	0.2837 ± 0.002
5	50	0.353	0.358	0.362	0.3577 ± 0.004
6	60	0.423	0.425	0.430	0.4267 ± 0.003
7	70	0.488	0.495	0.500	0.4943 ± 0.006
8	80	0.570	0.581	0.571	0.5740 ± 0.006
9	90	0.639	0.636	0.641	0.6387 ± 0.002
Absorbance (y) = 0.007*concentration(x) + 0.0078					
Correlation Coefficient (R^2) = 0.999					

TABLE 6: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN PHOSPHATE BUFFER PH 6.8

Sr. no.	Concentration µg/ml	Absorbance			Avg. Absorbance ± SD
		I	II	III	
1	10	0.117	0.116	0.118	0.1170 ± 0.001
2	20	0.208	0.210	0.209	0.2090 ± 0.001
3	30	0.293	0.293	0.295	0.2937 ± 0.001
4	40	0.399	0.396	0.393	0.3960 ± 0.003
5	50	0.494	0.492	0.492	0.4927 ± 0.001
6	60	0.586	0.585	0.587	0.5860 ± 0.001
7	70	0.684	0.682	0.680	0.6820 ± 0.002
8	80	0.783	0.787	0.785	0.7850 ± 0.002
9	90	0.882	0.881	0.880	0.8810 ± 0.001
Absorbance (y) = 0.0096*concentration(x) + 0.0144					
Correlation Coefficient (R^2) = 0.9997					

Evaluation of Optimized Formulation: The optimized film formulation was evaluated for Thickness, Tensile strength, Transparency, Surface texture, folding endurance, disintegration time, drug content and % CRP at 2 minutes. Results for all the parameters mentioned above are shown in **Table 7** and image of the optimized film shown in **Fig. 8.**

TABLE 7: EVALUATION OF OPTIMIZED FORMULATION

Evaluation Parameters							
Thickness# (nm)	**Tensile strength* (kg/cm^2)**	**Transparency**	**Surface Texture**	**Folding Endurance**	**Disintegration Time (sec)***	**Drug Content***	**%CRP at 2min***
0.11±0.001	0.59±0.014	Good	Smooth	>250	17±1.67	100.49±1.16	84.01±1.16

#Values are expressed as mean ± S.D, n=3 *Values are expressed as mean ± S.D, n=3.

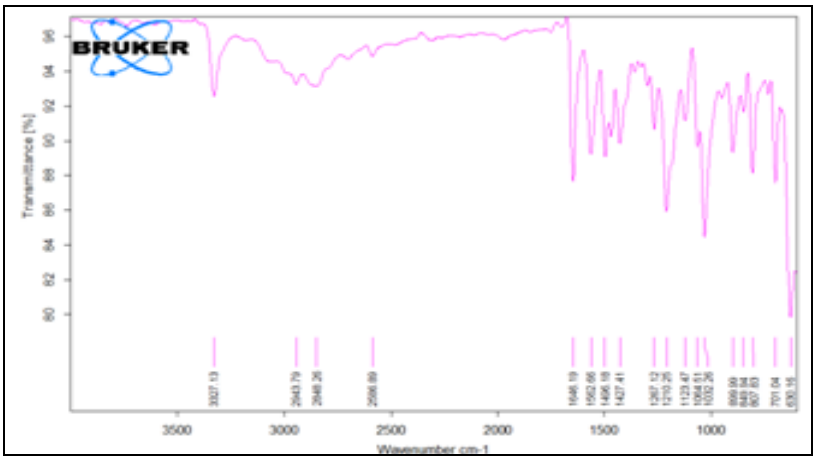

FIG. 1: FT-IR SPECTRA OF PURE DRUG (MIDODRINE HYDROCHLORIDE)

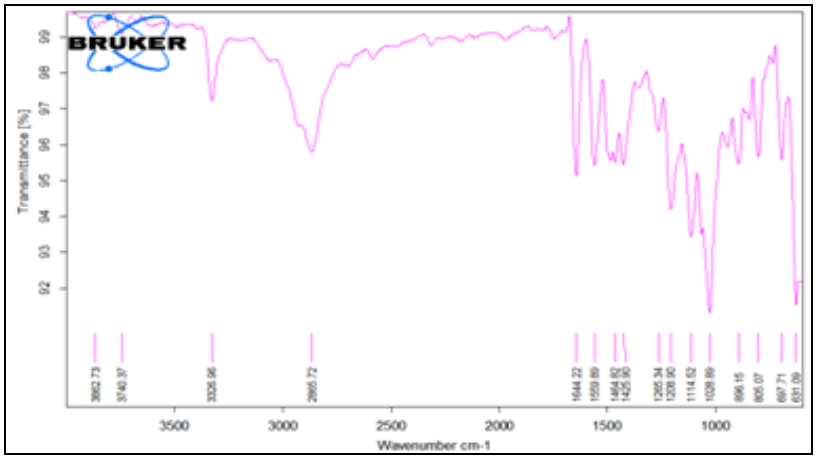

FIG. 2: FT-IR SPECTRA OF MIDODRINE HYDROCHLORIDE WITH EXCIPIENTS

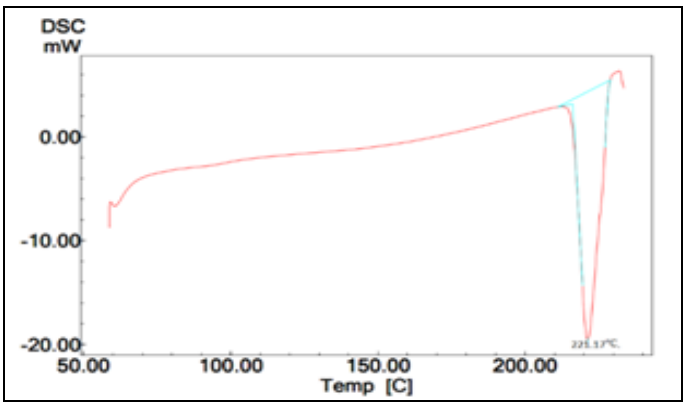

FIG. 3: DSC THERMOGRAM OF MIDODRINE HYDROCHLORIDE

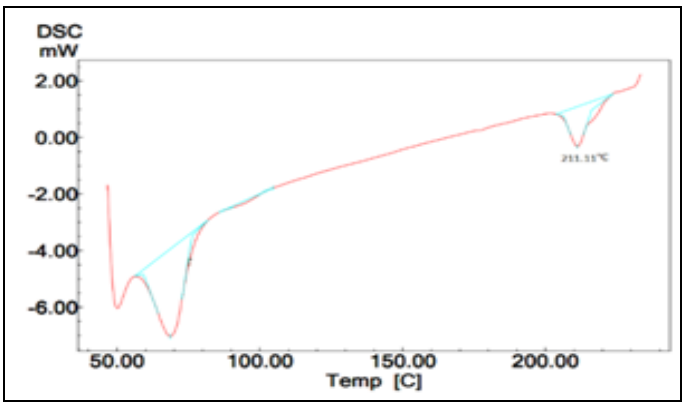

FIG. 4: DSC THERMOGRAM OF MIDODRINE HYDROCHLORIDE WITH EXCIPIENTS

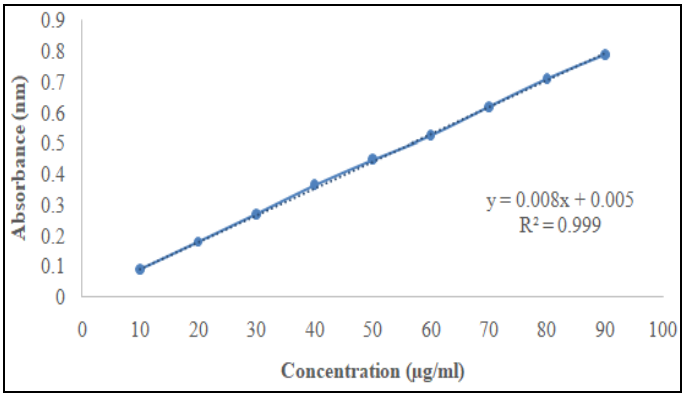

FIG. 5: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN WATER

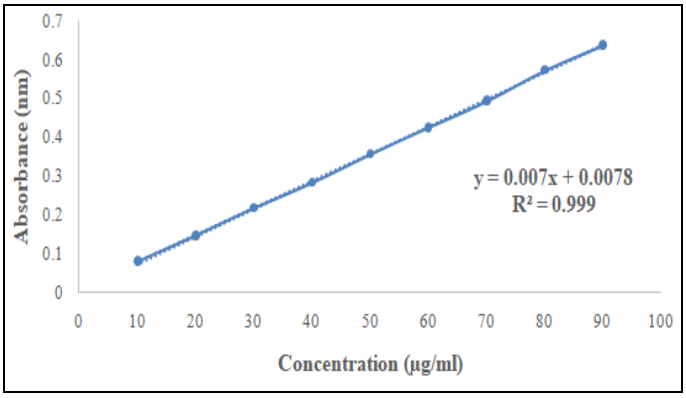

FIG. 6: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN 0.1 N HCL

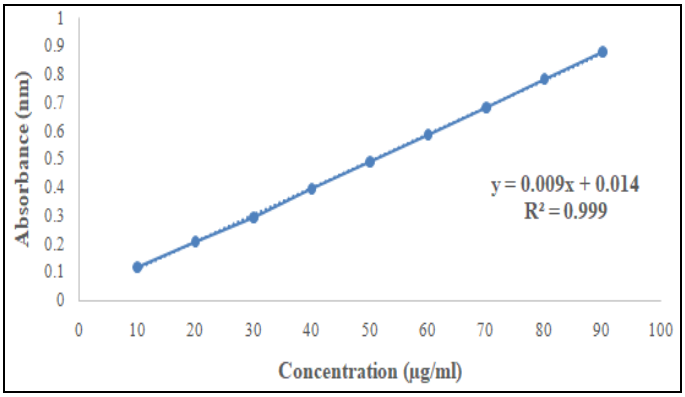

FIG. 7: CALIBRATION CURVE OF MIDODRINE HYDROCHLORIDE IN PHOSPHATE BUFFER PH 6.8

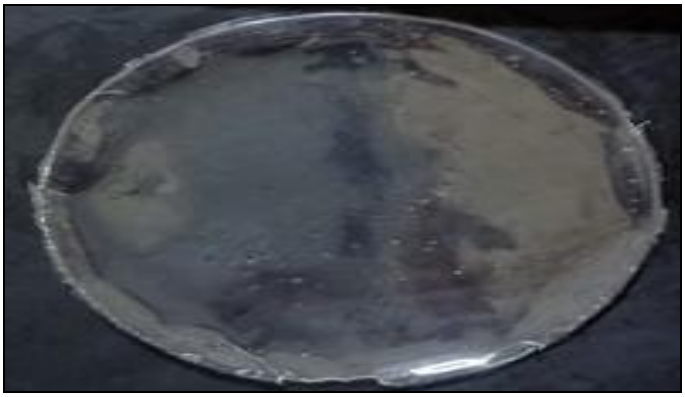

FIG. 8: IMAGE OF OPTIMIZED BATCH

CONCLUSION: The development of oral film drug delivery of Midodrine Hydrochloride is one of the alternative routes of administration to avoid first-pass metabolism and provide immediate action. In addition, these formulations enhance patient compliance. A combination of HPMC E15 LV, PEG 400, Sodium saccharin, Tartaric acid, and Poloxamer 407 showed fast dissolution, good permeability of the drug, and better morphological and mechanical properties.

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CONFLICTS OF INTEREST: Nil

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