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Formulation And *In-Vitro* Characterization of Mouth Dissolving Film of Clopidogrel Hydrogen Sulphate†

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Abstract: The purpose of the present investigation was to formulate a mouth-dispersing film of Clopidogrel Hydrogen Sulphate dosage form for a rapid onset of action, which is very easy for administration, without the issue of swallowing and using water. The mouth dissolving film of Clopidogrel Hydrogen Sulphate was prepared by Solvent Casting Method and its' in-vitro characterization was evaluated. The folding endurance of 173.6±0.22, the drug content is 96.33±1.15 The drug release rate of the optimized formula A4 is 96.00 % in 5 minutes, and it was concluded according to this result, that the film prepared by HPMC E5 polymer is forming superior film that offers rapid drug release.

Keywords: Clopidogrel Hydrogen sulphate, Mouth Dissolving Film, Solvent Casting Method, Rapid onset of action, HPMC E5.

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1. Introduction

Because of all of its benefits, Mouth Dissolving Film is a popular drug administration technique. When MDF comes into contact with saliva, it dissolves instantly and doesn't require any water. As a result, the formulation is enhanced for usage in patients of all ages and patient compliance is increased [1]. MDFs are preparations that come in the form of strips and include active chemicals that have been dissolved or dispersed in materials that create films [2]. It enables fast drug solubility, absorption, and instant bioavailability due to the high blood flow and permeability of buccal mucosa of 4- 1000 times greater than skin [3]. In conditions of various peripheral vascular disease, coronary artery disease, and cerebrovascular disease, clopidogrel is an oral, thienopyridine-class Anti-platelet medication used to block blood clots and reduce the risk of myocardial infarction and stroke. For the drug clopidogrel, the preparation of a Mouth Dissolving Film has been chosen since it has a low bioavailability. By creating the film, we may boost the drug's bioavailability by avoiding first pass metabolism, which also accelerates the drug's onset of action.

2. MATERIALS

Zentiva Pharmaceuticals, Ankleshwar, provided clopidogrel hydrogen sulphate as a gift sample. Polyvinylpyrrolidone (PVP) and Hydroxy Propyl Methyl Cellulose (HPMC) E5 of Analytical-grade were used. All of the testing was conducted using Distilled water.

3. Method

3.1 Method of preparation of Mouth Dissolving Film

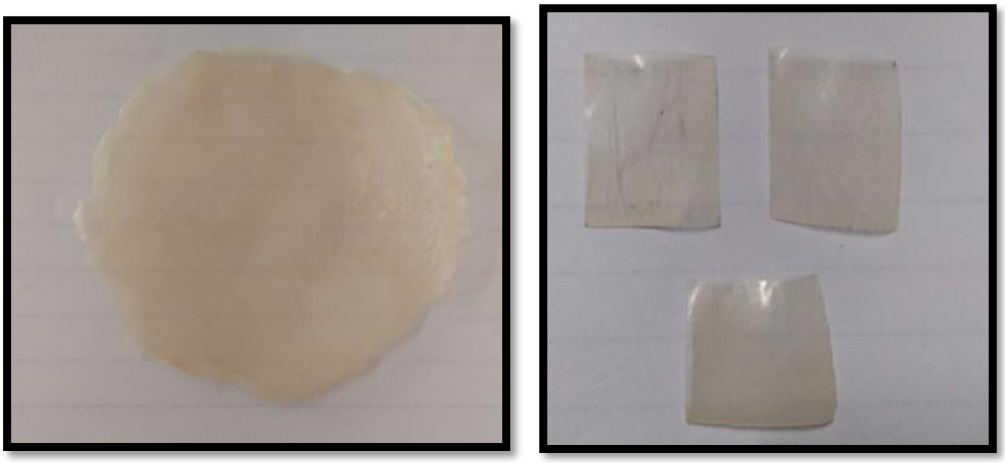
Solvent casting method is used for preparation of MDF of Clopidogrel Hydrogen Sulphate.

3.2 Steps for preparation of MDF of Clopidogrel Hydrogen Sulphate [4]

Films were prepared using the Solvent casting method in accordance with the formula (A 4) shown in table. A sufficient amount of HPMC E5 was precisely weighed, then dissolved in water by continually stirring and sonicated for 15 minutes to produce a transparent solution. The required quantity of plasticizer was added to the above solution. Clopidogrel Hydrogen Sulphate was dissolved in Methanol according to requirement by continually stirring and also sonicated for 15 minutes to produce a transparent result. The remaining quantity of water was mixed with the other excipients, and the mixture was also sonicated for 15 minutes. The three solutions are combined and stirred continuously for five minutes. For 24 hours, the solution was set down to allow trapped air bubbles to get out. The solution was then poured onto a glass petri dish and allowed to dry for 24 hours in a 50^0 c oven. The films were carefully removed from the Petri plate after drying, cut into the required shape (2 cm^2), and put on a glass Petri plate with a lid.

Table 1. Composition of Mouth Dissolving Film.

Ingredients	A1	A2	A3	A4	A5
Clopidogrel Hydrogen Sulphate	125	125	125	125	125
HPMC E5	300	350	400	450	500
PVP	50	50	50	50	50
Sucralose	20	20	20	20	20
Citric Acid	20	20	20	20	10
Flavor	5	5	5	5	5
Water (ml)	10	10	10	10	10
Methanol (ml)	5	5	5	5	5



(a) **(b)**

Figure 1. a) Picture of Mouth Dissolving Film (batch A4); b) Picture of MDF cut in desired shape and size.

4. Determination of λmax

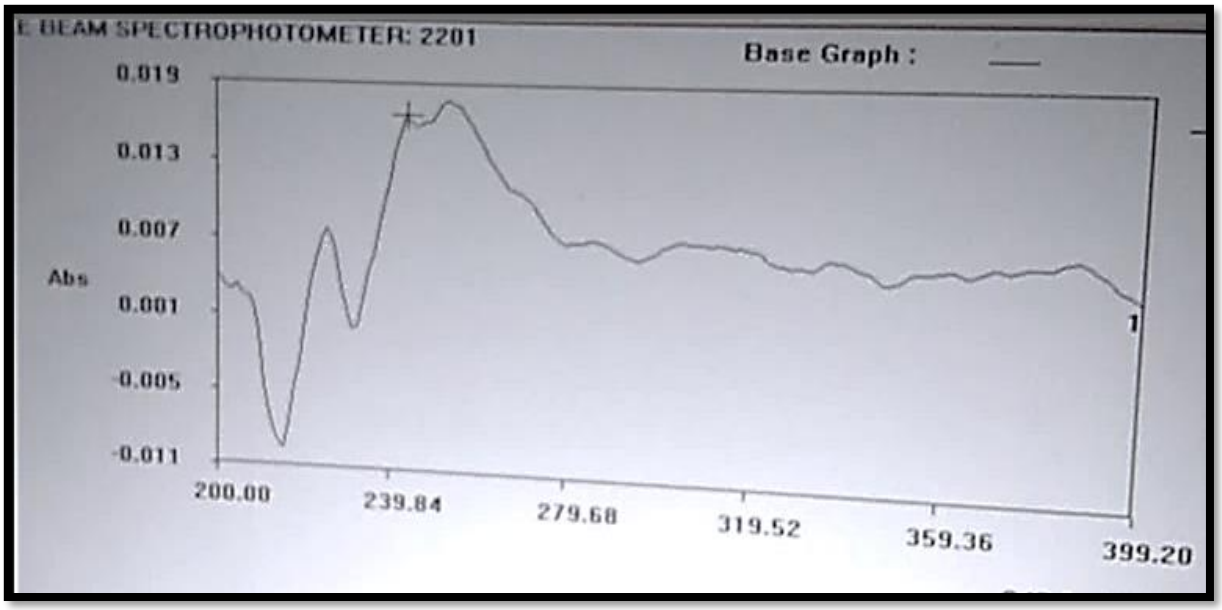


Figure 2. UV spectrum of Clopidogrel Hydrogen Sulphate.

The Clopidogrel Hydrogen Sulphate solution were prepared in 6.8 buffer solution, or pH 6.8, which is shown in Figure, had a wavelength of maximum absorbance (max) that was consistent with the available literature. At 240 nm, the maximum concentration of clopidogrel hydrogen sulphate was noted.

5. Preparation of calibration curve [5]

The calibration curves for clopidogrel hydrogen sulphate were made in phosphate buffer pH 6.8 using a UV visible spectrophotometer. Stock solutions of clopidogrel hydrogen sulphate were prepared by dissolving 2 mg of drug in 10 ml Phosphate buffer (pH 6.8). 200 µg/ml of Clopidogrel Hydrogen Sulphate standard stock solution was prepared in order to make the following dilutions of 20, 40, 60, 80, and 100 µg /ml. Ab-

sorbance of all the solutions was measured using a UV-VIS Spectrophotometer in comparison to a blank at 240 nm.

Table 2. Standard calibration curve of Clopidogrel Hydrogen Sulphate in phosphate buffer (pH 6.8).

Sr. No.	Concentration(µg/ml)	Absorbance
1	0.0	0.0
2	20	0.116
3	40	0.221
4	60	0.345
5	80	0.455
6	100	0.585

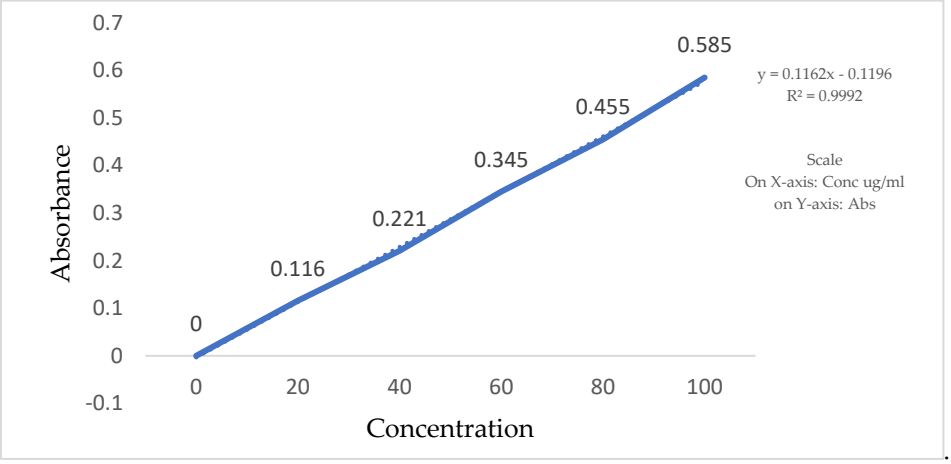


Figure 4. Standard calibration curve of Clopidogrel Hydrogen Sulphate in Phosphate buffer.

6. Drug-polymer compatibility study[6]

After keeping drug: Excipient sample in stability chamber at temperature of at 40° and 75% relative humidity. Drug and HPMC E5 and PVP compatibility was discovered. None of these excipients interfered with any of the peaks, according to IR data. It demonstrated that each excipient was acceptable for use with the medication.

Table 3. Interpretation of IR Spectra of Physical mixture

Sample	Wavenumber (cm^{-1})	Functional group

Clopidogrel Hydrogen Sulphate with HPMC E5 and PVP	1750.81, 1644.80, 1185.42, 1296.22, 1152.63, 1067.25, 944.31	C-O, C=O, C-O, C-N, C-O, C-O, O-H, C-C

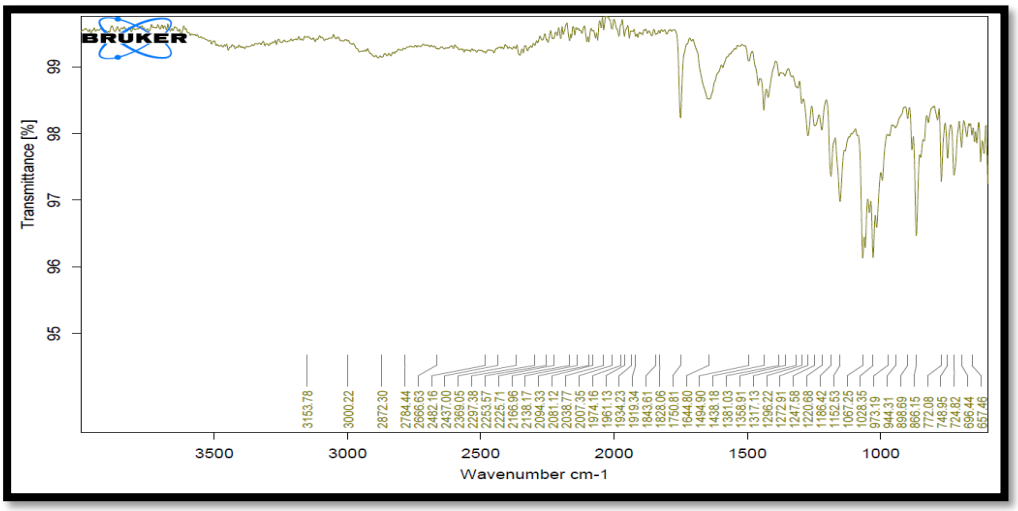


Figure 3. FTIR spectra of Clopidogrel Hydrogen Sulphate with HPMC E5and PVP

7. Result and Discussion

7.1 Thickness

The film's thickness was measured three different places using micrometer screw gauges and the average of those three readings was calculated.

7.2 Weight variation

One square inch sections were cut at three different positions. On an electronic scale the weight of each strip was recorded, and weight variation was calculated.

7.3 Folding Endurance

The exact value of folding endurance (a measure of fragility) is determined by how many times the strip could be folded at the same location without breaking. For prepared films 2×2 cm strip was cut uniformly, folded repeatedly on the same spot and the folding endurance was measured.

7.4 Percentage drug content

For determination of Clopidogrel Hydrogen sulphate content, complete strip (full petriplate) as well as film of known sizes (4×5 cm) were dissolved in phosphate buffer 0.2 M (pH 6.8). The amount of the drug present was determined by measuring the absorbance at 240 nm (UVVIS spectrophotometer, systronics2201, Ahmedabad. The drug content was determined by plotting a standard calibration curve of drug in phosphate buffer (pH 6.8).

7.5 Surface pH determination

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. By using pH meter the pH was noted after bringing the

electrode in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

7.6 Disintegration time

For Disintegration time, the film as per the dimension (2x2 cm) required for dose delivery was placed in 10 ml phosphate buffer. Disintegration time was noted as per time required by film to break.

Table 4. Evaluation of Clopidogrel Hydrogen Sulphate MDF

Batch	Thickness	Weight Variation	Folding endurance	Surface pH determination	Disintegration time	Drug content
A1	0.03±0.003	111.33±0.577	54.66±0.577	2.66±0.577	64.66±0.577	61±1
A2	0.05±0.005	72 ± 1	75.66±0.577	3.66±0.57	59.65±0.573	83.5±4.784
A3	0.08±0.005	100.66±0.577	95.66±4.932	4.033±0.95	54.66±0.577	92.7±3.223
A4	0.09±0.005	61.33 ± 0.57	173.6±0.22	6.13 ± 0.057	22.33±2.081	96.33±1.15
A5	0.04±0.004	98±1	120.33±0.57	3.76±1.594	48.33±0.577	81.36±1.06

7.7 In vitro dissolution study

The in vitro dissolution studies were conducted using 150mL glass beaker with 125mL of Phosphate buffer as dissolution medium. Film (2×2 cm2) was placed on one side of the beaker using double-sided tape. Medium was stirred at a speed of 200 rpm using magnetic stirrer bar. 5mL samples were withdrawn at 10, 20, 30, 40, 50, 60, 80, 100, 120sec time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analyzed by measuring UV absorbance at 240nm. The dissolution experiments were conducted in triplicate. Percent of drug dissolved at different time intervals are noted.

Table 4. In-vitro drug dissolution study of clopidogrel hydrogen sulphate

Time (min)	**% Drug Release**				
	A1	**A2**	**A3**	**A4**	**A5**
10 sec	24.01	30.25	22.68	38.20	38.59
1 min	33.46	40.25	30.85	50.49	55.21
2 min	48.25	59.26	37.10	56.18	62.01
3 min	58.45	75.15	47.01	75.14	78.63
4 min	60.20	81.21	64.72	87.12	80.20
5 min	79.21	85.20	79.60	96.00	90.15

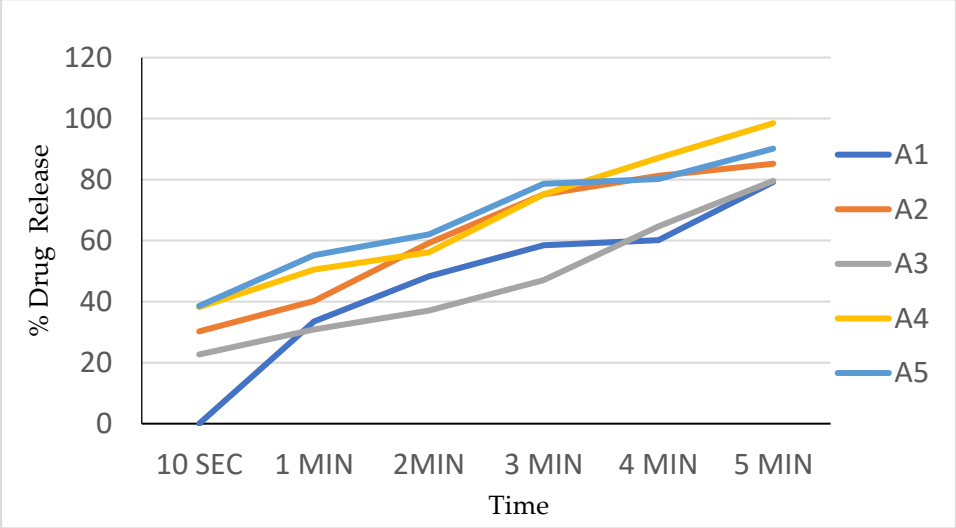


Figure 5. Drug release profile of batch A1 to A5.

8. Conclusion

According to the results of the current study, it is possible to create Clopidogrel Hydrogen Sulphate Mouth Dissolving Films using the Solvent Casting Process, which will increase therapeutic efficacy while increasing bioavailability and patient compliance. All films produced with PVP as the plasticizer and HPMC E5 as the film-forming polymer can be used as films. The enhanced formulation A4 has the quickest disintegration time of 22.33±2.081, the drug content of 96.33±1.15. A maximum folding endurance of 173.6±0.22, and the rapid in-vitro drug release of 96.00% in 5 mins. The manufactured films seem like a good alternative to conventional marketed formula.

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