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ORIGINAL ARTICLE

Formulation and Evaluation of Mouth Dissolving Film of Cyclizine Hydrochloride

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ABSTRACT
The aim of the present research work was to formulate the Mouth Dissolving Film, to minimize the current and future problems of engulfing the oral dosage form like tablets, capsules and less patient compliance especially of pediatric and geriatric. Therefore, to overcome the problems like dysphagia, bedridden and comatose patient and to improve the bioavailability of the drug mouth dissolving film can be a better option. The preparation of mouth dissolving film was carried out by simple method that was solvent casting method, the homogeneity and the thickness of the film obtained by this method was good. The film was tested for thickness, surface pH, weight variation, folding endurance, % moisture loss, ex vivo permeation study, tensile strength, % elongation, drug content uniformity, in-vitro dissolution studies and in-vitro disintegration test. The best formulation was F4 as it releases 99.17% of drug in 2 minutes, the drug release of the best formulation (F4) followed zero-order kinetics and the Correlation Coefficient R^2 was 0.993and ex-vivo permeation study of F4 formulation showed a drug release of 87.62% within 2 minutes. The study reveals that the formulation can be very useful for the treatment of the disease which requires quick-onset of action.
Keywords: *Mouth Dissolving Film, Natural Polymer, Solvent-Casting Method, Cyclizine Hydrochloride, Oral Mucosal Absorption.*

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INTRODUCTION

The common pharmaceutical dosage form like tablets, capsule, syrup are maximally used in market to deliver the dose and give therapeutic effect but the geriatric, pediatric and dysphagia patients have choking and swallowing problem so to overcome this problems mouth dissolving oral film are formed. Mouth dissolving oral film is the novel approach to deliver the dose in appropriate manner to enhance activity and making more convenient, they can be manufactured by different types of technologies like: solvent casting method, hot melt extrusion, semisolid casting method, rolling method and solid dispersion extrusion. The major advancement of this system is no requirement of water, painless and can be administered by ourselves (1). MDF (Mouth Dissolving Film) by pass the hepatic first pass metabolism so there is no or less chance of drug degradation and increase the bioavailability of the drug, the drug incorporated in MDF is used in less amount therefore it reduces the side-effects. This dosage form is the best option for the diseases which requires quick on-set of action like: high blood pressure, cardiac problems, allergic condition, shortness of breath, nausea, epilepsy, for comatose patients, accidental patients and in various disease or conditions in which patients are unable to engulf the tablets or pills or any other dosage forms(2).MDF are the dosage form which get adhere to the surface of oral mucosal layer and delivering the drug through polymeric layer achieved a greater success in the field of pharmaceutical science. When the films are placed on tongue it releases the active pharmaceutical ingredients as soon as it gets hydrated by saliva. First MDF was Listerine and Pfizer was the first company who manufactured it for mouth freshening purpose(3).

MATERIAL AND METHODS

Materials

Cyclizine hydrochloride was obtained as a gift sample from Tooba Pharmaceutical Private Limited, MIDC Paithan, Aurangabad, India, Aspartame from Oxford Lab fine chem LLP, Maharashtra, India; Gelatin from Merck Specialities Pvt. Ltd, Mumbai, PEG 400, Tween 80, Citric acid, Ethanol were supplied by Lobachemiepvt. Ltd.Mumbai, Maharashtra, India.

Method to Prepare MDF

The most appropriate and convenient method for the formation of film is solvent casting method. In this method water soluble polymer was dissolved in water on magnetic stirrer and the drug and other ingredients were dissolved in appropriate solvent after dissolving the solutions separately both the solutions were mixed and stirred to get an homogenous solution then after degassing, poured the solution in petriplate, dry the films so that they are ready to cut in desired shape and dimensions. (4)

Table 1: Formulation of mouth dissolving film of cyclizine hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Cyclizine Hydrochloride (mg)	25	25	25	25	25	25	25	25
Gelatin (mg)	700	750	800	850	900	950	1000	1050
PEG 400 (mg)	90	90	90	90	90	90	90	90
Citric Acid (mg)	30	30	30	30	30	30	30	30
Tween 80 (mg)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Aspartame (mg)	30	30	30	30	30	30	30	30
Water (ml)	9	9	9	9	9	9	9	9
Ethanol (ml)	1	1	1	1	1	1	1	1

Dose Calculations

Width of the plate = 8cm
Length of the plate = 15cm
No. of 3×2 cm^2 films present whole plate = 20
Each film contains 25mg of drug
20 no. of films contains mg of drug = 25×20
= 500 mg

Evaluation of MDF

Organoleptic Evaluation: The external appearance of film like transparency, color, odor and shape was observed visually and recorded.

Folding Endurance: Folding endurance of the film was estimated manually by folding the film continuously from the same position till the films get break. For experimental purpose the formulated dosage form of 3×2 cm^2 film was taken and folded at a same point again and again till it breaks.(5)

Thickness of Film: The thickness of the film was measured by vernier calipers so that accurate thickness of the film was observed and recorded. The thickness is measured by repeating the process approximately 3 times at different positions and get average thickness of the film.

Weight Variation: For determining the weight of the individual film 3-4 film of every formulation were weigh by digital weighing balance and average was recorded. (6)

Surface pH: The pH of the film was tested by moistened the film with the help of water and then the electrode was kept in contact with film for 1 min and pH was recorded by observing on three film, the mean was obtained. (7)

Tensile Strength: Tensile strength of the film is the test used to determine that at what maximum load the film get break. For this the film of 3×2cm^2 was placed longitudinal between the grips of tensile tester and load at breakage was recorded.

$$\text{Tensile strength} = \frac{\text{Load at Breakage} \times \text{Strip Width}}{\text{Strip Thickness}}$$

Percentage Elongation: The % elongation of the film was determined by dividing the Increase in the length to the original length.(8)

$$\% \text{ Elongation} = \frac{\text{Increase in Length} \times 100}{\text{Original Length}}$$

Drug Content Uniformity: Drug Content Uniformity: The film was transferred into a graduated flask, dissolved in 100 ml 6.8 pH buffer and the flask was shaken continuously. The solution was filtered after

suitable dilutions with buffer, the absorbance was measured at 225 nm and the drug content was calculated by the standard curve drawn. (9)

Percentage Moisture Loss: % moisture loss of the film was determined by keeping the films in desiccator for three days containing silica gel and then the before and after weight of three days was noted and moisture loss was evaluated. (10)

$$\% \text{ Moisture Loss} = \frac{(\text{Initial Weight} - \text{Final Weight}) \times 100}{\text{Initial Weight}}$$

***In-Vitro* Disintegration Test:** The disintegration of the film was conducted by putting the film of every formulation in beaker containing 25ml of distilled water and the time was recorded when the film starts break or disintegrates. (11)

***In-Vitro* Dissolution Study:** Dissolution study of film was carried out by using USP type II apparatus having 300ml of buffer solution (6.8pH) rotated at 50 rpm and temperature-maintained 37±0.5℃. The solution was withdrawn at every 15 sec and replace by the fresh solution, the withdrawn sample as filtered and then absorbance was recorded at 225nm.

Kinetic Study: In order to analyze kinetic release or drug release parameter the data was fitted in different orders zero-order, First-order and Higuchi model, Korsmeyer-Peppas Model, Hixson model.(12)

***In-Vitro* Permeation Release:** *In-Vitro* permeation release was conducted with the help of Franz diffusion cell, in which the cellophane membrane of 3cm was mounted between the receptor and donor compartment, receptor compartment was filled with 6.8 pH buffer (37±0.2℃) solution for maintaining dynamics magnetic bead was kept and the formulation (film) was moistened with same buffer solution and was held on donor compartment. After a fixed interval of time solution was withdrawn from the receptor compartment and replace by the 6.8 pH buffer. The % amount of drug release or permeated was determined by checking absorbance in UV spectrophotometry.(13)

RESULTS AND DISCUSSION

Evaluation of Mouth Dissolving Film of Cyclizine Hydrochloride

Table 2.Physical Appearance of the Film

Property	Observation
Color	White
Odor	Odorless
Shape	Rectangular

Thickness of MDF

The thickness of the film was measured with the help of vernier caliper. As the concentration of the polymer increase the thickness of the film also increases gradually. The thicknesses of the formulations are ranged from 0.030±0.00057 to 0.047± 0.00057 as shown in table 3.

Weight Variation

The average weight of the formulations was determined and was in the range of 43.4±0.057 to 84.2±0.057 and is shown in table 3.

Table 3. Evaluation of thickness, weight variation, folding endurance and surface pH of MDF

Formulation Code	Thickness (mm) (*Mean±SD)	Weight Variation(mg) (*Mean±SD)	Folding Endurance (*Mean±SD)	Surface pH (*Mean±SD)
F1	0.032±0.001	43.4±0.057	40±1.15	7.02±0.005
F2	0.035±0.0011	47.5±0.057	53±0.57	6.95±0.01
F3	0.039±0.0011	53.7±0.1	62±0.57	6.92±0.01
F4*	0.030±0.00057	59.4±0.057	74±1.0	6.82±0.005
F5	0.032±0.001	66.4±0.152	80±1.52	6.90±0.015
F6	0.041±0.00057	71.8±0.057	82±0.57	6.93±0.017
F7	0.043±0.00057	78.5±0.115	83±1.0	6.99±0.10
F8	0.047±0.00057	84.2±0.057	85±1.52	6.96±0.015

Values are represented as mean ± SD and n = 3

Folding Endurance

The value of folding was in the range of 40±1.15 to 85± 1.52. It was observed that with the increase in the concentration of the polymer folding endurance also increases and hence the chance of film rupturing decreases as shown in table 3 of films.

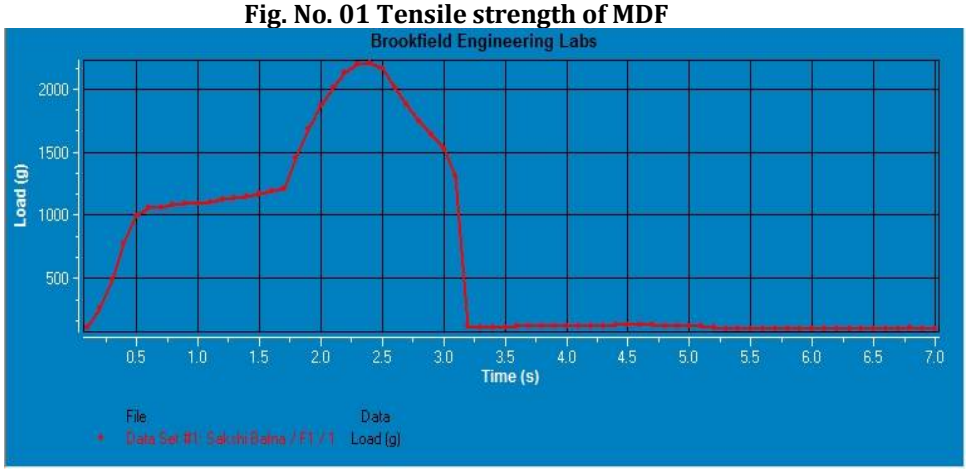
Surface pH of the Film

The surface pH of the strips was ranging from 6.90±0.015 to 7.02±0.005 as shown in table 3. The surface pH values assured that there will be no irritation to the oral mucosal lining.

Tensile Strength

Tensile strengths of the formulations was tested by TexturePro CT V1.3 Build 15 and were found to be in the range of 18.16±4.67 to 137±24.04N/mm^2.Tensile strength indicate that at how much of maximum weight the films get break so therefore we can assume it for transportation, packaging or dispensing as shown in table 4 and the graph in fig. 01

Fig. No. 01 Tensile strength of MDF



% Elongation

The % elongation was ranged from 100.76±0.21 to 126.5±1.49 as shown in table 4. It determines the elasticity of the MDF and with the increase in polymer the elasticity of the film increases.

Table 4. Evaluation of tensile strength and % elongation of MDF

Formulation Code	Tensile Strength (N/mm^2) (*Mean±SD)	% Elongation (*Mean±SD)
F1	18.16±4.67	100.76±0.21
F2	24.5±16.34	101.4±2.58
F3	59.66±7.82	105.06±2.05
F4*	124.83±4.09	126.5±1.49
F5	137±24.04	112.23±1.18
F6	104.16±3.29	113.33±3.005
F7	97.33±4.77	106.6±1.05
F8	75.83±3.75	103.33±1.16

Values are represented as mean ± SD and n = 3

Drug Content Uniformity of MDF

The % drug content in MDF of different formulation was ranges from 89.35±0.61 to 99.17±0.18% as shown in table 5.

***In-Vitro* Disintegration Test**

The disintegration time of the various formulations were ranging from 17±1.52 to 64±1.52 as shown in table 5, on increasing the concentration of the polymer disintegration time of the dosage form also increases.

Percentage Moisture Loss

The % moisture loss is used to determine the stability and the dosage form withstand or not at a particular conditions. The % moisture loss of the MDF was range from 1.01±0.616 to 2.31±0.616 as shown in table 5.

Table 5. Evaluation of % drug content, disintegration time and % moisture loss of MDF

Formulation Code	% Drug Content (mean±SD)	Disintegration Time (sec) (mean±SD)	% Moisture Loss (mean±SD)
F1	89.35±0.61	17±1.52	2.076±0.616
F2	92.01±0.85	23±0.57	2.31±0.616
F3	94.67±0.37	23±1.00	1.48±0.616
F4*	99.17±0.18	35±0.57	1.01±0.616
F5	96.86±0.97	44±0.57	1.05±0.616
F6	85.69±0.69	50±0.57	1.39±0.616
F7	83.74±0.55	57±1.52	1.52±0.616
F8	87.36±0.96	64±1.52	2.007±0.616

Values are represented as mean ± SD and n = 3

In-Vitro Dissolution Studies

In-vitro drug release from MDF was determined by USP type II apparatus as shown in Fig. no. 5

By increasing the concentration of the polymer film become thick and dissolve slowly. The *in-vitro* drug release of F4 formulation (99.17%) is good compared to other formulations.

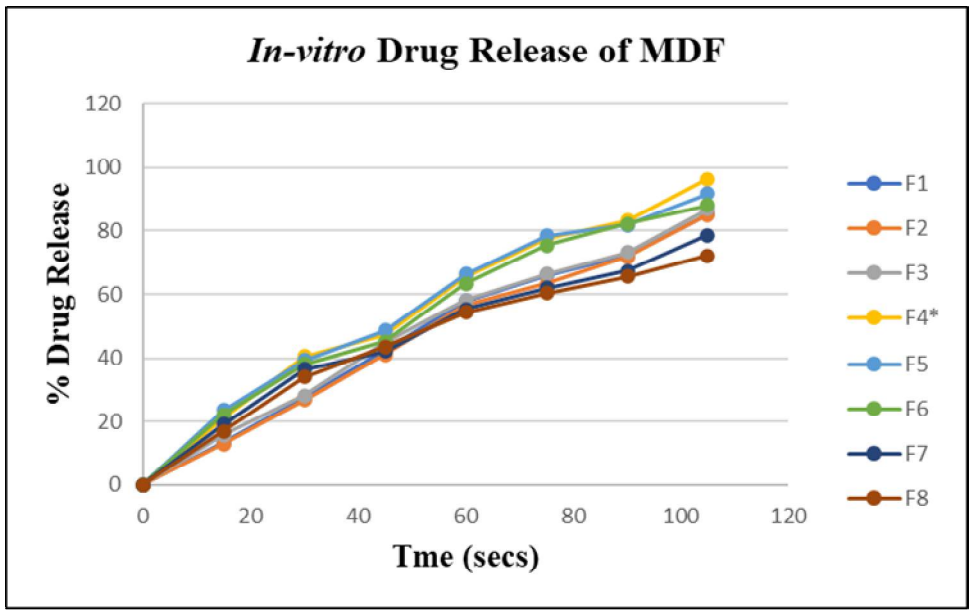


Fig. No. 05: *In-Vitro* Drug Release from MDF

In-Vitro Permeation Studies

In-Vitro permeation studies were conducted on every formulation, and F4 gave the maximum drug release (87.62%) that indicates that the formulation get easily permeate through the cellophane membrane bypass first-pass metabolism and enhance the bioavailability of the drug as shown in fig. 2.

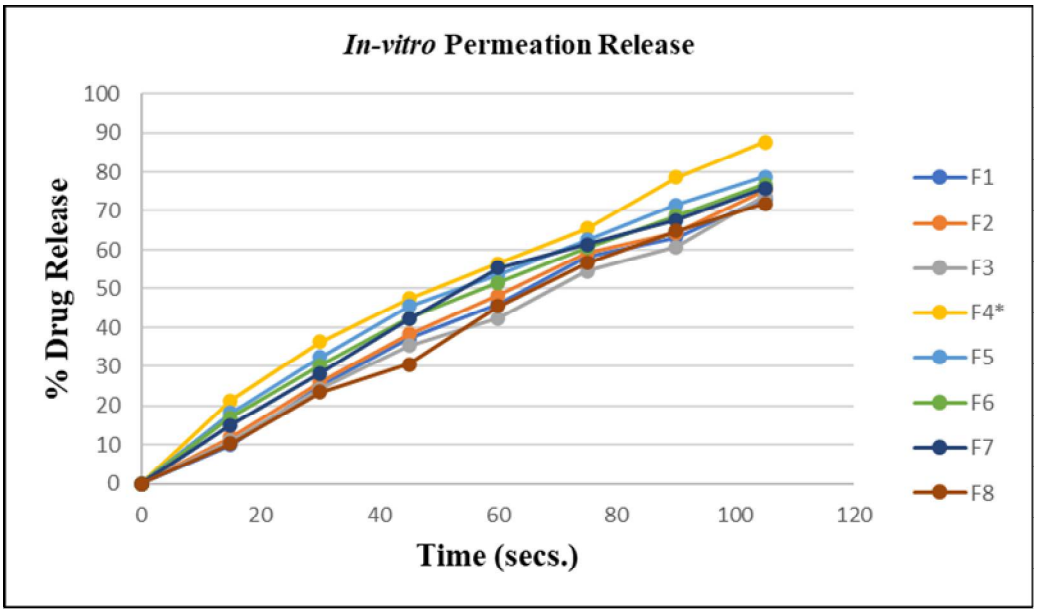


Fig. No. 02 *In-Vitro* Permeation Release

Drug Release Kinetic Studies of MDF

The ***in-vitro*** release data of the film was plotted in different kinetic model. According to the data it was found that the zero-order kinetic model of F4 is best suited formulation. R^2 value of zero-order kinetic equation (0.993) were found to be greater than the first-order kinetic equation (0.853), and according to zero-order kinetics the release of drug from the film (F4) is independent of the concentration of the drug present in the same formulation. Other mathematical model's value was shown in table 6.

Table 6.Mathematical model correlation coefficient values

S. No.	Mathematical Model	Correlation Coefficient R^2
1.	Zero Order	0.993
2.	First Order	0.853
3.	Higuchi Model	0.945
4.	Korsmeyer-Peppas Model	0.796
5.	Hixson Model	0.950

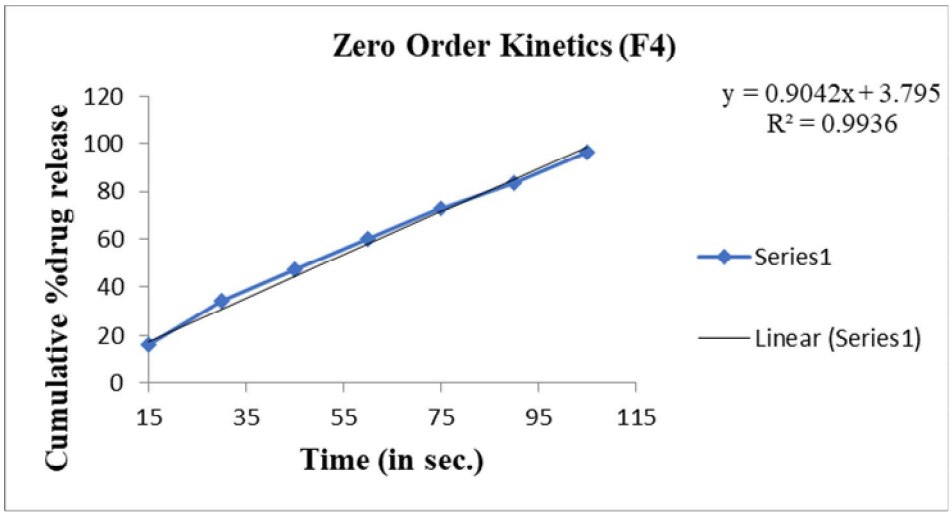


Fig. No. 03 Zero-Order Plot of F4

CONCLUSION

Mouth dissolving oral film is the best innovation in the field of novel drug delivery that is used in the critical situation of heart disease, epilepsy, allergy, high BP, or in the condition which require instant action. Gelatin is selects as a natural polymer for formulation and F4 formulation is best among all, it get

disintegrate within seconds (35sec) and the % drug content is maximum that is 99.17% and due to its better absorption in oral cavity it gives maximum bioavailability.
The research concluded that the mouth dissolving film of cyclizine hydrochloride is the promising approach for treating the allergy and it can overcome the problems associated with the conventional dosage form that is tablets or capsules that require water to engulf.

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CONFLICT OF INTEREST
The authors have no conflict of interest.

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