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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL THIN FILM CONTAINING PROCHLORPERAZINE MALEATE

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ABSTRACT

The main aim of the work is to develop a novel, fast dissolving product on the technology platform of a small and thin drug loaded film called oral thin films or oral wafers for achieving faster disintegration and dissolution with improved bioavailability. Prochlorperazine maleate which is a phenothiazine antipsychotic is used as the model drug for the development of oral thin films. It is used in the prevention and treatment of nausea, vomiting associated with migraine (or severe head ache) or drug induced emesis. Fast dissolving oral thin films from Prochlorperazine maleate were formulated by solvent casting method by using HPMC E15 as film forming polymer, glycerol and propylene glycol as plasticizers, tween 80 as surfactant, mannitol as sweetening agent, citric acid as saliva stimulating agent and sodium starch glycolate as superdisintegrating agent. The prepared films were then evaluated for physical appearance test, surface pH, thickness, weight variation, tensile strength, content uniformity, *in vitro* disintegration test and *in vitro* dissolution test. From the evaluation studies, all the films were found to show satisfactory results. The film F7 containing 200 mg of HPMC E15, 0.5 ml of tween 80, 0.6 ml of glycerol and 0.8 ml of PEG 400 was found to show more release of drug i.e. 99.23 % at the end of 16 minutes was selected as the best formulation. To the best formulation F7 5% of sodium starch glycolate was added and evaluated. The film was found to disintegrate in 25.67±0.5774 seconds and released 94.59 % of drug at the end of 10 minutes. The kinetics studies indicated that the film showed zero order with Korsmeyer – Peppas plot indicating non- fickian diffusion.

KEYWORDS: Oral thin films, Prochlorperazine maleate, Non-fickian diffusion, Fast dissolving.

INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturers due to highest acceptability of patients. About 60% of all the dosage forms are available as oral solid dosage forms. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenteral and liquid orals. But the liquid orals have the problem of accurate dosing mainly and parenteral are painful drug delivery, so most patient incompliance.[1] Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to tablets, capsules and syrups for paediatric and geriatric patients who experience difficulty in swallowing traditional oral solid dosage forms.[2] By definition, fast dissolving oral thin films are the most advanced form of oral solid dosage forms typically of the size of a postage stamp prepared by using hydrophilic polymers which can rapidly dissolves the active drug within 1 minute in the oral cavity by contacting the saliva without chewing or without the need of water for administration.[3] They can be placed under the tongue or along the inside of the cheek. The technology behind the development of these films was that of transdermal patches.[3] The technology behind the development of these films was that of transdermal patches.[3] It provides rapid absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4- 4000 times greater than that of skin but less than that of intestine.[1] The surface of the buccal cavity comprises of stratified squamous epithelium separated from the underlying tissue of lamina propel and sub mucosa by an undulating basement membrane. Hence the buccal delivery serves as an excellent platform for the absorption of molecules that have poor dermal penetration.[4]

Prochlorperazine maleate is a phenothiazine antipsychotic drug used It is used in the prevention and treatment of nausea, vomiting associated with migraine (or severe head ache) or drug induced emesis. The oral bioavailability of its tablet dosage form is about 12- 15 %. Hence by formulating it into oral thin films we could increase the oral bioavailability thereby bypassing the first pass metabolism and improve the patient compliance.

MATERIALS AND METHODS

Prochlorperazine maleate was obtained as a gift sample from Mehta Pharmaceutical Industries, Mumbai. HPMC E15 (confirming to USP), Sodium Starch Glycolate IP, Glycerol, Potassium dihydrogen phosphate, Monobasic sodium phosphate, Dibasic sodium phosphate (LOBA

Chemie Laboratory Reagent and Fine Chemicals, Mumbai, India). PEG 400 (Sigma chemical company), Tween 80, mannitol (E merck, Mumbai), Ethanol (Sigma chemical company).

Preparation of oral thin films

Solvent casting method[5,6] is used for the preparation of oral thin films. Specified amount of polymer HPMC E15 of different concentration was weighed and dissolved in specified amount of water and kept overnight to get a uniform dispersion of the solution in a beaker. Required quantity of drug, and sodium starch glycolate, mannitol and vanillin and tween 80 were dissolved in small amount of purified water in another beaker and then added to the polymeric dispersion. In a separate beaker add plasticizers were dissolved in required quantity of ethanol and this ethanolic solution was then added to the drug polymer mixture and stirred using a mechanical stirrer for 1 hour at a speed of 1100 to 1200 rpm for 40-120 minutes to get a uniform dispersion. The obtained uniform mixture was then casted on each petri plates. It was then dried at room temperature for 24 hours. The obtained films were then stored in butter paper which was covered by aluminium foil and was stored in a desiccator. Table number 01 showing the formulations oral thin film.

Table No. 01 Formulation of oral thin film containing HPMC E15

Ingredients	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
PCM (mg)	10	10	10	10	10	10	10	10
HPMC E15 (mg)	50	100	200	300	50	100	200	300
Glycerol (ml)	0.2	0.4	0.6	0.8	0.2	0.4	0.6	0.8
PEG 400 (ml)	0.4	0.6	0.8	1.2	0.4	0.6	0.8	1.2
Tween 80 (ml)	-	-	-	-	0.5	0.5	0.5	0.5
Ethanol (ml)	1	1	1	1	1	1	1	1
Mannitol (mg)	5	5	5	5	5	5	5	5
Citric acid (mg)	4	4	4	4	4	4	4	4
Vanillin	5	5	5	5	5	5	5	5
Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Calibration curve of Prochlorperazine Maleate in Sorenson's buffer

The aliquots 1, 2, 3, 4, 5and 6 µg/ml were prepared in Sorenson's buffer (pH 6.8) .The curve was found to be linear and the solutions obeyed Beer Lambert's law with regression value of 0.999.

EVALUATION OF MOUTH DISSOLVING FILMS

Visual inspection of film and film formation.[7]

The prepared films were evaluated visually for its clarity, transparency and stickiness. If it was satisfactory, then it was taken for further evaluation. If the formed films were not satisfactory they were discarded.

Surface pH[5]

The pH of the prepared films were determined by dissolving a film in 2 ml of distilled water and the pH of the obtained solution was measured using a pH meter.

Thickness[8,9]

The thickness of the film was measured using micrometer screw gauge with least count 0.01 mm at three different locations of the film. The thickness was measured and the average was taken and the standard deviation was calculated.

Weight variation[7]

This test ensures the uniformity of the formed films. From the whole film three small films of area 4cm^2 (2cm× 2cm) were taken and were weighed individually and the standard deviation from the value was calculated.

Folding endurance[7]

Folding endurance of the prepared films was determined by repeatedly folding a small strip of (2cm×2cm) at the same place until the film had broken. The number of times the film could be folded at the same place without breaking gives the folding endurance value.

Tensile strength[10]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile strength was measured by using tensile strength measuring equipment which has been fabricated. The equipment consists of a pan in which the weights are placed. The film whose tensile strength is to be evaluated was placed in between the two clips. The initial length of the film was noted. Weights were added to the pan until the film breaks. The tensile strength can be calculated using the formula.

$$Tensile\ strength = \frac{[Break\ force]}{a \times b}\frac{[1 + \Delta L]}{L}$$

Where a is the thickness of the film

b is the width of the film

ΔL is the length of elongation
L is the length of the film

Drug content and content uniformity[11]
For determining the drug content of the prepared batches of formulation, each strip at three different places containing 10 mg of the drug was cut and dissolved in 50 ml of pH 6.8 phosphate buffer solution with continuous stirring. The solution was filtered using Whatmann filter paper and the filtrate was diluted to 100 ml with same buffer in a volumetric flask. From the resultant solution 5ml of the solution was taken and placed in a 100 ml volumetric flask and the solution was then made up to 100 ml using the same phosphate buffer of pH 6.8. The absorbance was measured at 254 nm using UV spectrophotometer.

***In vitro* disintegration time[10]**
Disintegration test was performed by taking 5 ml of pH 6.8 phosphate buffer in a petri plate and the film was placed on the water surface. The time taken for the disintegration of film was noted as the disintegration time. This experiment was done on three films of the same batch and the average of the three values was taken.

***In vitro* dissolution test[10,12]**
The dissolution test was performed using the USP apparatus II. The dissolution test was performed using the 500 ml of simulated saliva solution, which consist of pH 6.8 phosphate buffer as dissolution medium. The temperature of the medium was maintained at 37± 0.5◦C. The apparatus was set at 50 rpm. A film sample of $4cm^2$ (2cm × 2cm) was cut and placed in the basket. 5 ml of samples were withdrawn at an interval of 2 minutes for 16 minutes and the same amount of the dissolution medium was replaced with fresh phosphate buffer at the same time in order to maintain the sink condition throughout the dissolution medium. The withdrawn samples were filtered using Whatmann filter paper. Appropriate dilutions were made to the withdrawn sample and were analyzed through UV spectrophotometer at a wavelength of 254 nm. The percentage of drug release was calculated by using the standard graph of Prochlorperazine maleate. The dissolution study was performed in triplicates and the average value of percentage release was taken.

RESULTS AND DISCUSSIONS

Visual inspection of the formulation
From the visual inspection studies it was found that as the concentration of the polymer increases the flexibility of the film decreases. Films with very low concentration of polymer are sticky and brittle in nature. The films with optimum concentration of polymer were found have good, flexible film forming property.

The pH of the films was found to be in the range between 6.3±0.1330 to 6.7± 0.0748. The thicknesses of the films were found to be from 0.05± 0.00577 mm to 0.15±0.0115 mm. The thicknesses of the films were found to increase with increase in concentration of the polymer.

The weight variations of the samples were found to be in the range 32.84±1.341 to 38.56±2.133 mg. It was observed that slight increase in the weight of films was due to increase in concentration of the polymer. The folding endurance of the film was found to be in the range 98.66± 4.041 to 242.67± 3.512. The folding endurance was found to increases with increase in concentration of the polymer.

The tensile strength of the prepared films was found to lie in between 1.133±0.0763 to 2.492±0.02346 Kg/mm^2.Tensile strength was found to increase with increase in concentration of polymer.

Drug content and uniformity test
Drug content of the films with all polymers was found to be in the range of 97.13 ± 0.3215 % to 99.20 ± 0.3606 % .Estimation of drug content indicated that the drug is uniformly distributed throughout the film for most of the films evidenced by the low values of standard deviation.

***In vitro* disintegration test**
The disintegration time of the films were found to be from 20.33 ± 0.557 to 56.67±1.528 seconds. It was observed that disintegration time of a film increases with increase in concentration of the polymer. It was observed that the presence of surfactants decreased the disintegration time of a film prepared with same concentration of polymer. The disintegration time of films prepared from HPMC E15 F1 to F4 varied from 23.67± 1.557 to 67.00±2.646 and for F5 to F8 varied from 20.33± 0.577 to 56.67± 1.528.

Table No. 02. Various Evaluation Results for Prepared Formulations

Formulation code	Weight variations (mg)	Thickness (mm)	Folding endurance	Tensile strength	Drug content uniformity	*In vitro* disintegration time
F1	32.84±1.341	0.05± 0.0057	98.66±4.041	1.238±0.03009	97.13±0.3215	23.67±1.557
F2	34.54±1.251	0.08± 0.0100	131.67± 3.512	1.437±0.01656	97.63±0.5132	37.00±1.732
F3	36.78±1.231	0.11± 0.0200	176.33± 5.132	2.013±0.01323	99.20±0.3606	45.33±2.082
F4	38.56±2.133	0.14±0.0152	219.33± 4.041	2.492±0.02346	97.57±0.5686	67.00±2.646
F5	33.37±1.465	0.06±0.0115	121.00±4.483	1.133± 0.00763	98.13±0.2082	20.33±0.577
F6	34.86±1.168	0.09±0.0100	158.67± 4.041	1.402±007024	98.56±0.3876	33.67±1.528
F7	35.46±1.585	0.14±0.0115	197.59± 4.619	1.945±0.04957	99.09±0.2050	40.00±1.000
F8	37.74±1.877	0.15±0.0115	242.67± 3.512	2.380±0.08220	97.97±0.4163	56.67±1.528

Values are mean± SD, n=3

***In vitro* dissolution studies**

It was observed that the drug release was found to decrease with increase in concentration of polymer. It indicates that increase in level of polymer, results in formation of high viscous gel layer caused by more intimate contact between the particles of polymers resulting in decreased mobility of drug particles in swollen matrices, finally leading to decreased release rate. The dissolution profile of formulation F1 to F4 was compared with that of F5 to F8 it was observed that presence of surfactant increases the drug release of the films. From the formulation containing HPMC E15, the film F7 was found to release more amount of drug 99.23% drug in 16 minutes. From the results obtained it was found that presence of surfactant decreases the disintegration time of the time there by increases the dissolution rate.

Table No. 03. The dissolution profile of oral thin films containing HPMC E15

Time (min)	% Drug release of Prochlorperazine maleate							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	30.45	27.46	23.75	18.3	32.86	31.57	27.59	21.79
4	47.98	43.95	37.45	27.29	50.45	46.93	44.95	33.9
6	57.8	55.68	49.73	38.63	59.32	61.79	54.71	40.1
8	69.41	65.32	57.93	49.39	72.45	74.38	65.57	52.67
10	81.89	78.19	70.52	65.91	84.36	82.7	77.84	69.39
12	93.65	89.31	86.95	79.26	94.78	95.57	91.94	82.83
14	96.43	92.86	94.37	85.27	98.24	97.28	96.49	87.3
16	98.41	96.27	97.36	94.29	98.68	98.25	99.23	95.39

Values are mean± SD, n=3

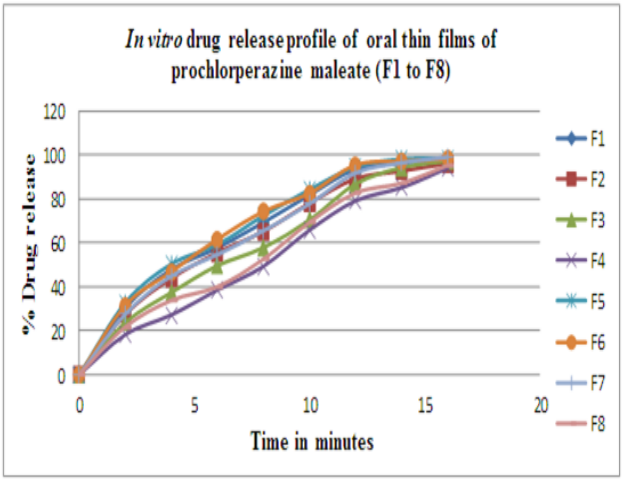

Figure No. 01 *In vitro* dissolution profile of formulations, F1 to F8

EVALUATION OF OPTIMIZED FORMULATIONS

From the formulation F1 to F8, film F7 containing 200mg of HPMC E15 and 0.5 ml of tween 80 selected as the optimized formulation

To the optimized formulation 5% concentration of superdisintegrant (Sodium starch glycolate) was added (F9) and evaluated for its super disintegrating property.

F9 was evaluated for its drug content uniformity and *in vitro* drug disintegration time and the results are given in table no.04

Table No. 04. Drug Content Uniformity and *In vitro* disintegration time of F9.

Formulation code	F 9
Drug content uniformity (%)	98.4±0.2517
In vitro disintegration time (seconds)	25.67±0.5774

***In vitro* dissolution studies of optimized formulation**

In vitro dissolution study was conducted on the formulation containing 5% of sodium starch glycolate. The dissolution profile of F9 is tabulated in table no. 05.

Table No.05 *In vitro* dissolution profile of F9

TIME (minutes)	Percentage drug release F9
0	0
2	38.74
4	57.46
6	71.68
8	85.23
10	94.59

Kinetics / release pattern of selected formulation f9.

For analyzing the mechanism of drug release kinetics of the film F9, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model.

The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data are shown in Figure No. 02 to 03 and regression coefficients are summarized in Table No. 06.

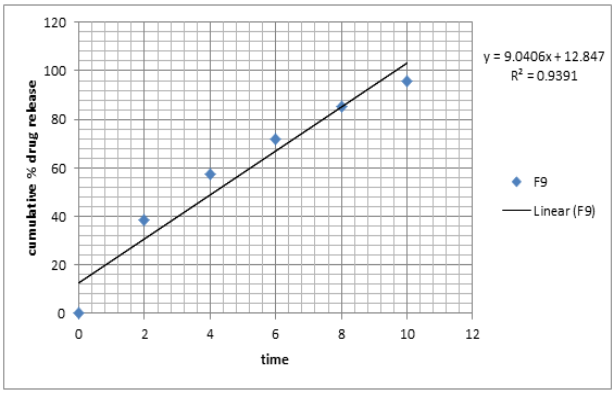

Figure No. 02 Zero order release of oral thin film, F9

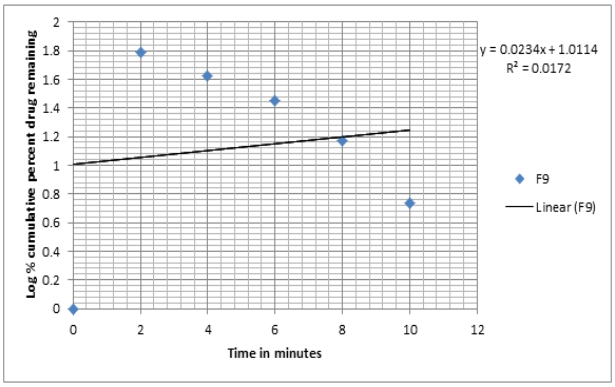

Figure No.03 First order release of oral thin film, F9

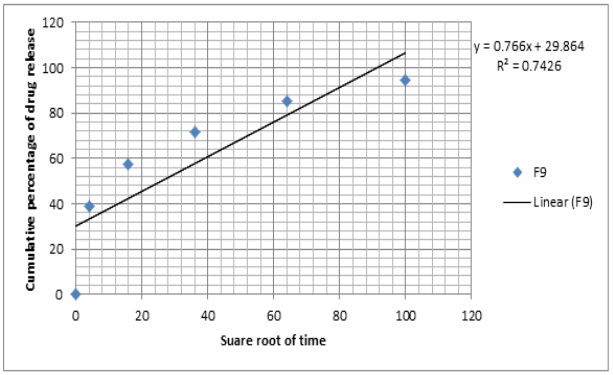

Figure No. 04 Higuchi Release model of oral thin film, F09

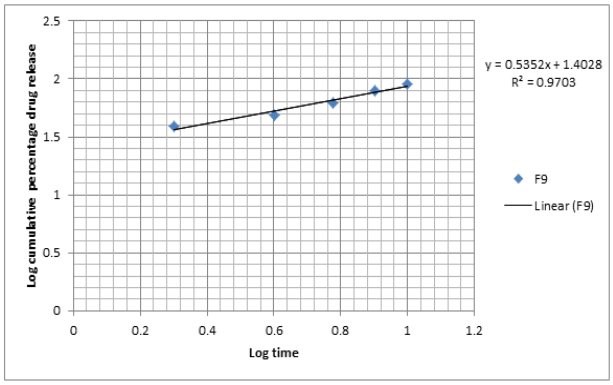

Figure No.05 Korsmeyer- Peppas release profile of oral thin film, F09

Table: 06 Data of regression coefficient of different kinetic models

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)
F9	0.939	0.017	0.742	0.970

From the evaluation of the selected films, formulation F9 which was prepared from HPMC E15 was found to release 94.49% of drug at the end of 10 minute. The results obtained from the study indicates that the presence of sodium starch glycolate as super disintegrating agent showed an increase in drug release from the film which was understood by comparing it with the drug release pattern of film having same concentration of polymer where super disintegrating agent has not been added.

Data analysis (curve fitting analysis)

The linear regression coefficient of each kinetic model was calculated and pattern of drug release from the dose was predicted. It was found that the optimized formulation F9 follows zero order kinetic model as it had highest R^2 value with Korsemayer – Peppas mechanism. The 'n' exponent value of optimized batch was found to be 0.535. Hence it shows non-fickian diffusion.

Stability studies

The optimized formulation F9 was evaluated for the stability studies which was stored at three different temperature conditions i.e. at room temperature (30± 2^0C;60 ± 5 %) , 40+ 2 ◦ C/ 75 % and refrigerated temperature; 4◦ C for six months. From the evaluation, it was found that there is no significant change in appearance, pH, folding endurance, drug content, *in vitro* disintegration and percentage drug release.

CONCLUSION

The formulation F09 containing 200mg HPMC E15, 0.6ml glycerol and 1.2 ml of PEG 400, 0.5 ml of tween 80 and 2 g of sodium starch glycolate was considered as the best formulation as it showed maximum *in vitro* drug release of 94.59% in 10 minutes showing zero order kinetics and Korsmeyer- Peppas plot indicates non-fickian diffusion.

From the present work, it was concluded that fast dissolving film formulation can be an innovative and promising approach for the delivery of Prochlorperazine maleate with improved bioavailability, enhanced dissolution rate and as an effective therapy for the treatment of severe nausea and vomiting associated with migraine and drug induced emesis.

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