ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation And Characterization Of Fast Dissolving Oral Film Of Prochlorperazine Maleate For Antiemetic Treatment.

Tushar M Phalke*, SS Pimple, and DL Visokar.

Department of Pharmaceutics, PES's Modern College of Pharmacy, Nigdi, Pune-411044, Maharashtra, India.

ABSTRACT

This research work was aimed to enhance the oral bioavailability and provide faster onset of action of Prochlorperazine maleate (used for the treatment nausea and vomiting) by formulating its mouth dissolving film (MDF). Prochlorperazine belongs to BCS II and oral bioavailability of it's about 11-15%. The MDF of Prochlorperazine maleate was prepared by solvent casting method using HPMC E15 (film forming agent), Propylene glycol (plasticizer), Betacyclodextrin (solubilizing agent), Citric acid (saliva stimulating agent), Mannitol (sweetening agent). The formulation was optimized by two dependent variables, three independent variables (2*3) was used for the formulation optimization of fast dissolving film of Prochlorperazine maleate and experimental trials are performed on all 8 formulation. In which the amount of HPMC, Propylene glycol and sonication time were selected as independent variables (factor) varied at low (-1) and high (+1) levels are the three categories. As dependent variables (response), the folding endurance and disintegration time were used. Additionally, the formulation's weight variation, thickness, folding toughness, in-vitro disintegration, and stability study were assessed. According to the findings, MDF (F5) demonstrated improved bioavailability and a quicker onset of action.

Keywords: Prochlorperazine, Oral film, Antiemetic, Factorial design, Fast dissolving.

https://doi.org/10.33887/rjpbcs/2023.14.6.2

Corresponding author

ISSN: 0975-8585

INTRODUCTION

About 60% of all drug formulations are in solid dosage form, with the oral route being one of the most popular. The most popular dose form is a tablet since it is convenient to transport, more effective financially, and easier to administer, which results in higher patient compliance. However, there are drawbacks to oral medication administration, such as liver degradation and gastrointestinal tract enzymatic degradation, which prevent the oral administration of many different types of pharmaceuticals, particularly peptides and proteins. The buccal region appears to be one of the favoured routes for systemic medication administration within the mouth mucosal cavity. It benefits include preventing hepatic first pass metabolism in the digestive system and improving the enzyme flora for absorption of drugs.

In the 1970s, a fast-dissolving medicine delivery system was created to help elderly and paediatric patients who had trouble swallowing tablets and capsules. Drug administration via the oral mucosa is essential. The usage of films for buccal distribution, also known as oral thin strips, as well as mucoadhesive tablets, gels, ointments, patches, and other bioadhesive oral mucosal dosage forms have all been developed.

Stratified squamous epithelium, which is distinct from the lamina propria and submucosa, lines the buccal cavity. The buccal mucosa has a penetrability that is 4-4,000 times greater than that of the skin and lower than that of the intestine. As a result, the buccal administration provides an excellent platform for molecular absorption with low skin penetration. In oral mucosa, intercellular objects produced from "membrane covering granules," which are found in the top 200 m layer, are the main impediment to permeability. Based on the active pharmaceutical ingredient, these oral film strips have a shelf life of two to three years, however they are incredibly sensitive to environmental dampness [1-8].

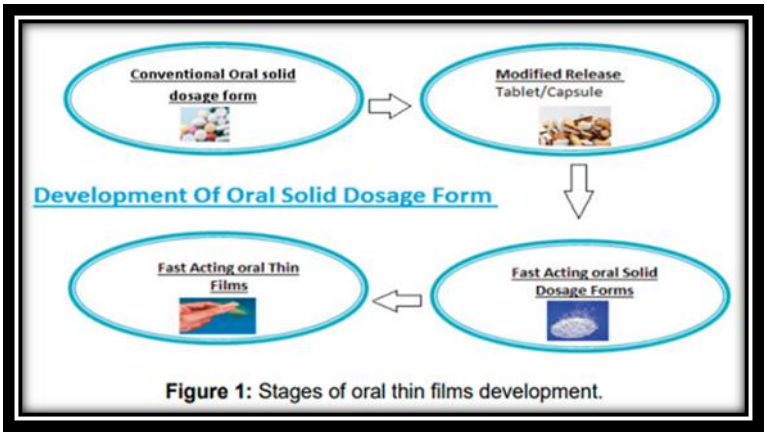


Figure 1: Stages of oral thin films development

Special features of mouth dissolving films

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration

The ideal characteristics of a drug to be selected

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

ISSN: 0975-8585

MATERIAL AND METHODS

Materials

Table 1: List of materials used

Sr. No	Materials	Use	Material suppliers
1	Prochlorperazine	API	Chemdyes Corporation Rajkot Gujarat
2	HPMC E 15	Polymer	Loba chemie Pvt Ltd, Mumbai, 400 005
3	Sodium Starch Glycolate	Super disintegrant	Research labs fine chem industries Mumbai, India
4	Propylene Glycol	Plasticizer	Loba chemie Pvt Ltd, Mumbai, 400 005
5	Beta-cyclodextrin	Solubilizer	Sisco Research labs Taloja 410208
6	Mannitol	Sweetening agent	Loba chemie Pvt Ltd, Mumbai, 400 005
7	Citric acid	Saliva stimulating agent	Loba chemie Pvt Ltd, Mumbai, 400 005

Methods

Pre-formulation Study

Identification of Drug

When the drug Prochlorperazine maleate was examined in the range 220 nm to 360 nm, the 0.001% w/v solution in ethanol (95 percent) containing 0.01percent v/v of strong ammonia Solution shows an absorption maximum at 255 nm.

Determination of Melting Point

Melting point of drug sample was determined by using melting point apparatus. Drug sample was taken and placed in a thin walled capillary tube; the tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary was placed in melting point apparatus and gradually temperature rises when drug sample was melted the melting point of sample powder was recorded.

Determination of solubility

Preparation of calibration curve of Prochlorperazine maleate

The calibration curves of Prochlorperazine maleate were prepared in distilled water and phosphate buffer pH 6.8 by using Shimadzu 1800 UV visible spectrophotometer. Accurately weighed 50 mg of Prochlorperazine maleate was transferred into a 50 ml volumetric flask and the volume was made up by using co solvent with distilled water to obtain a 1000µg/ml stock solution of Prochlorperazine maleate. From the stock solution 1 ml was taken and transferred into a 10 ml volumetric flask and rest of the volume was made up with solvent to obtain a 100µg/ml of solution from which further dilutions of 5, 10,15,20,25 µg/ml were prepared. Same procedure was followed for phosphate buffer pH 6.8 to prepare calibration curve.

Determination of solubility of Prochlorperazine maleate in various medium

The solubility of Prochlorperazine maleate in various medium was determined by equilibrium solubility method. In this method 5 ml of each solvent was taken into a separate vial and excess amount of Prochlorperazine maleate was added in to vials containing distilled water and phosphate buffer pH 6.8. The

vials put on magnetic stirrer at 37±20C for 12 hrs. The solutions were allowed to equilibrate for next 24 h. The solution was transferred into eppendroff tubes and centrifuged for 5 min. at 2000 rpm. The supernatants of each vial were filter through 0.45micron membrane filter, make appropriate dilutions and analysed by UV visible spectrophotometer (UV-1800 Shimadzu, japan) at 255 nm, the studies was performed in triplicate.

Formulation of MDFs of Prochlorperazine maleate

Oral dissolving films were prepared by solvent casting method as per the composition shown in table 1.In this method, the required quantity of water soluble polymer HPMC was dissolved in distilled water in a beaker (covered with aluminium foil) with continuous stirring on magnetic stirrer to make required percentage of polymer solution and then the weighed quantity of ingredients like Prochlorperazine maleate as drug and like as drug and beta-cyclodextrin solid dispersion, propylene glycol as plasticizer, citric acid as saliva stimulating agent, Mannitol as Sweetening agent was dissolved in distilled water in another beaker and then this mixture was added to the polymer solution. After continuous stirring for 2 hours the solution was left undisturbed for 12 – 16 hours to remove all the air bubbles. This polymeric – drug solution was then poured on to the mould, allowed to air dry , packed in aluminium foil and then stored in desiccators until use.

Drug-excipient interaction study

The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed and kept undisturbed at 40°C temperature for 14 days. After 14 days incompatibility (if any) was confirmed by TLC [6].

Table 2: Formulation of fast dissolving film using DOE software

Batch → / Ingredients ↓	F1	F2	F3	F4	F5	F6	F7	F8
Drug	79.45	79.45	79.45	79.45	79.45	79.45	79.45	79.45
Beta-CD	79.45	79.45	79.45	79.45	79.45	79.45	79.45	79.45
SSG	20	20	20	20	20	20	20	20
HPMC E15	100	250	100	100	250	250	100	250
Propylene glycol	0.2	0.15	0.15	0.2	0.15	0.2	0.15	0.2
Citric acid	20	20	20	20	20	20	20	20
Mannitol	20	20	20	20	20	20	20	20
Water	20	20	20	20	20	20	20	20

Characterization of fast dissolving oral film

Organoleptic Evaluation

Colour is a vital means of identification for many pharmaceutical products and is also important for consumer acceptance. The colour of the product must be uniform within a dosage form. Odour is also important for consumer acceptance of oral dosage forms and can provide an indication of the quality of oral films as the presence of an odour in a batch could indicate a stability problem. Taste is also an essential factor for consumer acceptance. Taste preference is subjective, and the control of taste in the production of oral soluble films is based on the presence or absence of a specified taste.

Weight of films

9 films were weighed on analytical balance and average weight was determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper

amount of excipients and API.

Film thickness

The thickness of the film was measured by micrometer screw gauge (Acculab) at three different places; averages of three values were calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is the folding endurance value. This indicates the brittleness of the film. The folding endurance of the strips was determined by repeatedly folding one film at the same place till it broke.

Drug Content Uniformity

Drug content was determined by dissolving the prepared mouth dissolving film (MDF) of prochlorperazine maleate drug in 100 ml of phosphate buffer pH 6.8 .The aliquot of 1ml was taken and diluted to 10ml with distilled water. Then solution was filtered through whatman filter paper and solution was analyzed on UV spectrophotometer at desired wavelength to calculate the amount of drug present in the film.

In- vitro disintegration test

The in vitro disintegration study of the fast dissolving film was carried out using 10 ml of water at 36^0C and it was placed in a petri-dish of 10 cm diameter. Each MDF was carefully kept at the centre of the petri-dish and the time required for the MDF to completely disintegrate was noted.

Surface pH

The film is placed on a Petri dish and moistened with 0.5 ml of distilled water. Kept for 30 sec. The pH is noted after bringing the electrode of the pH meter in contact with the surface of the film. The final result is determined by taking the mean of 3 readings.

Dryness test

For moisture uptake film along with anhydrous calcium chloride is placed in a desiccator for three days. After three days calculate the film.

The percent moisture loss is then measured as follows:

$$\text{Loss of moisture} = [(\text{initial weight} - \text{final weight}) \div \text{initial weight}] \times 100$$

RESULT AND DISCUSSION

Identification of drug

Using UV

The UV spectrum of Prochlorperazine maleate shows prominent absorbance maxima at wavelength 255 mm which is similar to the standard peaks therefore confirmed the identity of sample drug as Prochlorperazine maleate. Reported absorbance maxima were Prochlorperazine maleate were λmax at 255nm.

ISSN: 0975-8585

Using FTIR

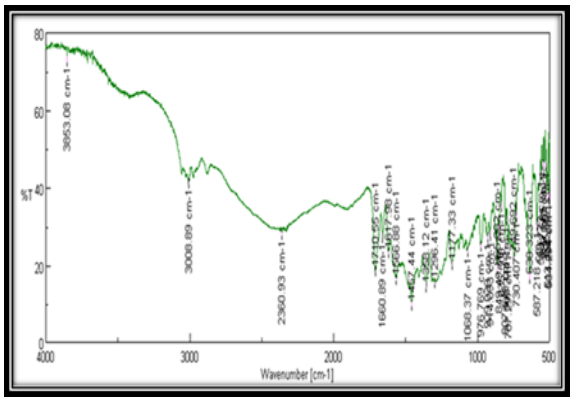


Fig. 2: FTIR spectra of Prochlorperazine

Functional group	Standard Frequency(cm^{-1})	Observed Frequency(cm^{-1})
O-H	3300-3700	3420
C-H	3000-3100	3056
C-H	2850-2960	2877
C=O	1620-1670	1617 & 1660
C-N	1000-1400	1096
C-Cl	550-850	709

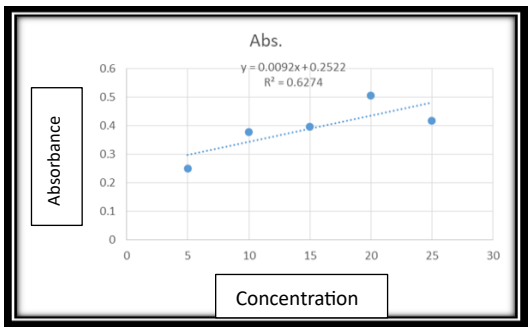
Table 3: Interpretation of FTIR

Preparation of calibration curves

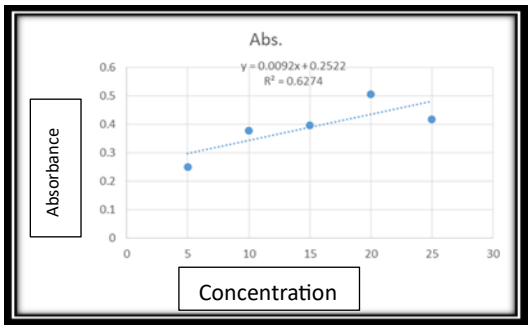
The calibration curves of Prochlorperazine maleate in various solvents e.g. Distilled water, 6.8 pH phosphate buffers and artificial saliva were prepared.

Absorbance data of Prochlorperazine maleate in distilled water for preparation of calibration curve, at 255nm

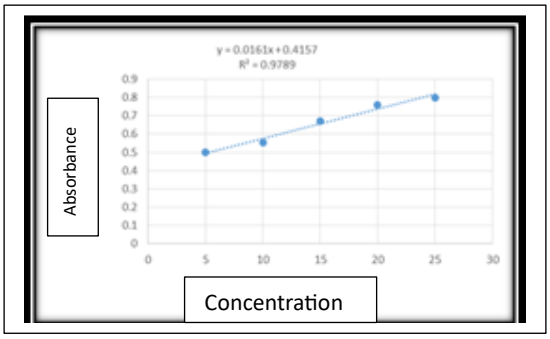
(A)



(B)



(C)



A) Calibration curve for Prochlorperazine Maleate in distilled water
B) Calibration curve for Prochlorperazine Maleate in phosphate buffer PH 6.8
C) Calibration curve for Prochlorperazine Maleate in artificial saliva

ISSN: 0975-8585

Determination of solubility of Prochlorperazine maleate in various medium

The solubility of Prochlorperazine maleate in various medium was studied and the results of study were shown in below table

S.No.	Solvent	Solubility (mg/ml) Mean±SD
1	Distilled water	0.0138±0.03
2	Phosphate buffer pH 6.8	1.152±0.00
3	Artificial Saliva	0.650±0.04

Drug-excipient interaction study

The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed and kept undisturbed at 40°C temperature for 14 days. After 14 days incompatibility (if any) was confirmed by TLC [6].

Sr. No.	Drug/ drug+ Excipient Ratio (1:1)	Physical appearance (initial)	Present Day (Rf)	Physical appearance (final)	After15 Days (Rf)	Inference
1	Drug (Prochlorperazine maleate)	White	0.42	White	0.42	No Change
2	Pure Drug + β Cyclodextrin	White	0.4	White	0.46	No Change
3	Pure Drug + HPMC	Light brown	0.48	Light brown	0.5	No Change
4	Pure Drug + Propylene glycol	White	0.42	White	0.44	No Change
5	Pure Drug + Mannitol	White	0.43	White	0.46	No Change
6	Pure Drug+ Citric acid	White	0.41	White	0.39	No Change
7	Pure Drug+ SSG	White	0.44	White	0.46	No Change

Table 4: Data of drug interaction study

Evaluation study of optimized batch of fast dissolving film

Parameter	Observations
Weight of film	33.3 ± 0.1mg
Thickness of film	0.1 ± 0.06 mm
Surface PH	6.9 ± 0.1
Folding Endurance	148 ± 1 folds
Moisture content	10 ± 1 %
Drug content uniformity	97.97 ± 0.01%
Disintegration test	23 ±1 sec

CONCLUSION

The results suggests a positive approach of the fast-dissolving films of prochlorperazine as alternative to conventional tablets for clinical use in the treatment vomiting with minimized side effects. The solvent casting method is simple procedure with minimum ingredients in cost effectiveness [9-12].

REFERENCES

[1] Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm 2013; 3(2):67–76.

[2] Dixit RP and SP Puthli. Oral strip technology: Overview and future potential. Journal of Controlled Release 2009; 139:94-107.

[3] Mandeep K, Rana A, Nimrata S. Fast Dissolving Films: An Innovative Drug Delivery System. Int J Pharma Res Allied Sci 2013;2:14-24.

[4] Dharmasthala S, Shabaraya AR, Andrade GS, Shriram RG, Hebbar S, et al. Fast Dissolving Oral Film of Piroxicam: Solubility Enhancement by forming an Inclusion Complex with β-cyclodextrin, Formulation and Evaluation. J Young Pharm 2019;11.

[5] Niese S, BreitkreutzJ, Quodbach J. Development of a dosing device for individualized dosing of orodispersible warfarin films. Int J Pharm 2019;561:314-323.

[6] Solanki A, Gupta N, Jain S. Formulation, development and evaluation of fast dissolving oral film of antipsychotic drug. J Drug Delivery Ther 2019;9:181-185.

[7] Radhakisan UR, Chavan V, Tribhuvan N. Mouth Dissolving Film And Their Patent: An Overview. Int Res J Pharm 2012; 3:39-42.

[8] Qin ZY, Jia XW, Liu Q, Kong BH, Wang H. Fast dissolving oral films for drug delivery prepared from chitosan/pullulan electro spinning nano fibers. Int J Biological Macromolecules 137:224-231.

[9] Montenegro-Nicolini M, Morales JOJ. Overview and future potential of buccalmucoadhesive films as drug delivery systems for biologics. AAPS Pharm Sci Tech 2017;18:3-14.

[10] Kumar RS, Yagnesh TNS. Oral dissolving films: an effective tool for fast therapeutic action. J Drug Delivery Ther 2019;9:492-500.

[11] Mahajan A, Chhabra N, Aggarwal G. Formulation And Characterization Of Fast Dissolving Buccal Films: A Review. Der Pharmacia Lettre 2011;3:152-165.

[12] Radhakisan UR, Chavan V, Tribhuvan N. Mouth Dissolving Film And Their Patent: An Overview. Int Res J Pharm 2012;3:39-42.