Available online on 15.11.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation and Evaluation of Mouth Dissolving Film of Prochlorperazine Maleate

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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 (film forming agent),Glycerol (plasticizer), Betacyclodextrin (solubilizing agent), Citric acid (saliva stimulating agent), Mannitol (sweetening agent). The formulation was optimized by two factors, three levels (3^2) was used for the formulation optimization of fast dissolving film of Prochlorperazine maleate and experimental trials are performed on all 9 formulation. In which the amount of HPMC, Glycerol were selected as independent variables (factor) varied at three different level: low (-1), medium (0), and high (+1) levels. The drug release and disintegration time used as dependent variables (response). and formulation was evaluated for weight variation, thickness, folding endurance, drug content, in- vitro disintegration, in vitro dissolution study and stability study. Based on results it was concluded that MDF (F3) showed enhanced bioavailability and faster onset of action.

Keywords: Prochlorperazine maleate, Mouth dissolving film, bioavailability

Article Info: Received 10 Sep 2019; Review Completed 21 Oct 2019; Accepted 28 Oct 2019; Available online 15 Nov 2019

Cite this article as:

Pawar R, Sharma R, Darwhekar G, Formulation and Evaluation of Mouth Dissolving Film of Proclorperazine Maleate, Journal of Drug Delivery and Therapeutics. 2019; 9(6):110-115 http://dx.doi.org/10.22270/jddt.v9i6.3679

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INTRODUCTION

The oral route is one of the most favoured routes of drug administration about 60% of all the formulations are solid dosage form. Tablet is the most preferred dosage form due to ease of transportation, as it is more suitable, cost effective, and ease of administration leads to high degree of patient compliance. However, peroral administration of drugs has demerits like liver degradation and enzymatic degradation within the gastrointestinal tract, that di sallow oral administration of various types of drugs especially peptides and proteins. Within the oral mucosal cavity, the buccal area seems to be one of the preferred routes for delivery of drug systemically. It provides benefits like prevention of hepatic first pass metabolism within the gastrointestinal tract, also provides improved enzyme flora for absorption of drugs [1].

Fast dissolving drug delivery system was developed in 1970s to beat swallowing problems linked with tablets and capsules for children and elderly sufferers. Oral mucosal drug delivery is vital route of drug administration. Several bioadhesive oral mucosal dosage forms have been invented, which includes mucoadhesive tablets, gels, ointments, patches, and the use of films for buccal delivery, also known as oral thin strips **[1].**

Buccal cavity is made up of stratified squamous epithelium i.e separated from the lamina propria and sub mucosa. The penetrability of buccal mucosa is 4-4,000 times larger than the skin, and is less than that of the intestine. Therefore, the buccal delivery is an outstanding platform for absorption of molecules with poor skin penetration[2]. The prime obstacle to permeability in oral mucosa is the outcome of intercellular objects generated from the 'membrane covering granules' which is present at the topmost 200 µm layer. These oral film strips have a shelf life of 2-3 years, based on the active pharmaceutical ingredient but are tremendously responsive to environment humidity **[2].**

MATERIAL AND METHODS

Materials:

Prochlorperazine maleate was obtained as Yarrow chem. pvt. Ltd. HPMC, Glycerol, Betacyclodextrin, Mannitol, Citric acid was obtained from loba chemicals.

Methods:

Preformulation 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 [3].

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[4].

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±2^{0}C 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 analyzed by UV visible spectrophotometer (UV-1800 Shimadzu, japan) at 255 nm, the studies was performed in triplicate[5].

Formulation of MDFs of Prochlorperazine maleate

Mouth 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 betacyclodextrin solid dispersion, glycerol 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 aluminum 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 1. Formulation optimization of Mouth dissolving film

BATCH NO.INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug+Betacyclodextrin solid dispersion	40	40	40	40	40	40	40	40	40
HPMC (mg)	500	500	500	350	350	350	250	250	250
Glycerol (ml)	0.05	0.1	0.075	0.05	0.1	0.075	0.05	0.1	0.075
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Mannitol (mg)	20	20	20	20	20	20	20	20	20
Distilled water (ml)	10	10	10	10	10	10	10	10	10

Evaluation of Mouth dissolving films:

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.[7]

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[8]

Folding endurance:

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place, either to break the specimen or to develop visible cracks). This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The folding endurance of the strips was determined by repeatedly folding one film at the same place till it broke. [8]

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.[9]

In- vitro disintegration test:

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

In- vitro Dissolution test:

The dissolution study of the Mouth dissolving film was determined in Electrolab Dissolution Apparatus type II following USP Paddle method. All tests were conducted in 900 ml of Phosphate buffer pH 6.8. The dissolution medium was maintained at 37±0.5^{0}C with paddle rotation speed at 50 rpm. Aliquot of 5ml was withdrawn at specific intervals and were immediately filtered through Whatman filter paper and analyzed spectrophotometrically. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally measured on UV spectrophotometer[8].

Stability Studies

Stability studies were conducted on prepared films to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40° C/65 % RH for 2 months. Samples were withdrawn at 0, 30, and 60 days.[11]

RESULT AND DISCUSSION

Identification of drug:

The UV spectrum of Prochlorperazine maleate shows prominent absorbance maxima at wavelength 255 nm (fig No. 1.1) 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.

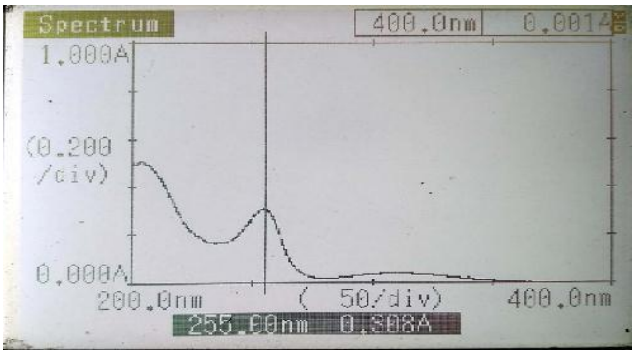
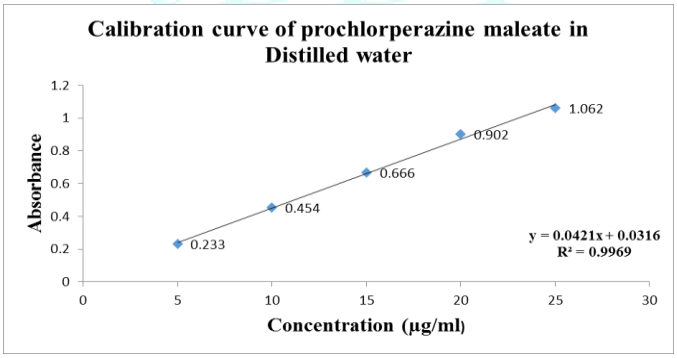


Fig.No.1.1 UV Spectrum of Prochlorperazine maleate

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

Table 2. Absorbance data of Prochlorperazine maleate in distilled water for preparation of calibration curve, at 255nm

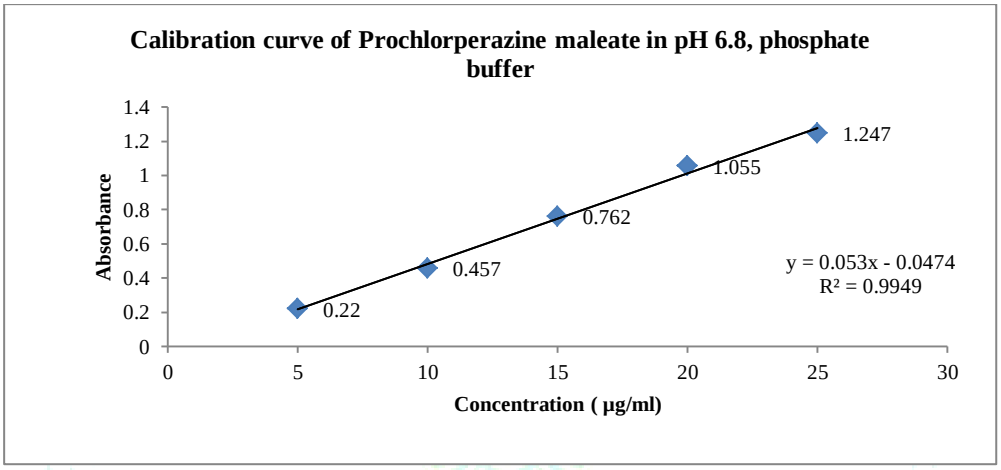
S. No.	Concentration (µg/ml)	Absorbance
1	5	0.233
2	10	0.454
3	15	0.666
4	20	0.902
5	25	1.062



Calibration curve of Prochlorperazine maleate in distilled water 255.0nm

Table 3. Absorbance data of Prochlorperazine maleate in phosphate buffer pH 6.8 for preparation of calibration curve, at 255 nm.

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.220
2	10	0.457
3	15	0.762
4	20	1.055
5	25	1.247



Calibration curve of Prochlorperazine maleate in pH 6.8 255.0nm

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

Table 4. Solubility data of Prochlorperazine maleate different mediums

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

Determination of solubility of Solid Dispersion:

The solubility of inclusion complex in phosphate buffer pH 6.8 and distill water was studied and the results of study were shown in below table:

Table 5. Solubility data of solid Dispersion:

S.No.	Solvent	Solubility (mg/ml) Mean±SD
1	Distilled water Drug:β-CD (1:3)	1.135±0.00
2	Phosphate buffer pH 6.8 Drug:β-CD (1:3)	13.195±0.87

Drug-excipient interaction study: The drug (Prochlorperazine maleate) was found to be compatible with various excipients which were selected for formulation of fast dissolving film. The compatibility was assessed by TLC and the retention factors of all ratios found similar.

Table 6: Data of drug-excipient interaction study:

S.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	0.49	White	0.49	No Change
2.	Pure Drug + β-Cyclodextrin	White	0.51	White	0.53	No Change
3.	Pure Drug + HPMC	Light brown	0.50	White	0.56	No Change
4.	Pure Drug + Glycerol	White	0.48	White	0.49	No Change
5.	Pure Drug + Mannitol	White	0.52	White	0.51	No Change
6.	Pure Drug+ Citric acid	White	0.54	White	0.56	No Change

Table 7 Evaluation data of Mouth dissolving film of prochlorperazine maleate

Formulation	Weight variation (mg) Mean±SD	Thickness (mm) Mean±SD	Folding endurance (Times)	Drug Content (%)	Disintegration Time (sec) Mean±SD
F1	48.9±0.02	0.1±0.07	142	85.1	36
F2	34.5±0.05	0.08±0.04	126	86.6	30
F3	29.8±0.04	0.09±0.02	151	97.4	18
F4	31±0.06	0.07±0.08	124	86.6	20
F5	39±0.04	0.09±0.4	141	93	31
F6	49±0.09	0.1±0.09	130	92.2	35
F7	34±0.08	0.09±0.06	137	92.3	36
F8	47.8±0.05	0.08±0.07	145	87.7	32
F9	35±0.07	0.07±0.05	140	86.4	35

Stability studies

The result of stability study indicated that the drug product falls well within the proposed stability specification. The data showed that there is no significant physical or chemical change indicating that the formulation would maintain its efficacy and quality throughout its proposed shelf life.

CONCLUSION

In the present research work an attempt has been made to optimized, formulate and evaluate Mouth dissolving film of Prochlorperazine maleate. Prochlorperazine maleate is a antiemetic drug belongs to BCS class-II (Low Solubility and high permeability). It has poor bioavailability and low solubility. In the present work solubility and bioavailability of drug was enhanced using inclusion complex. The inclusion complex of Drug: β-cyclodextrin was prepared in different ratio by physical mixture method. The solvent casting method was used to formulate and evaluate fast dissolving film of Prochlorperazine maleate. Addition of Drug: β-cyclodextrin inclusion complex leads to improve the dissolution characteristics and solubility of drug at optimum concentration (1:3). So, considering the above results it was found that the formulation F3was found to be optimized formulation from the data obtained. It is observed from the formulation F3 which shown disintegration time 18 sec. and percentage cumulative drug release shown 96.39% within 180 second. Thus, it can be concluded that the drug given in the form of fast dissolving films should be advantageous for patients suffering from nausea and vomiting, providing better patient compliance and an effective mode of treatment.

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