

Development and Evaluation of Fast Dissolving Film for Oro-Buccal Drug Delivery of Chlorpromazine

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ABSTRACT

Objective: Objective was designed to prepare, develop and evaluate fast dissolving films (FDFs) for oro-buccal drug delivery of chlorpromazine. **Background:** The drug delivery through oro-buccal mucosa is very interesting one but it partially lacked oro-buccal delivery products in the market. **Methods:** FDFs of chlorpromazine were prepared by solvent casting method using polymers PVA, HPMCE-5, HPMCE-15 and were evaluated for film specific parameters. FDFs were also evaluated for dissolution and percentage drug release by *in vitro* and *ex vivo* dissolution or drug permeation study. **Results:** The prepared films DPF1, DHF2, DHF3, DHPF4 and DHPF5 were of smooth surface without bubbles and cracks; flexible and non-sticky; uniform in weight without any significant weight variation; around to neutral surface pH; unchanged folding endurance; 84-95 %mg drug content variation. Thickness of DPF1 was less compared to DHF2, DHF3, DHPF4 and DHPF5. DPF1 showed excellent elasticity and undergone disintegration in less time. Chlorpromazine was rapidly released *in vitro* from all formulations and release was found to be maximum 97.2% over a period of 150s in DPF1. Chlorpromazine was significantly more rapidly released *ex vivo* from DPF1 and release was found to be 85.10% over a period of 150s. **Conclusion:** The prepared FDFs of chlorpromazine were in accordance to the standard range of film specific parameters and comply it. FDF of chlorpromazine prepared with the polymer PVA is better than other prepared films with other polymers for oro-buccal drug delivery of chlorpromazine in buccal cavity for the treatment of either psychosis or emesis.

Key Words: Chlorpromazine, Fast dissolving film, Oro-buccal drug delivery, *in vitro*, *ex vivo*.

INTRODUCTION

The oral solid dosage form accounting about 60% of all the dosage forms faces many problems which can be overcome by the development of other dosage forms such as fast dissolving oral films (FDOFs) devoid of such problems.¹ The concept of fast dissolving drug delivery system emerged from the desire to provide patient with a conventional mean of taking their medication.² It emerged out as a new drug delivery system as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms and that provides a very convenient means of taking

medications and supplements.³ FDOFs are thin films with an area of 5-20 cm² containing an active pharmaceutical ingredient.⁴ Buccal cavity is an attractive route of administration for systemic drug delivery of FDOFs among the various routes with their higher bio-availability, quick action and most patient compliance due to high blood flow and permeability of oral mucosa.³ It is useful in patients such as paediatric-geriatrics with swallowing difficulties, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful where local action is desired such as local anaesthetic for

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toothaches, oral ulcers, cold sores or teething.⁵ It remains as a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application, rapidly disintegrates and dissolves to rapidly release the medication for oromucosal absorption.⁶ It also has an established shelf-life of 2-3 years depending on the active pharmaceutical ingredients.⁷ It is the most advanced form of solid oral dosage form due to their flexibility plus comfort and improves the efficacy of APIs by getting dissolved within few sec in the oral cavity after coming in contact with saliva without chewing.^{8,9} Some suitable drugs incorporated in FDOFs are selective serotonin reuptake inhibitors (Fluoxetine, Sertraline), Anti-emetics (Ondansetron, Granisetron), 5HT₃ antagonists (Alosetron, Ondansetron, Granisetron, Palonosetron), Anti-epileptics (Carbamazepine, Clonazepam, Phenyloin), Anti-migrains (Almotriptan, Zolmitriptan), Dopamine D1 and D2 antagonists (Bromperidol, Domperidone).¹⁰

Chlorpromazine (CPZ) is an antipsychotic-antiemetic indicated for the treatment of schizophrenia. It also exerts sedative and antiemetic activity. It is in the typical antipsychotic class. Its mechanism of action is believed to be related to its ability as a dopamine antagonist. It also has antiserotonergic and antihistaminergic properties.¹¹ Its bioavailability is 10-80%, t_{max} 1-4h (*p.a.*) and 6-24 h (*i.m.*), protein binding 90-99%; V_d 10-35 L/kg and $t_{1/2}$ 30 ± 7 h.¹² The FDOFs of chlorpromazine was not reported in literature. Hence, the present study was designed to develop and evaluate fast dissolving oral film for oro-buccal drug delivery of chlorpromazine.

MATERIALS AND METHODS

Chemicals and equipment's used in the experiments

All the chemicals used were of analytical grade and purchased from various manufacturers. Chlorpromazine (Healthy Life pharma Pvt.Ltd.), Hydroxy Propyl Methyl Cellulose Ethocel-5(HPMCE-5, Balaji Drugs Pvt. Ltd.), Hydroxy Propyl Methyl Cellulose Ethocel-15 (HPMCE-15, Balaji Drugs Pvt. Ltd.), Poly Vinyl Alcohol (PVA, SD fine chem Ltd.), Propylene Glycol (Fisher Scientific), Glycerol (Fisher Scientific), Citric Acid Extrapure (SD fine chem Ltd.), Sorbitol (SD fine chem Ltd.), Mannitol, 70% liquid (Fisher Scientific), Ethanol (ChangshuY-angyuan Chemical, China), Sodium Chloride (Fisher Scientific), Disodium Hydrogen phosphate, Anhydrous Purified (SD fine chem Ltd.), Potassium dihydrogen Phosphate (Merck Specialities Pvt. Ltd.), Phosphoric acid (Fisher Scientific), Colours- Apple green, Lemon

yellow and Orange red (Shreetex Navrang), Digital balance (Shimadzu), Hot plate magnetic stirrer (Decibel), Micropipette (100-1000 μ m, Microlit), Dissolution test apparatus USP I (Esico International), UV-visible Spectrophotometer (UV-1700 Shimadzu), pH meter (Cyberlab), Digital Vernier caliper (Aerospace), FTIR (Shimadzu-FTIR 8400)

Preparation of fast dissolving films of chlorpromazine

Fast dissolving films were prepared using some of the best film forming polymers polyvinyl alcohol (PVA), hydroxypropyl methylcellulose ethocel-5 (HPMCE-5) and hydroxypropyl methylcellulose ethocel-15 (HPMCE-15) either alone or in combination. For the desired elasticity of the films glycerol and propylene glycol were used as plasticizers. Another major ingredient used was citric acid, which will stimulate the secretion of saliva when the film will be placed in the buccal cavity. Mannitol was used as a sweetener and some artificial colours were added to enhance its organoleptic property. The films of different formulations were prepared using solvent casting method in which firstly the polymer was dissolved in sufficient quantity of distilled water on a hot plate magnetic stirrer. Then, the remaining ingredients (plasticizer, saliva stimulator and sweetener) were added in the polymer solution. Another solution was prepared containing the drug dissolved in minimum quantity of the suitable solvent i.e., ethanol. Then, both polymer solution and the drug solution were mixed thoroughly. After that sufficient quantity of colour was added drop by drop to the above solution. Then solution was kept aside for a few min for the removal of bubbles. After the bubbles were removed the solution was casted on plastic petri plates of area 41.83 cm². The plates were kept overnight at room temperature for drying. Then the dried films were scraped out carefully.¹³ Different formulations were prepared as per given Tables (Table 1 and Table 2).

Preparation of simulated saliva fluid (phosphate buffer of pH 6.8) and chlorpromazine standard plot

Artificial simulated saliva fluid or phosphate buffer of pH 6.8 was prepared by adding 2.38 g of disodium hydrogen phosphate, 0.19 g of potassium dihydrogen phosphate and 8 g of sodium chloride in a 1000 ml of volumetric flask. These ingredients were dissolved in sufficient quantity of distilled water. After the ingredients were dissolved volume was made up with distilled water up to 1000 ml and pH was adjusted to 6.8 using phosphoric acid.¹⁴ The standard plot of chlorpromazine was prepared in ethanol. 10 mg of chlorpromazine was weighed accurately and dissolved in 10 ml of phosphate

Table 1: Preparation of placebo fast dissolving films with PVA, HPMCE-15, and HPMCE-5.

Films Ingredients	PF1	PF2	HF3	HF4	HF5	HF6	HPF7	HPF8
PVA	0.5 g	1 g	-	-	-	-	-	-
HPMCE-15	-	-	0.5 g	1 g	-	-	-	-
HPMCE-5	-	-	-	-	0.5 g	1 g	-	-
HPMCE-15+PVA	-	-	-	-	-	-	0.5+0.5g	-
HPMCE-5+PVA	-	-	-	-	-	-	-	0.5+0.5g
Propylene glycol	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Citric acid	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Mannitol	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g
Distilled water	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml

Table 2: Preparation of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5.

Films Ingredients	DPF1	DHF2	DHF3	DHPF4	DHPF5
Chlorpromazine	10 mg	10 mg	10 mg	10 mg	10 mg
PVA	0.5 g	-	-	-	-
HPMCE-15	-	1 g	-	-	-
HPMCE-5	-	-	1 g	-	-
HPMCE-15+PVA (1:1)	-	-	-	0.5+0.5 g	-
HPMCE-5+PVA (1:1)	-	-	-	-	0.5+0.5 g
Ethanol	2 ml	2 ml	2 ml	2 ml	2 ml
Propylene glycol	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml
Citric acid	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Mannitol	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g
Distilled water	15 ml	15 ml	15 ml	15 ml	15 ml
Colour	-	qs	qs	-	-

Where, DPF1 denotes to drug loaded film of PVA; DHF2 to drug loaded film of HPMCE-15; DHF3 to drug loaded film of HPMCE-5; DHPF4 to drug loaded film of HPMCE-15+PVA; and DHPF5 to drug loaded film of HPMCE-5+PVA.

buffer (primary stock of 1000 µg/ml capacity). Secondary stock of 100 µg/ml was prepared by taking 1 ml of primary stock and adding to it 10 ml of phosphate buffer. Appropriate dilutions were made from the secondary stock with buffer to obtain test solutions ranging from 0.5 µg/ml to 8.5 µg/ml. The absorbance of the drug in the buffer was then measured by UV-visible spectrophotometer at the wavelength (λ_{max}) of the drug against the respective blank. UV-visible spectrophotometer was allowed to scan the solution by setting scanning range at 400-200 nm and wavelength (λ_{max}) of the drug against the respective blank was determined.

Evaluation of the prepared fast dissolving films of chlorpromazine

Organoleptic evaluation of prepared fast dissolving films

The both sides of the films were checked for outer surface. The colour, odour and taste are vital means of identification for many pharmaceutical products and are

also important for consumer acceptance. Thus, these were checked.¹⁵

Weight variation evaluation of prepared fast dissolving films

Weight variations of prepared fast dissolving films were determined by cutting three pieces of 2×2 cm² dimension from every formulated films and weighing them individually on digital balance. The average weight was calculated.¹⁶

Thickness test of prepared fast dissolving films

Three films of 2×2 cm² dimension from each formulated films were taken and their thickness was determined by digital Vernier calliper at three different positions. Mean thickness and standard deviation were calculated.¹⁶

Folding endurance test of prepared fast dissolving films

Three films of 2×2 cm² dimension from each formulated film were cut and subjected to this test by folding

the film at the same place repeatedly 100 times until visible cracks were seen manually. Mean folding endurance, standard deviations were calculated if number of folds were less than 100.¹⁷

Measurement of surface pH of prepared fast dissolving films

The film to be tested was cut into 2×2 cm² dimension, placed in a petri dish and was moistened with 2 ml of phosphate buffer solution of pH 6.8 and kept for 30 sec. The pH of the sol was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations were calculated and reported.¹⁸

Evaluation of percentage elongation of prepared fast dissolving films

The selected films were cut into 2×2 cm² dimension and were pulled by two clamps, placed over a scale, from both the sides till it cracked. The elongation was determined by noting the increase in length of the film.¹⁹ The percentage elongation was calculated by using formula [% Elongation = (increase in length / original length) × 100].

Disintegration test of prepared fast dissolving films

The disintegration time is the time when a film starts to break or disintegrate. Every formulated fast dissolving films was cut into 2×2 cm² dimension and its *in vitro* disintegration time was determined visually in a beaker of 20 ml containing distilled water with swirling every 10 sec. The mean of three readings were determined.²⁰

Drug content uniformity test of prepared fast dissolving films

Limit of content uniformity should be 85-115%.²¹ The test for the content uniformity was carried out taking a sample film of 2×2 cm² dimension which was placed in a beaker containing 50 ml of phosphate buffer, pH 6.8. The contents were stirred to dissolve the film which was then filtered. The absorbance of the solution was measured against the corresponding blank solution at particular wavelength using a standard assay method described for the particular active pharmaceutical ingredient (API) mentioned in any of the standard pharmacopoeia. These absorbance values were substituted in the equation of the standard curve of drug ($y = mx + c$) and the value of concentration of drug (x) was determined for each absorbance value. This concentration obtained was in µg/ml so it was converted to mg/50ml and then the percentage drug content was calculated by using the formula [% drug content = {practical yield (x in 50 ml) / theoretical yield (drug incorporated)} × 100.

Drug-polymer compatibility study

Study to check the drug-polymer compatibility of their physical mixture in formulation of fast dissolving films of chlorpromazine, it was confirmed by taking FTIR spectrum of drug, polymer and physical mixture of drug-polymer like Drug+PVA, Drug+HPMCE-5 and Drug+HPMCE-15, Drug+PVA+HPMCE-15 and Drug+PVA+HPMCE-5. This study can also be termed as drug-polymer interaction.²⁰

Dissolution test and percentage drug release of prepared fast dissolving films

***In vitro* dissolution test and percentage drug release of prepared fast dissolving films**

The dissolution time is the time when the film completely dissolves. The *in vitro* dissolution test was carried out in a USP-I rotating basket dissolution apparatus. Drug loaded films were cut into 2 cm diameter and placed in the basket of the disso-apparatus. The volume of dissolution medium (simulated saliva fluid *i.e.*, phosphate buffer pH 6.8) was 900 ml and was maintained at the temperature of 37±4°C and the basket was rotated at 25 revolutions per min (rpm). Samples of 10 ml were withdrawn at predetermined time intervals and replaced with 10 ml of fresh medium. The withdrawn solution was filtered using Whatman filter paper. The absorbance was recorded at the wavelength of 260 nm against blank using UV-visible spectrophotometer. For percentage drug release, the absorbance values obtained by performing the dissolution test were substituted in the equation of the standard curve of drug ($y = mx + c$) and the value of concentration of drug (x) was determined for each absorbance value. This concentration obtained was in µg/ml so it was converted to mg/900ml and then the percentage drug release was calculated by using the formula [% Drug release = (x in 900 ml buffer / drug incorporated) × 100].²²

***Ex vivo* dissolution test and percentage drug release of prepared fast dissolving films**

***Ex vivo* permeation studies through goat oral mucosa was carried out using the modified Franz's diffusion cell of internal diameter of 2.5 cm.** The buccal mucosal membrane was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized to remove soluble components and then, mounted between donor and receptor compartments. The receptor compartments were filled with 200 ml of isotonic phosphate buffer of pH 6.8 which was maintained at 37±4°C and hydrodynamic was maintained by stirring with a

magnetic bead at 50 rpm. One film of 2 cm diameter previously moistened with a few drops of simulated saliva was kept in the compartment. The donor compartment was filled with 1 ml of phosphate buffer of pH 6.8. Sample was withdrawn at suitable interval replacing the same amount with fresh medium. The percentage of drug permeated was determined by measuring the absorbance in a UV-visible spectrophotometer using the formula [% Drug release = $(x \text{ in } 900 \text{ ml buffer} / \text{drug incorporated}) \times 100$].²³

Statistical analysis

All the results were expressed as mean \pm Standard deviation (S.D.). The values obtained in dissolution test and percentage drug release were subjected to one way analysis of variance (ANOVA). The variance in a set of data had been estimated by Dunnett's test. The values of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Fast dissolving films of chlorpromazine were prepared using polymers PVA, HPMCE-5 and HPMCE-15 either alone or in combination (Figure 1).

The UV spectrum of chlorpromazine solution in ethanol was established using UV-visible spectrophotometer by setting scanning range at 400-200 nm and the wavelength maximum (λ_{max}) was found to be 260 nm (Figure 2A). The standard plot prepared with the absorbance of the different dilutions of chlorpromazine in ethanol measured at the wavelength maximum (λ_{max}) 260 nm showed an equation as $y = 0.093x - 0.008$ and R^2 value was 0.999 (Figure 2B).

The films were of smooth surface from both the sides with no bubbles and cracks. Colourless films were transparent. The colour of the product was uniform within the dosage form. The films were flexible and non-sticky. The films tasted slightly sour due to the presence of citric acid.

The average weights of different pieces of formulated films are shown in Table 3. From the results, it was observed that mostly all the batches were uniform in weight with no significant difference in the weight of the individual formulation from the average value.

Mean thickness and standard deviation of different pieces of formulated films are shown in Table 4. Thickness of films with PVA was less as compared to the films with other polymers HPMCE-15 or HPMCE-5. The standard deviation values were low indicating uniformity in thickness.

Folding endurance test measures the ability of the film to withstand rupture. The folding endurance is

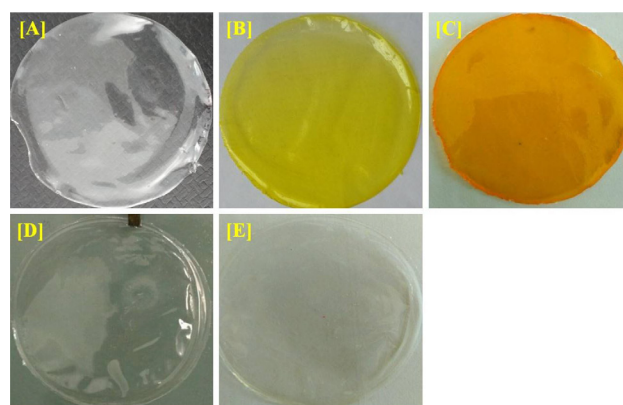


Figure 1: Formulated fast dissolving films of chlorpromazine: [A]. Fast dissolving film of chlorpromazine with PVA (DPF1), [B]. Fast dissolving film of chlorpromazine with HPMCE-15 (DHF2), [C]. Fast dissolving film of chlorpromazine with HPMCE-5 (DHF3), [D]. Fast dissolving film of chlorpromazine with HPMCE-15 and PVA (DHPF4), and [E]. Fast dissolving film of chlorpromazine with HPMCE-5 and PVA (DHPF5).

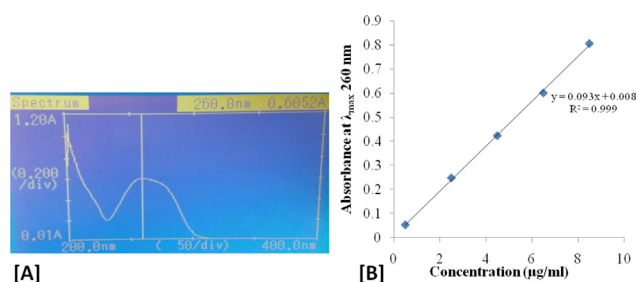


Figure 2: [A]. UV spectrum of chlorpromazine solution in ethanol showing λ_{max} at 260 nm, [B]. Standard plot of chlorpromazine at λ_{max} 260 nm.

expressed as the number of folds (number of times a film is folded at the same plane) required to break the film or to develop visible cracks. This gives an indication of brittleness of the film. The results indicated that the endurance increases on increasing polymer content in the film. Most of the films remained unchanged even after 100 folds. So the results in Table 4 indicated that the films were not brittle.

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. Since the surface pH of the films was found to be around to the neutral pH, as shown in Table 3, there will not be any kind of irritation to the mucosal lining of the oral cavity.

It was observed from Table 4 that the film with polymer PVA showed excellent elasticity, while the films of HPMC possessed less elasticity property. It was observed that PVA film showed excellent elasticity and HPMC film showed minimum elasticity.

In disintegration test, most of the films were found to disintegrate within 30 sec It was observed from Table 4

Table 3: Evaluation of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5 for surface pH, weight variation and percentage drug content.

Formulations	Surface pH	Weight variation (mg)	Percentage drug content
DPF1	6.8±0.54	31.5±1.6	95.3±3.12
DHF2	6.4±0.45	40.7±3.8	91.8±4.12
DHF3	6.3±0.55	25.0±0.68	83.64±3.83
DHPF4	6.4±0.51	55.8±4.2	83.7±4.21
DHPF5	6.5±0.52	65.7±4.5	93.3±5.98

All the values were expressed as mean±SD where the experiments were performed in triplicate (n=3). Where, DPF1 denotes to drug loaded film of PVA; DHF2 to drug loaded film of HPMCE-15; DHF3 to drug loaded film of HPMCE-5; DHPF4 to drug loaded film of HPMCE-15+PVA; and DHPF5 to drug loaded film of HPMCE-5+PVA.

Table 4: Evaluation of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5 for thickness, folding endurance, percentage elongation and disintegration time.

Formulations	Parameters			
	Thickness (mm)	Folding endurance (no. of folds)	Percentage Elongation	Disintegration time (sec)
DPF1	0.1100±0.005	>100	91.3±5.5	15.0±1.0
DHF2	0.1400±0.007	>100	23.5±2.5	25.5±1.5
DHF3	0.1300±0.001	>100	11±0.9	45.3±3.0
DHPF4	0.1200±0.009	>100	45.66±2.47	23.30±1.30
DHPF5	0.1200±0.002	>100	15±0.95	33.3±1.1

All the values were expressed as mean±SD where the experiments were performed in triplicate (n=3). Where, DPF1 denotes to drug loaded film of PVA; DHF2 to drug loaded film of HPMCE-15; DHF3 to drug loaded film of HPMCE-5; DHPF4 to drug loaded film of HPMCE-15+PVA; and DHPF5 to drug loaded film of HPMCE-5+PVA.

that films containing PVA were undergoing disintegration in less time and the HPMCE-5 films were taking more time to disintegrate.

The result showed good uniformity of drug content throughout the films without any significant variation as shown in Table 3. Drug content was found to vary from 84-95% mg in films. Formulation DPF1 having PVA was found to be having maximum percentage drug content.

The interpretations of FTIR spectra of chlorpromazine and different physical mixtures of drug-polymer like chlorpromazine plus PVA, chlorpromazine plus HPMCE-5 and chlorpromazine plus HPMCE-15 are shown in Figure 3.

The principal absorption peaks of chlorpromazine (Figure 3 A) were observed at 3401, 3019 cm⁻¹ (CH-stretching), 2401 cm⁻¹ (H₃C-NH stretching), 1508.43, 1599.85, 1670.05 cm⁻¹ (phenyl ring), 1385.36, 1508.43 cm⁻¹ (C-H deformation) and 668.88, 756.59, 1113.87 cm⁻¹ (aromatic C-H Bending). HPMCE-5 and HPMCE-15 (Figure 3 B, D, E) showed their absorption peaks at 3500-3400 cm⁻¹ (OH stretching), 2990 cm⁻¹ (methyl and hydroxypropyl group stretching), 2550-2500 cm⁻¹ (OH

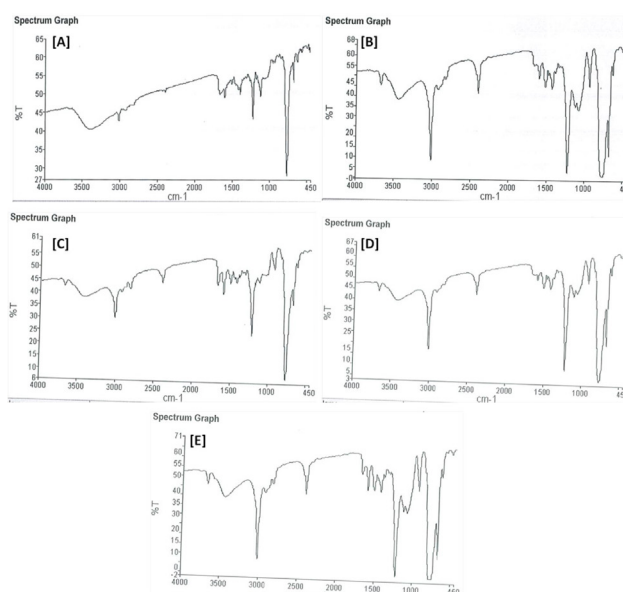


Figure 3: FTIR spectra of: [A]. pure chlorpromazine, [B]. A mixture of chlorpromazine with HPMCE-5, [C]. A mixture of chlorpromazine with PVA, [D]. A mixture of chlorpromazine with HPMCE-15, [E]. A mixture of chlorpromazine with PVA and HPMCE-15.

stretching), 1300-1250 cm⁻¹ epoxide (cyclic C-O-C), 1100-1000 cm⁻¹ (stretching vibrations of C-O-C group), 1000-950 cm⁻¹ pyranose ring. Characteristic peaks of

Table 5: *In vitro* percentage drug release of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5.

Time (sec)	Percentage Drug Release				
	DPF1	DHF2	DHF3	DHPF4	DHPF5
0	0	0	0	0	0
15	2.39±0.13	2.0±0.42	3.7±0.33	1.68±0.32	1.95±0.56
30	14.2±0.81	2.3±0.52	18.6±0.46	6.5±0.35	5.76±0.53
45	26.0±1.21	14.3±0.95	26.1±0.48	14.2±0.43	14.8±0.46
60	37.3±1.22	25.6±0.86	39.6±0.45	25.2±0.42	25.9±0.46
75	49.1±1.87	38.4±0.87	52.8±0.45	29.8±0.43	37.6±0.43
90	60.9±1.82	49.3±0.77	60.7±1.7	45.9±1.2	40.0±1.34
105	72.3±1.84	60.9±0.4	71.7±1.4	52.5±1.42	50.0±1.41
120	84.1±2.1	72.3±0.2	83.9±2.03	70.3±2.24	61.7±2.41
135	94.5±2.24	84.3±0.23	87.2±2.02	83.9±2.04	74.2±2.11
150	97.2±2.24	95.8±0.33	95.4±2.12	85.7±2.42	84.3±2.57

All the values were expressed as mean±SD where the experiments were performed in triplicate (n=3). Where, DPF₁ denotes to drug loaded film of PVA; DHF₂ to drug loaded film of HPMCE-15; DHF₃ to drug loaded film of HPMCE-5; DHPF₄ to drug loaded film of HPMCE-15+PVA; and DHPF₅ to drug loaded film of HPMCE-5+PVA.

PVA (Figure 3 C, E) were observed at 3600 cm⁻¹ (OH stretching), 3030-308 cm⁻¹ medium bands (CH stretching, characteristics of vinyl group), 1674 cm⁻¹ (C-C stretching), 1475 cm⁻¹ (CH₂ group stretching), 1330 cm⁻¹ (OH bending), 1145 cm⁻¹ (CO stretching vibration), 986 cm⁻¹ (CH bending, vinyl vibrations). Same peaks of absorption bands of chlorpromazine were present in all the spectra without significant shifting in the spectra of physical mixtures containing drug and polymer suggested no chemical interaction between the drug and polymers.

According to specifications led down by Harika *et al.*, 2013, the standard range of percent elongation should be 35-55%, thickness 0.1±0.03 mm, folding endurance >100 folds, average weight 18±2 mg per film, content uniformity by assay method 85-115% of average (of 10 units) and disintegration time 180 sec (in 5 ml water at room temperature). The present prepared fast dissolving films of chlorpromazine were evaluated for the organoleptic properties, weight variation, thickness test, folding endurance test, surface pH, percentage elongation, disintegration test, drug content uniformity test. All of the parameters evaluated were in accordance to the standard range led down by Harika *et al.*, 2013.²⁴ Thus, the prepared fast dissolving films of chlorpromazine is in accordance to the standard rule of fast dissolving film and comply all the evaluation parameters of fast dissolving films.

The *in vitro* dissolution profile of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5 and percentage drug release at different time interval were recorded up to 150 sec in Table 5.

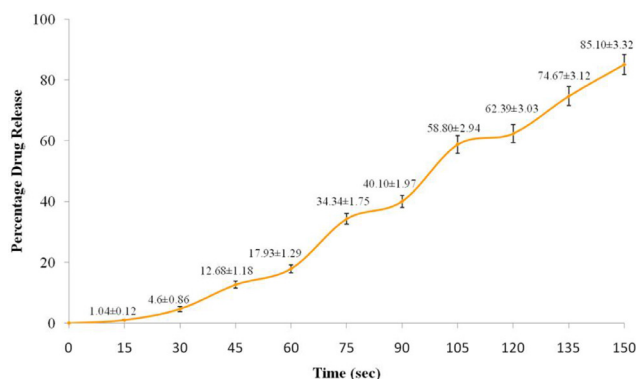


Figure 4: Ex vivo percentage drug release of chlorpromazine from its fast dissolving film (DPF1) with PVA at different time intervals. All the values were expressed as mean±SD where the experiments were performed in triplicate (n=3). Where, DPF₁ denotes to drug loaded film of PVA.

It showed that the drug chlorpromazine get rapidly released from all formulations. Maximum *in vitro* release was found to be 97.2% over a period of 150 secs in batch DPF1 while minimum *in vitro* release was found to be 84.3% in batch DHPF5.

According to specifications led down by Harika *et al.*, 2013, the *in vitro* drug release should not be less than 80% in 15 min in 500 ml of buffer of pH 6.8.²⁴ The *in vitro* dissolution profile of drug loaded fast dissolving films of chlorpromazine with PVA, HPMCE-15, and HPMCE-5 also led down that it is in accordance to the specification led down by Harika *et al.*, 2013.²⁴

The *ex vivo* dissolution profile of drug loaded fast dissolving films of chlorpromazine with PVA was recorded and percentage drug release at different time interval were recorded. A graph was plotted between *ex vivo* percent drug release and time which is shown in Figure 4.

It showed that the drug chlorpromazine get rapidly released *ex vivo* from the formulation DPF1. Maximum *ex vivo* release was found to be 85.10% over a period of 150 sec.

CONCLUSION

The prepared fast dissolving films of chlorpromazine i.e., DPF1, DHF2, DHF3, DHPF4, and DHPF5 (chlorpromazine with either PVA or HPMCE-15 or HPMCE-5 or combination polymer) were in accordance to the standard range of film specific parameters and comply it. DPF1 (film of chlorpromazine with the polymer PVA) is better fast dissolving film of chlorpromazine where the drug chlorpromazine was rapidly released *ex vivo* suggesting that the fast dissolving film of chlorpromazine prepared with the polymer PVA is better than other prepared films with other polymers or their combination for oro-buccal drug delivery of chlorpromazine in buccal cavity for the treatment of either psychosis or emesis.

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CONFLICT OF INTERSET

There is no conflict of interest.

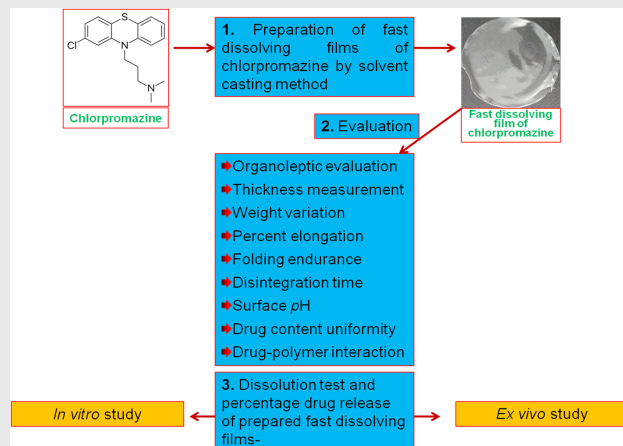
ABBREVIATIONS USED

FDF: Fast Dissolving Films; **FDOFs:** Fast Dissolving Oral Films; **CPZ:** Chlorpromazine; **HPMCE:** 5-Hydroxy Propyl Methyl Cellulose Ethocel-5; **HPMCE-15:** Hydroxy Propyl Methyl Cellulose Ethocel-15; **PVA:** Poly Vinyl Alcohol.

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PICTORIAL ABSTRACT



SUMMARY

- FDFs of chlorpromazine were prepared by solvent casting method using polymers PVA, HPMCE-5, HPMCE-15 and were evaluated for film specific parameters. FDFs were also evaluated for dissolution and percentage drug release by *in vitro* and *ex vivo* dissolution or drug permeation study.
- FDF of chlorpromazine prepared with the polymer PVA is better than other prepared films with other polymers for oro-buccal drug delivery of chlorpromazine in buccal cavity for the treatment of either psychosis or emesis.

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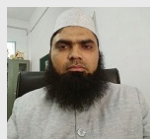
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