

## Formulation Development and Evaluation of Orodispersible films of Chlorpheniramine Maleate

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### ABSTRACT

This study aimed to formulate Orodispersible films (ODFs) of Chlorpheniramine maleate (CPM) and develop a dosage form with rapid onset of action and ease of administration, circumventing the need to swallow or use water. The solvent casting method was employed to prepare three optimized films (F1, F2, and F3) containing varying proportions of sodium alginate and pectin as polymers, polyethylene glycol (PEG-400) and glycerol as plasticizers, sodium starch glycolate as a super disintegrant, and sodium benzoate as a preservative. The formulated ODFs were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, determination of moisture content, and mouth dissolving time which gave satisfactory results. The formulations were also subjected to disintegration test and in-vitro drug release tests. All three formulations released greater than 65% of the drug within 6 minutes but F3 displayed superior performance by releasing almost half the amount of the drug within 1 minute and  $82.27 \pm 11\%$  drug within 6 minutes. The films of chlorpheniramine maleate containing natural polymer showed folding endurance ( $300.00 \pm 1.00$  No. of folds), in-vitro disintegration time ( $57 \pm 0.57$  sec.), surface pH ( $5.5 \pm 0.10$  pH), thickness ( $0.07 \pm 0.01$  mm) and percentage content uniformity ( $99.53 \pm 0.37\%$ ).

**Keywords:** Orodispersible film, chlorpheniramine maleate, sodium alginate, pectin, natural polymers, solvent casting.

### I. INTRODUCTION

The oral route of drug administration is commonly preferred due to its ease of use, affordability, non-invasive nature, and superior patient adherence. While conventional oral dosage forms offer many advantages as listed above, they have their limitations. Solid dosage forms like tablets and capsules pose swallowing and

administration challenges particularly in geriatric, paediatric, or uncooperative patients, and patients with dysphagia<sup>1,2</sup>. Although liquid oral forms can address these challenges, they have drawbacks like imprecise dosing and the requirement for shaking before administration<sup>1,3</sup>. Orodispersible dosage forms such as orodispersible tablets and films represent an innovative, patient-oriented solution to address these limitations<sup>4</sup>. However, the orodispersible tablets (ODTs) being fragile and brittle are prone to damage during transport<sup>5</sup>. Along with this, dysphagic patients may still be apprehensive about choking even though the tablet disintegrates in the mouth within minutes<sup>1,5</sup>. Therefore, Orodispersible films (ODFs) serve as a practical solution tailored to the needs of this patient population.

ODFs are thin films designed to quickly disintegrate and dissolve in the mouth, releasing the drug immediately<sup>5</sup>. They are also known as mouth-dissolving films or oral thin films. ODFs aim to enhance patient compliance, especially for patients who struggle to swallow oral dosage forms like tablets or capsules<sup>3</sup>. Since the drug is released and absorbed directly through the oral mucosa, ODFs lead to quicker onset of action and improved bioavailability compared to conventional oral routes<sup>3</sup>.

To use an ODF, the patient must place the film in the oral cavity and allow it to disintegrate. Part of the drug is absorbed in the mouth which bypasses the first-pass metabolism, and the rest proceeds into the gastrointestinal system<sup>2,3</sup>.

ODFs are typically made from a blend of polymers, plasticizers, and active pharmaceutical ingredients. They can be manufactured by solvent casting, hot-melt extrusion, semi-solid casting, solid dispersion extrusion, and rolling<sup>6</sup> and are available in a range of shapes, sizes, and flavours to improve patient acceptability<sup>7</sup>.

**Table 1** outlines key benefits of ODFs when compared to more traditional oral dosage forms.

Overall, ODFs offer a promising alternative to traditional dosage forms, offering several

advantages in terms of convenience, accurate dosing, compliance, and stability<sup>8</sup>.

**Table 1: Advantages of ODF**

Advantages <sup>3-6,8</sup>
1. Rapid onset of action: ODFs dissolve quickly in the mouth, allowing for rapid absorption of the drug. This can result in a faster onset of action and may be particularly beneficial for drugs used to treat acute conditions such as pain or anxiety.
2. Convenient and easy to use: ODFs are thin, flexible, and easy to handle. They do not require water or any other liquid for administration, making them particularly convenient for patients who have difficulty swallowing pills or who are on the go.
3. Accurate dosing: ODFs are pre-measured and uniform in dose, ensuring accurate dosing and reducing the risk of medication errors.
4. Improved compliance: ODFs are easy to swallow, which may improve patient compliance, particularly in paediatric, geriatric, and dysphagic patients.
5. Enhanced stability: ODFs are more flexible and robust when compared to orally disintegrating tablets which are brittle in nature and may get damaged during transport.
6. Versatility: ODFs can be formulated with a wide range of active pharmaceutical ingredients, including both water-soluble and water-insoluble compounds.

Chlorpheniramine maleate is a BCS Class 1 drug characterised by high solubility and high permeability<sup>9</sup>. It is an antihistamine medication widely used to relieve symptoms associated with allergies, such as itching, sneezing, nasal congestion, and runny nose<sup>10,11</sup>. Its mechanism involved inhibiting H1 histamine receptors to block the effects of histamine. Common side effects of chlorpheniramine maleate include drowsiness, dizziness, dry mouth, and blurred vision<sup>10,11</sup>. It is a widely used OTC medication for treatment of cold and cough in the paediatric population and is the drug of choice for treatment of allergies during pregnancy<sup>12</sup>.

Due to its favourable properties- low dose, high solubility and permeability, it is well-suited to be incorporated in an ODF<sup>13</sup>. ODFs also provide a rapid therapeutic onset of action which is required for anti-histamine therapy.

## II. MATERIALS AND METHODS

### Materials

Chlorpheniramine maleate was a gift sample by Ankur Pharmacy as a gift sample. HPMC (5cps and 15cps), Sodium alginate, Pectin, PEG-400, PEG-4000, PEG-6000 (Polyethylene Glycol), Sorbitol, PVA, PVP carboxymethyl cellulose (CMC), Sodium Starch Glycolate and Glycerol were purchased from SD Fine Chem Limited, Carbopol 940 was procured from Research-Lab Fine Chem Industries. Ingredient used for phosphate buffer pH 6.8 were di-Sodium hydrogen orthophosphate and Potassium dihydrogen orthophosphate and for phosphate

buffer pH 7.4 were Potassium dihydrogen phosphate with Potassium Hydroxide which were also purchased from SD Fine Chem-Limited. All the ingredients of analytical grade were used.

### Melting point determination of CPM

The melting point was determined by Thiele's tube method. A capillary tube which is sealed from one end is taken and filled with CPM until a densely packed column is formed. This tube was then attached to the thermometer with the sealed end on the side of the bulb. The thermometer capillary tube assembly was placed in the Thiele's tube and heat was applied. When the CPM in the tube started to melt, the temperature was recorded as the melting point of the drug. The test is conducted in triplicates.

### Calibration curve of CPM in distilled water

10 mg of CPM was weighed accurately and taken in a 10 mL volumetric flask. The volume was made up using distilled water to get a standard solution of 1mg/ml. 1 mL of this solution was diluted to 10 mL with distilled water to get a solution of concentration 0.1 mg/mL or 100 µg/mL. This solution was scanned on the spectrophotometer and its  $\lambda_{max}$  was found to be 268nm. The standard solution was suitably diluted to get solutions with concentrations of 20-100µg/mL. The absorbance of these solutions was recorded at 268nm using UV spectroscopy and plotted against respective concentrations to obtain Beer-Lambert's plot for the standard curve.

### Calibration curve of CPM in phosphate buffer

10 mg of CPM was weighed accurately and taken in a 10 mL volumetric flask. The volume was made up using freshly prepared phosphate buffer of pH 6.8 to get a standard solution of 1mg/mL. 1 mL of this solution was diluted to 10 mL with buffer to get a solution of concentration 0.1 mg/mL or 100 µg/mL. This solution was scanned on the spectrophotometer and its  $\lambda_{max}$  was found to be 245nm. The standard solution was suitably diluted to get solutions with concentrations of 10, 20, 30, 40, 50, 60, 70, 80 µg/mL. The absorbance of these solutions was recorded at 245nm using UV spectroscopy and plotted against respective concentrations to obtain Beer-Lambert's plot for the standard curve.

### Saturation solubility

The saturation solubility of pure CPM was estimated by adding 10-20 mg of pure CPM with 0.5 mL of solvent in an Eppendorf tube. The solvents used were distilled water, isopropyl alcohol, ethyl alcohol, and PEG 400. The drug was dissolved using a vortex mixer. If the CPM dissolved in the solvent, then an additional amount of the drug was added to the solution until it became supersaturated. This solution was then placed on a shaker water bath for 48 hours to ensure complete dissolution of the drug. The tubes were then centrifuged for 10 minutes to separate

the excess drug from the saturated supernatant. The supernatant was pipetted out using a micropipette and suitably diluted. The resulting solution was analysed at 268 nm by UV spectroscopy.

### Formulation of Chlorpheniramine maleate Orodispersible films

The Orodispersible films of CPM are prepared by solvent casting method. The film-forming polymers weigh as per the formulation table and are added to a beaker. A polymeric dispersion is prepared by dissolving the polymer in a fixed amount of solvent and stirring it for 15 minutes. The plasticizers, super disintegrant, and sodium benzoate were then added to this polymeric solution in measured quantities as per the formulation table (Table 2, 3, 4, & 5). The solution was stirred for 15 minutes until a homogenous dispersion is obtained. To this dispersion, chlorpheniramine maleate is added and the mixture is stirred for 15 minutes. The mixture was degassed by sonicating it for 15 minutes to remove any entrapped gasses. This mixture is then poured into a petri dish of fixed diameter. The formulations that contain only IPA as solvent are placed under an IR lamp overnight till the patches are dry. The formulations that contain water as vehicles are dried in the oven for 2 hours before placing them under an IR lamp to remove the residual solvent.

**Table 2: Formulation table for primary selection of polymers in the ODF**

Ingredients	P1	P2	P3	P4	P5	P6	P7	P8	P9	10
PVA (mg)	225	-	-	-	225	225	-	-	-	-
PVP (mg)	225	-	-	-	-	-	-	-	-	-
HPMC 15cps (mg)	-	50	300	-	-	-	-	449	449	-
HPMC 5 cps (mg)	-	-	-	400	225	225	225	-	-	200
Pectin (mg)	-	50	100	-	-	-	-	-	-	-
Sodium Alginate (mg)	-	-	-	-	-	-	-	-	-	200
CMC (mg)	-	-	-	-	-	-	225	-	-	-
Carbopol (mg)	-	-	-	-	-	-	-	1	1	-
PEG 400 (mL)	-	1	1	1	-	1	-	1	1	-
PEG 4000 (mg)	1	-	-	-	-	-	-	-	-	-
PEG 6000 (mg)	-	-	-	-	1	-	1	-	-	-

Sorbitol (mL)	-	0.15	0.15	-	-	-	-	-	-	1
Water (q.s) (mL)	10	10	10	10	10	10	-	10	-	10
Water: IPA (4:1) (q.s) (mL)	-	-	-	-	-	-	10	-	10	-

**Table 3: Formulation table for final selection of polymers**

Ingredients	S1	S2	S3	S4	S5
HPMC 15cps (mg)	300	300	300	-	-
Sodium Alginate (mg)	100	-	-	250	150
CMC (mg)	-	100	-	-	-
PVP (mL)	-	-	100	-	-
PEG 400	1	-	-	-	-
Pectin (mg)	-	-	-	250	50
Glycerol (mL)	-	0.4	-	2	0.2
Mannitol (mg)	-	50	-	-	-
Sorbitol (mL)	-	-	0.2	-	-
Sodium starch glycolate (mg)	50	-	50	-	50
SLS (mL)	-	20	-	-	-
Tween 80 (mL)	-	-	-	0.02	-
Water (mL)	10	-	-	10	10
Water: Ethanol (1:1) (mL)	-	10	-	-	-
Water: IPA (1:1) (mL)	-	-	10	-	-

**Table 4: Formulation table for selection of plasticizer polymer concentration**

Ingredients	T1	T2	T3	T4	T5	T6	T7
Sodium Alginate (mg)	500	500	250	125	125	187	187
Pectin (mg)	300	300	150	75	75	112	112
PEG400 (mL)	0.64	-	0.3	0.2	-	0.1	0.1
PEG 6000 (mg)	-	10	-	-	10	-	-
Glycerol (mL)	-	-	-	-	-	0.05	0.1
Sodium Starch Glycolate (mg)	500	500	175	175	175	262	300
Water (mL)	10	10	10	10	10	15	15

**Table 5: Formulation table of the final batch of films**

Ingredients	F1	F2	F3
Chlorpheniramine maleate (mg)	78	78	78
Sodium Alginate (mg)	187	187	187
Pectin (mg)	112	112	112
PEG400 (mL)	0.1	0.1	0.06
Glycerol (mL)	0.05	0.1	0.15
Sodium Starch Glycolate (mg)	262	300	262
Sodium Benzoate (mg)	0.015	0.015	0.015
Water (mL)	15	15	15

### Evaluation of Orodispersible films

#### Morphological properties of the film

The colour, texture, and appearance of the patch were visually inspected as a primary elimination criterion for formulations of films.

#### Thickness

The thickness of the film was measured by Vernier Calliper. The thickness was measured at 5 different strategic points. Each film was measured at 5 positions (centre and four corners) and mean thickness was calculated.

#### Weight uniformity

10 patches of size 2x2 cm<sup>2</sup> were cut from different parts of the casted films. The weight of each strip was taken, and the weight variation was calculated.

#### Folding Endurance

Folding endurance is expressed as the number of folds required for breaking the specimen or developing visible cracks. This gives an indication of the brittleness of the film. A small strip of 2x2 cm<sup>2</sup> was subjected to this test by folding the film at the same point repeatedly several 18 times until a visible crack was observed, this indicates the brittleness of the film. The test was conducted in triplicates.

#### Surface pH

Surface pH was performed by 2 methods:

1. The surface pH of the films was evaluated by placing the films on 1.5% w/v of agar gel. A pH paper was then placed on the film, and based on the change in colour the pH was determined.

2. A small strip of film was taken and dissolved in 0.5 ml of distilled water, then the pH of the resulting solution was determined by using pH paper.

#### In vitro Disintegration time

A film of size 2x2 cm<sup>2</sup> was placed in a petri dish containing 10mL of distilled water and the dish was swirled gently. The time taken for the films to completely disintegrate was noted. The test was conducted in triplicates.

#### Percentage of moisture content

Films of size 2x2 cm<sup>2</sup> were cut and weighed individually. After weighing, they were placed in a desiccator containing fused anhydrous calcium chloride at room temperature for 72 hr. After 72 hr, they were weighed again, and percentage moisture loss of films was measured by using the formula: Percent moisture loss = (Initial weight – Final weight)/Initial weight × 100

#### Mouth Dissolving Time

The mouth dissolving time was determined by placing the film of size 2 x 2 cm<sup>2</sup> into a beaker containing 50ml of 7.4 pH phosphate buffer and even in pH 6.8 buffer. The amount of time taken for the film to dissolve was recorded at end of the test. The test was conducted in triplicates.

#### Drug content uniformity

Six films of size 2x2 cm<sup>2</sup> equivalent to 4mg dose representing six different regions of the film were cut and dissolved in 100mL of phosphate buffer of pH 6.8. The mixture was stirred on a

magnetic stirrer for 60min at 100rpm followed by filtering through Whatman filter paper. The filtrate was appropriately diluted and analysed at 245nm using UV spectroscopy to determine the amount of CPM.

### In-vitro Dissolution Study

In vitro dissolution studies were performed in triplicate in a USP type II (basket) dissolution apparatus using 250mL of phosphate buffer (pH 6.8) as the dissolution medium. The temperature and rotation speed were maintained at 37°C and 100 rpm respectively. Film of size 2x2 cm<sup>2</sup> equivalent to 4mg dose were cut and placed in the basket. Samples of 5mL were withdrawn at predetermined time intervals of 1, 2, 3, 4, 5 and 6 min, and replaced with 5mL of fresh dissolution medium. The withdrawn samples were filtered and diluted and was further analysed at 245 nm using UV spectroscopy.

## III. RESULTS AND DISCUSSION

### Melting point of CPM

The melting point of the sample was found to be 131°C ± 2°C. Since this lies within the melting point range of CPM, it indicates the purity of the sample.

### Calibration curve of CPM in Distilled water

The  $\lambda_{max}$  was found to be 268nm. The curve has a linearity range of 20 – 100 µg/mL. The slope and intercept were found to be 0.0089 and 0.0081 respectively. The correlation coefficient was calculated to be 0.9992.

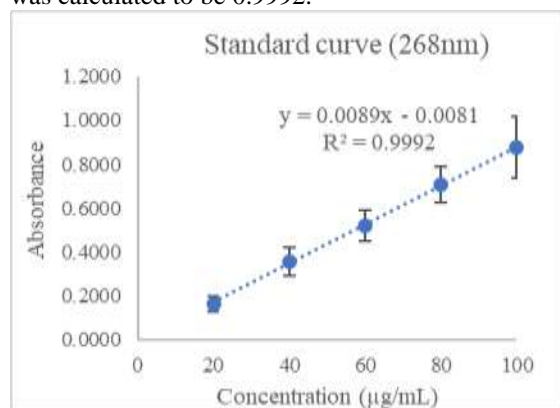


Figure 1: Calibration curve of CPM in distilled water

### Calibration curve of CPM in Phosphate Buffer of pH 6.8

The  $\lambda_{max}$  was found to be 245nm. The curve has a linearity range of 10 – 80 µg/mL. The

slope and intercept were found to be 0.0118 and 0.043 respectively. The correlation coefficient was calculated to be 0.996.

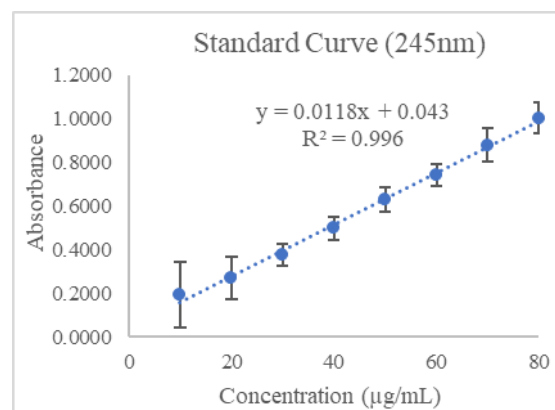


Figure 2: Calibration curve of CPM in Phosphate buffer

### Saturation Solubility

CPM is a polar molecule hence, polar solvents like water, isopropyl alcohol (IPA), Ethanol, and PEG were primarily selected to be used as solvents for the formulation. Saturation solubility was the selection parameter to finalize the solvents to be used in the formulation of the ODF. Based on the values obtained after analysis (Table 6), the solubility of CPM was found to be better for IPA (1825.96 mg/mL) and water (628.37 mg/mL). The lower solubility of CPM in ethanol (62.84 mg/mL) is assumed to be due to interaction of CPM with the solvent. Therefore, water and IPA were further used in the formulation of films.

Table 6: Estimations of Saturation solubility of CPM

Solvent	Saturation solubility (mg/mL)
Water	628.37
IPA	1825.96
Ethanol	62.84
PEG	11.55

### Evaluation and Optimization of ODFs

The films in Table 2, Table 3, and Table 4 were evaluated in a stepwise process to optimize the formulation and the preparation procedure.

Films P1 to P10 were formulated using different polymers, alone and in combination to

examine the ability of the polymers to form an intact film (Table 2). These films were visually

inspected, particularly their texture and transparency

**Table 7: Evaluation of polymers based on film forming capacity and appearance.**

Sr. No.	Formulation	Polymers Used	Film Forming Capacity	Appearance
1	P1	PVA (225mg) + PVP (225mg)	++	Sticky, Transparent
2	P2	HPMC-15cps (50mg) + Pectin (50mg)	+	Semi-transparent, Sticky
3	P3	HPMC-15cps (300mg) + Pectin (100mg)	+	Not Transparent, Sticky
4	P4	HPMC-5cps (400mg)	+++	Transparent, Smooth, Good Appearance
5	P5	PVA (225mg) + HPMC-5cps (225mg) + PEG 6000 (1mg)	++	Semi-transparent, Brittle, Turbid
6	P6	PVA (225mg) + HPMC-5cps (225mg) + PEG 400 (1ml)	++	Sticky, Transparent
7	P7	HPMC-5cps (225mg) + CMC (225mg)	+	Not Transparent, Rough, Dry
8	P8	HPMC-15cps (449mg) + Carbopol (1mg) + PEG 400 (1ml)	+	Not Transparent, Rough, Turbid
9	P9	HPMC-15cps (449mg) + Carbopol (1mg) + PEG 6000 (1mg)	++	Sticky, Transparent
10	P10	HPMC-5cps (200mg) + Sodium Alginate (200mg)	+	Not Transparent, Rough, Dry

Based on the observations (Table 7); HPMC 15cps, Polyvinylpyrrolidone, Sodium alginate, and Pectin were taken forward for further evaluation as polymers for the film as they demonstrated adequate film forming capacity. Films with Carbopol as a co polymer made the preparation procedure complex. This is because, it takes a long time for Carbopol to dissolve in water and then there is a need to neutralize the polymeric dispersion

by addition of sodium hydroxide solution which will then lead to in situ gelling of Carbopol. For

these reasons, Carbopol was excluded from CPM ODF formulations.

Films S1 to S5 were formulated using the selected polymers with different types of plasticizers (Table 3). These films were visually inspected, particularly their texture and transparency.

Based on the observations made from evaluation of these films (Table 8), it was concluded that HPMC, Sodium alginate, and pectin have good film forming abilities and gave a disintegration time which can be decreased by subsequent modification it the film formulation. HPMC as a film forming polymer, has been widely

used and there is extensive data available for the same. HPMC is as ideal polymer for making ODFs. However, sodium alginate and pectin, both of which are natural polymers showed results which were comparable to films which had HPMC as copolymer. Even, the disintegration time for film

with sodium alginate and pectin was less when compared to HPMC films and therefore, sodium alginate and pectin were selected to be used as polymers in the formulation of ODFs.

Disintegration Time- S5 < S1 < S4

**Table 8: Evaluation of polymers based on film forming capacity, appearance, and disintegration time.**

Sr. No.	Formulation	Polymers Used	Film Forming Capacity	Appearance	Disintegration Time
1	S1	HPMC- 15cps Sodium Alginate	+ ++	Transparent, and sticky	160 sec
2	S2	HPMC- 15cps CMC	+ ----	Does not form film	-
3	S3	HPMC- 15cps + PVP	++	Transparent, thin, and fragile	-
4	S4	Sodium (250mg) + Alginate (250mg) + Pectin	+	Not transparent, rough, and sticky	>180 sec
5	S5	Sodium (150mg) + Alginate (50mg) + Pectin	+++	Transparent, good appearance	120 sec

Films T1 to T6 were prepared first (**Table 4**), where the total polymer concentration was varied while keeping the proportion of co-polymers the same. The ratio of sodium alginate to pectin was kept 5:3, respectively. The total polymer concentration for T1, T2, T3, T4, T5 were 8% w/v, 8% w/v, 4% w/v, 2% w/v, and 2% w/v respectively to get a concentration with optimum thickness and disintegration time while maintaining adequate pourability during preparation.

Based on the observations made (**Table 9**) it was found that as the polymer concentration increased, the opacity and disintegration time of the films also increased and the pourability of the

mixture decreased. Films T4 and T5 of 2% w/v gave good disintegration time results (81s and 51s respectively) with desired appearance, however, the solutions were viscous with poor pourability. Formulations containing PEG 6000 as plasticizer formed more viscous solutions and films that were dry and brittle. Hence, the volume of the solution was increased from 10mL to 15mL to improve pourability, and PEG 400 and glycerol were employed as plasticizers for T6 and T7. These formulations had the desired properties in terms of appearance, texture, and disintegration time (58s and 60s respectively) and were used as base to postulate the final formulations.

**Table 9: Evaluation of films with sodium alginate and pectin as polymers based on film forming capacity, appearance, and disintegration time.**

Sr. No.	Formulation	Polymers and Plasticizers Used	Film Forming Capacity	Appearance	Disintegration Time
1	T1	Sodium (500mg) + Alginate (300mg) + Pectin (0.64ml)	+	Semi-transparent, moderate plasticity	90 sec
2	T2	Sodium (500mg) + Alginate (300mg) + Pectin (10mg)	+	Semi-transparent, viscous	110 sec
3	T3	Sodium (250mg) + Alginate (150mg) + Pectin (0.3ml)	++	Transparent, Moderate plasticity	81 sec
4	T4	Sodium (125mg) + Alginate (75mg) + Pectin (0.2ml)	++	Transparent, Moderate plasticity	81 sec
5	T5	Sodium (125mg) + Alginate (75mg) + Pectin (10mg)	+	Not transparent, rough, and viscous	51 sec
6	T6	Sodium (187mg) + Alginate (112mg) + Pectin (0.1ml) + Glycerol (0.05ml)	+++	Transparent, good appearance, improved plasticity	58 sec
7	T7	Sodium (187mg) + Alginate (112mg) + Pectin (0.1ml) + Glycerol (0.1ml)	+++	Transparent, good appearance, improved plasticity	60 sec

**Evaluation of CPM ODFs**

Orodispersible films should be robust, have appropriate drug release, and disintegrate within minutes<sup>14</sup>. A combination of natural polymers, sodium alginate and pectin were selected

to obtain a firm, compact and a flexible mouth dissolving film.

Preliminary investigations were carried out as mentioned above. PEG- 400 is used as plasticizer as it gives good flexibility, and homogeneity to the film. Glycerol is also used as

plasticizer due to its compatibility with sodium alginate and other natural polymers<sup>15</sup>. Glycerol increases the smooth texture and plasticity of the patches but, increasing its quantity beyond optimum concentration made the patches stickier and more viscid. Hence, a combination of glycerol and PEG 400 was used in different proportion in the final formulations. Sodium starch glycolate, a

super-disintegrant was also incorporated for decreasing the disintegration time of the films. Water soluble preservative, sodium benzoate was added as preservative to prevent contamination of the films, over-time. With this rationale, films F1, F2, and F3 were postulated and incorporated with chlorpheniramine maleate (Table 5).

**Table 10: Evaluation of physicochemical parameters of CPM ODFs**

Formulation	Weight variation (mg)	Thickness(mm)	Folding endurance	pH	Disintegration time (s)	Drug Content (%)
F1	58.83 ± 2	0.050 ± 0.008	281	5.5	57	99.73 ± 1.55
F2	50.33 ± 2	0.066 ± 0.008	>300	5.5	57	100.20 ± 0.89
F3	42.33 ± 3	0.054 ± 0.006	>300	5.5	60	100.22 ± 0.92

#### Thickness

The thickness of films F1, F2 and F3 were observed to be in the range of 0.050 ± 0.008 mm, 0.066 ± 0.008 mm, and 0.054 ± 0.006 mm respectively (Table 10). Films which are thinner would be beneficial because it causes minimum discomfort to patients. As the polymer concentration for these films were kept the same, the plasticizer ratio played a major role in thickness of the film. Therefore, films F1 and F3 with a lower plasticizer concentration of 1.17% w/v were thinner than F2 with plasticizer concentration of 1.6% w/v. Sodium alginate films tend to be rigid and brittle but, incorporating glycerol increases plasticity by increasing the interchain spacing and reduced interchain reaction<sup>15</sup> which can be a contributing factor to increase in the film's thickness<sup>15</sup>.

#### Weight uniformity

Homogeneity of the film is a key parameter to establish the uniform distribution of the drug as well as predictable drug release from it. Polymers influences the weight of the films. Since the Standard Deviation of the weight of films F1, F2 and F3 is less we can conclude that the polymers were uniformly distributed. Weight variation of film F1, F2 and F3 were observed to be 58.83 ± 2 mg, 50.33 ± 2 mg, and 42.33 ± 3 mg respectively (Table 10). All the films showed minimum variation.

#### Folding endurance

The folding endurance was manually evaluated (Table 10). It is a measure of pliability,

durability, and robustness of the films. F2 and F3 retained high endurance values (>300) and F1 broke after 281 folds. The highest folding endurance value was shown by F2 and F3. This can be due to the plasticity imparted to the film by incorporation of greater concentration of glycerol. The higher folding endurance value was significant because mechanically strong film would resist tearing as well as detachment of the film from the site during application.

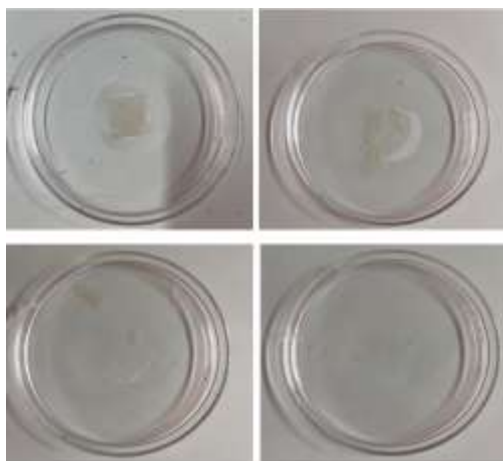
#### Surface pH

Since acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the ODFs was determined to optimise both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close as possible to the salivary pH, by the proper selection of the polymers during developing the films. The surface pH of all the films F1, F2, and F3 was found to be 5.5 which is close to the salivary pH (Table 10).

#### In vitro Disintegration time

The Disintegration time is one of the most important parameters for developing an ODF (Figure 3). The films F1, F2, and F3 disintegrated within 1 minute due to addition of super-disintegrant and by keeping the polymer in the optimum range of 2% w/v as discussed in the above section. The disintegration time did not show much variation for three formulations, as the polymer concentration was kept constant. Based on the results from Table 12, it can be concluded that the concentration of glycerol and PEG 400 did not

have much effect on the disintegration time of the films. Increasing the concentration of sodium starch glycolate beyond 1% did not lead to faster disintegration of the films.



**Figure 3: In vitro Disintegration of film**

#### Percentage moisture content

Adequate moisture content is required to maintain desirable flexibility and folding endurance however, excess moisture can lead to growth of microorganisms and may lead to drug degradation due to unwanted reaction. Hence, moisture content of the films was estimated and found to be 12.5% for F1 and 0% for F2 and F3.

**Table 11: Estimations of percentage moisture content for CPM ODFs**

Formulation	Moisture Content (%)
F1	12.5%
F2	0%
F3	0%

#### Mouth dissolving time of ODF

Mouth dissolving time was performed for all three batches using phosphate buffer of 6.8 pH and 7.4 pH. All the three batches were dissolved within 95 seconds. Based on the results from Table 14, it can be concluded that the pH of the oral cavity influenced the film disintegration time. However, the effect of pH on the disintegration time of the film was inconclusive.

**Table 12: Mouth dissolving time of CPM films in Phosphate buffer**

pH	Mouth dissolving film (min)		
	F1	F2	F3
6.8	95 sec	89sec	67sec
7.4	90 sec	75sec	70sec

#### Drug Content Uniformity

Uniformity of content is a critical pharmaceutical quality control parameter to ensure drug availability in pharmaceutical products. The data displayed in (Table 10), signifies higher drug content > 99% in films F1-F3. The consistent values among formulations signify that variations in the composition did not influence chlorpheniramine maleate content.

#### In-vitro Dissolution Study

In-vitro drug release studies are important to understand the liberation of therapeutic activities from the film into the GIT and subsequent permeation through the biological membrane. Further it is a well-known fact that drug delivery from a formulation is primarily dictated by the properties of the drug and polymers. The effect of film composition on the release of CPM from the films F1, F2 and F3 was determined and illustrated in Table 13. It was observed that maximum drug release was obtained at 6 minutes for the three formulations.

**Table 13: In vitro dissolution test results for formulations F1, F2, and F3**

Time (min)	Cumulative Drug Release (%)		
	F1	F2	F3
1	46.80 ± 10	34.38 ± 23	47.14 ± 1
2	52.26 ± 2	50.74 ± 20	51.92 ± 2
3	58.74 ± 8	57.20 ± 18	59.23 ± 1
4	63.19 ± 5	63.74 ± 17	62.41 ± 10
5	66.19 ± 4	65.46 ± 15	64.19 ± 13
6	70.58 ± 2	65.23 ± 11	82.27 ± 11

It is apparent from Figure 4 that drug release was relatively higher in F3 and lower in F2 (F3 > F1 > F2) indicating the film composition influenced the chlorpheniramine maleate release. The oral mucosa shows greater permeability and hence, higher drug release within the first 1- minute increases the potential oromucosal absorption. F1

and F3 release 46.80% and 47% respectively and F3 shows a greater release than other formulation.

#### IV. CONCLUSION

The study was undertaken with the intention to develop orodispersible films (ODFs) of Chlorphenamine Maleate and provide a convenient means of administration to paediatric, geriatric, dysphagic, bed-ridden, and non-compliant patients. In this study, the films were formulated with various polymer matrices and plasticizers. Evaluation of these films allowed for identifying optimal formulations with sodium alginate and pectin as polymers, and glycerol and PEG as plasticizers. The final three formulations F1, F2, and F3 showed similar results for disintegration time (<60 seconds), pH (pH 5), and drug content ( $100 \pm 1$ ). The values for folding endurance of F2 and F3 exceed 300 and indicates the robustness and plasticity of the films. Based on the dissolution studies, it can be inferred that F3 has a better drug release profile, and it releases CPM up to  $82.27\% \pm 11\%$  in 6 minutes. F3 gave optimum films with the desirable characteristics established for the formulation of ODFs

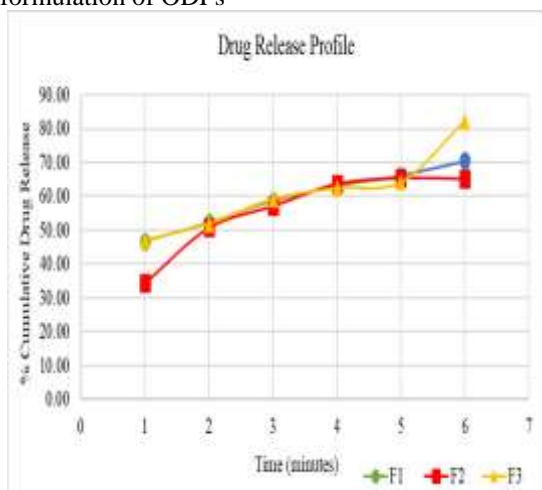


Figure 4: Drug release profile for formulations F1, F2, and F3

#### Future Scope

This study can be further extended for better evaluation of the films. It was concluded that pH influences the disintegration of the films, so for a more conclusive relation between pH and disintegration time, in vivo disintegration studies can be done. This may also uncover other parameters which affect disintegration time. Along with this, ex vivo permeation studies can be done to get a better understanding of the absorption pattern of CPM from the oral mucosa and estimate

the potential oromucosal absorption. Ex vivo studies can be done using rabbit mucous membrane<sup>16</sup>.

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