IJPSR (2014), Vol. 5, Issue 5 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 December, 2013; received in revised form, 20 January, 2014; accepted, 09 March, 2014; published 01 May, 2014

ORAL DISSOLVING FILMS OF CHLORPHENIRAMINE MALEATE

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Keywords:

Fast dissolving oral films, Oral mucosa, Permeability, HPMC, Chlorpheniramine maleate, Solvent casting method.

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ABSTRACT: In this present study, we investigated phytochemical constituents screening and *In-vitro* antioxidant activity of hydro-alcoholic (methanol 70%v/v) extracts of *Soymida febrifuga* bark. *Soymida febrifuga* is a huge tree bearing deciduous foliage and having a tough bark belonging to the family Meliaceae. Traditionally the different parts of plant such as root, leaves, bark, and flower are used for various human ailments. The bark extracts are used in treatment of rheumatoid arthritis asthma and good for ulcers .The decoction of the bark has bitter resin used in vaginal infections, rheumatic pains , stomach pains, wounds, dental diseases, uterine bleeding and haemorrhage .The bark is also used as an acrid, refrigerant, laxative, good for sore throat, removes 'vata' and cures 'tridosha' in Ayurveda. Apart from many uses various active constituents like methyl angolensate, luteolin 7-O-glucoside, quercetin, sitosterol, myrecetin were isolated. It also possesses various pharmacological activities such as anticancer, antihelmenthic, antioxidant ant malarial and antimicrobial. In view of this the hydro alcoholic bark extract of *S. febrifuga* produced a dose dependent inhibition of free radical generation of superoxide anion, hydroxyl radical and DPPH radical *In vitro* antioxidant activity.

INTRODUCTION: Fast dissolving oral films are most advanced form of solid dosage form due to more flexibility and comfort. It improves the efficacy of API dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablet without chewing and no need of water for administration [1]. It gives quick absorption and instant bioavailability of drug due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(5).1859-73

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(5).1859-73

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passed into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Fast dissolving oral films are useful in patients such as pediatric, geriatric, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething [2].

Fast dissolving drug delivery has become a novel and widely accepted dosage forms by consumers and gaining the interest of large number of pharmaceutical industries, due to several advantages. This fast dissolving drug delivery system is suited for the drugs which undergo high first pass metabolism and is used for improving

bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. OFDFs are very similar to postage stamp in their shape, size and thickness that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension for rapid absorption. Fast Dissolve technologies can be divided in to three broad groups Lyophilized systems, compressed tablet based systems and Thin Film strips [3, 4, 6].

Advantages of Oral Fast Dissolving Films [7, 8]:

- Oral dissolving films can be administered without water, anywhere, any time.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable so they provide ease in transportation.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing, mentally ill and the patients who are un-cooperative or are on reduced liquid intake plans or are nauseated.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- As compared to liquid formulations, precision in the administered dose is ensured from each strip of the film.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing and enhance the efficacy and safety profile of the medicament.
- Provide new business opportunity like product differentiation, product promotion.
- The films are thin and can be carried in a patients pocket, wallet.

Disadvantages:

- High doses cannot be incorporated into the film.
- Expensive packaging of the film.

Application of Oral strip in drug delivery [9, 10, 11]:

- **Topical applications:** The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

- **Gastro retentive dosage systems**: Dissolvable films are being considered in dosage forms for which water soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.

- **Diagnostic devices:** Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

TABLE 1: DIFFERENCE BETWEEN ODF AND ODT [12]

Orally dissolving films	Orally disintegrating tablets
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Comparatively better durable	Comparatively less durable
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of chocking	It has a fear of chocking

TABLE 2: GENERAL COMPOSITION OF FAST DISSOLVING ORAL FILMS [13, 14]

Ingredients	Quantity (%)
API	1 to 30
Film forming polymer	45
Plasticizer	0 to 20
Saliva stimulating agent	2 to 6
Sweetening agent	3 to 6
Flavors, colors, fillers	Quantity sufficient

Drug Compatibility Studies [15, 16]:

Fourier Transforms Infrared (FTIR) Spectroscopy studies: The FTIR samples (pure drug Chlorpheniramine maleate, placebo and Chlorpheniramine maleate fast dissolving oral film formulation) were obtained, using Perkin Elmer FT-IR system BX series (Beaconsfield, Buckinghamshire, UK), in the frequency range of 4000- 550cm-^{1} at 4 cm-^{1} resolution. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions.

The IR spectra of pure Chlorpheniramine maleate drug showed the characteristic absorption bands and drug-polymer interaction was not observed in the FTIR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture [17].

Differential Scanning Colorimetry (DSC): Individual coils that are heated and cooled at the same rate heat DSC in which sample and reference containers are not contiguous and heated them separately. Platinum resistance thermometers monitor the temperature of the sample and reference holders and electronically maintain the temperature of the two holders constant.

For thermal analysis of drug and drug-excipients mixtures, a differential scanning calorimeter (DSC) (DSC60 Shimadzu Corporation, Japan) was used. Individual samples (drug and selected excipients (all passed through sieve 60-mesh) were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 50-300^{0}C (at the heating rate of 100C/min.) under an atmosphere of dry nitrogen [18].

Scanning Electron Microscopy (SEM): Scanning electron microscopy (SEM) is utilized to assess the surface morphological characteristics of the optimised formulations.

Evaluation of Fast Dissolving Films [19-30]:

a) **Thickness:** As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations. The thickness was measured at three different spots of the films and average was taken.

b) **Tensile strength:** Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross sectional area of the strip [1].

$$\textbf{Tensile strength} = \frac{\text{load at breakage}}{\text{strip thickness x strip width}}$$

c) **Percent elongation:** When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

$$\textbf{\% Elongation} = \frac{\text{Increase in length x 100}}{\text{original length}}$$

d) **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 computed as the folding endurance value.

e) **Physical appearance and surface texture of patch:** These parameters were checked simply with visual infection of films and by feel or touch.

f) **Weight uniformity of films:** Film (size of 2.5 cm^{2}) was taken from different areas of film. The weight variation of each film is calculated.

g) **Drug Content uniformity or Assay of film:** The films were tested for drug content uniformity by UV Spectrophotometrical method. Films of 2.5cm x 2.5cm square size were cut from three different places from the casted films. Each patch was placed in 100 ml volumetric flask and dissolved in 6.8 phosphate buffer. The absorbance of the solution was measured at 265nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for all the formulations.

h) ***In vitro* Disintegration time:** The *in vitro* disintegration time of fast dissolving films was determined visually in a glass dish of 25 ml 6.8 pH phosphate buffer with swirling action. The disintegration time is the time when a film starts to break or disintegrate. The *in vitro* disintegration time was calculated for different patches of the same film and average value was taken.

i) ***In vitro* Dissolution Study:** *In vitro* dissolution of chlorpheniramine maleate oral dissolving films was studied in paddle type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used as dissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 265nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of chlorpheniramine maleate release was calculated and plotted against time.

Stability Studies [31-35]**:** According to WHO and ICH guidelines the stability of the films was studied at 40°C± 2°C with RH 75%± 5%. The films were weighed and wrapped in aluminum foil and placed in Petriplates. These containers were stored for a period of three months. All the films were observed for any physical changes, such as color, appearance, or flexibility. The drug content and *in vitro* drug release was estimated at an interval of each month.

TABLE 3: STORAGE CONDITIONS FOR STABILITY STUDIES

Storage Condition	Test Period
40°C±2°C/75% ±5% RH	1st month 2nd month 3rdmonth

MATERIALS AND METHODS: Chlorpheniramine maleate is a gift sample from Nihal Traders pvt. Ltd. Hyderabad, HPMC E3, HPMCE6, HPMCE15 are procured from Hi Media labs Pvt Ltd, Mumbai. PEG 400, methonal are collected from S.d.fine chemicals, Mumbai. Citric Acid is collected from Signet Chemical Crop, Mumbai. Tio2, Aspartame are collected from Micro labs, Banglore, India.

Preparation of Oral Fast Dissolving Films [36, 37]: Following processes are generally used to manufacture the mouth dissolving film.

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method

The fast dissolving films of Chlorpheniramine maleate were prepared by solvent casting technique. The fast dissolving films were prepared using different polymers like HPMC (E3, E6 and E15), hydroxy propyl cellulose. Poly ethylene glycol was used as plasticizer. The calculated amount of polymer was dispersed in the solvent with continuous stirring using magnetic stirrer and the homogenous solution is formed. Then the sweetener and flavor was added to drug mixed polymeric solution. Then the solution was kept in sonicator for degassing. Then the bubble free solution was casted on to petriplate and was kept in hot air oven. Dried film is then cutted into the desired shape and size (2.5cm x 2.5cm) for the intended application. By carrying out the trial and error method different concentrations of film forming polymers were used for optimizing the formulation.

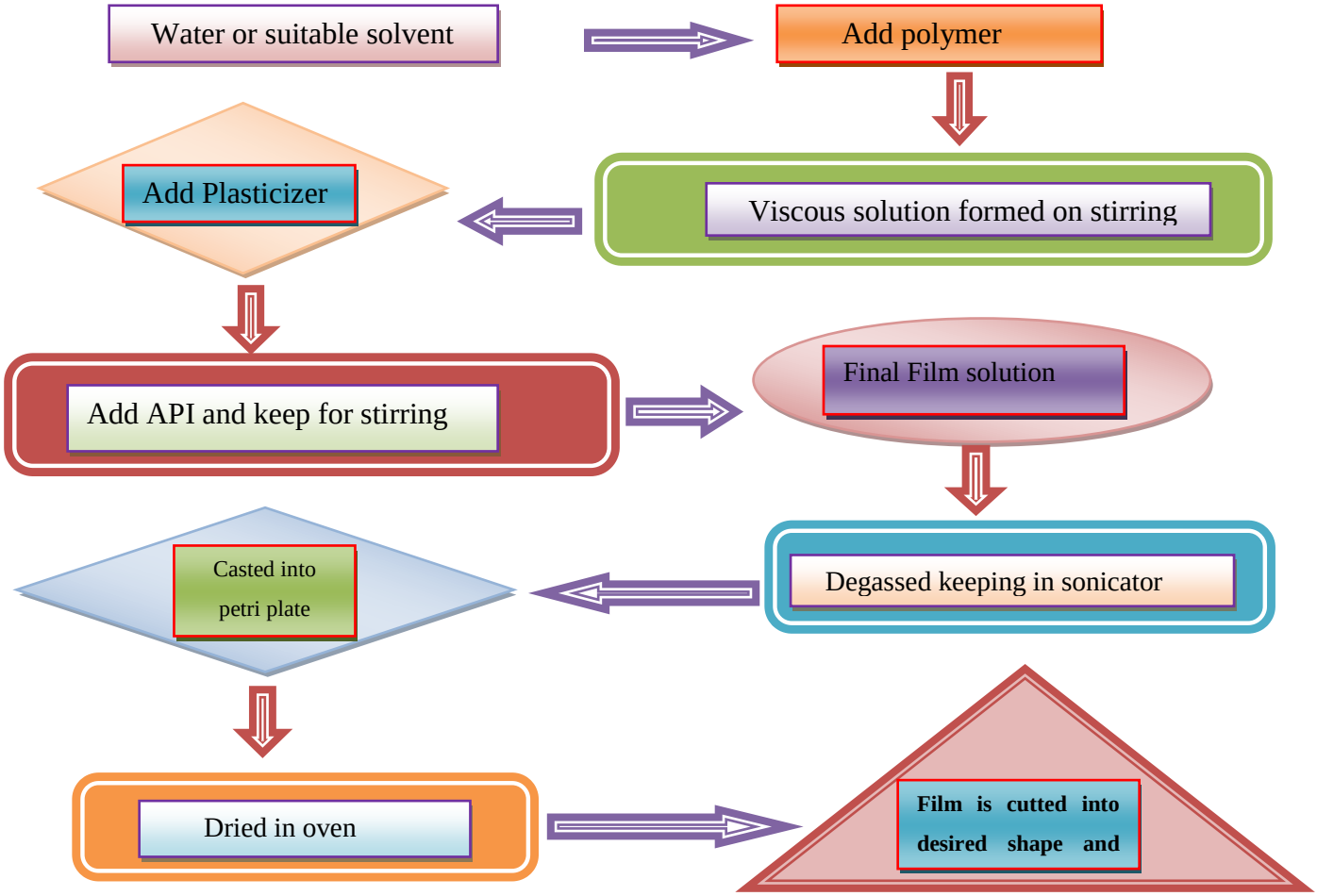


FIG: 1 SOLVENT CASTING METHOD

Dose calculation for Chlorpheniramine maleate: The dose of chlorpheniramine maleate is 4mg. Therefore amount of chlorpheniramine maleate required in 2.5cm x 2.5cm square film is 4mg.

Area of petriplate $=\pi r^2$
$=3.14 \times 3.5 \times 3.5$
(Petriplate diameter 7cm) $=38.46cm^2$

Number of patches = Area of petriplate/size of the square film = 38.46/5
= 7.69

Total amount of the drug = Number of patches x Dose
= 7.69 x 4
= 30.7mg

Therefore, $38.46cm^2$ of petriplate should contain 30.7mg of drug. It is fixed for all formulations.

TABLE 4: FORMULATION CHART OF CHLORPHENIRAMINE MALEATE ORAL DISSOLVING FILM

Code	Drug	HPMC E3	HPMC E6	HPMC E15	PEG	PG	Citric Acid	Aspartame	Methanol
F1	31	92	-	-	9	-	4	6	Q.S
F2	31	154	-	-	15	-	6	8	Q.S
F3	31	215	-	-	22	-	8	10	Q.S
F4	31	92	-	-	-	9	4	6	Q.S
F5	31	154	-	-	-	15	6	8	Q.S
F6	31	215	-	-	-	22	8	10	Q.S
F7	31	-	92	-	9	-	4	6	Q.S
F8	31	-	154	-	15	-	6	8	Q.S
F9	31	-	215	-	22	-	8	10	Q.S
F10	31	-	92	-	-	9	4	6	Q.S
F11	31	-	154	-	-	15	6	8	Q.S

F12	31	-	215	-	-	22	8	10	Q.S
F13	31	-	-	92	9	-	4	6	Q.S
F14	31	-	-	154	15	-	6	8	Q.S
F15	31	-	-	215	22	-	8	10	Q.S
F16	31	-	-	92	-	9	4	6	Q.S
F17	31	-	-	154	-	15	6	8	Q.S
F18	31	-	-	215	-	22	8	10	Q.S

Drug = Chlorpheniramine maleate, PEG = Poly ethylene glycol, PG = Propylene glycol, HPMC = Hydroxy propyl methyl cellulose, Q.S = Quantity sufficient.

RESULTS AND DISCUSSION:

Evaluation Parameters:

TABLE 5: EVALUATION PARAMETERS OF ALL FORMULATIONS OF ORAL FAST DISSOLVING FILMS

Code	Mean weight (mg) ± S.D	Mean Thickness (mm) ± S.D	Mean Tensile strength (Kg/mm^2) ± SD	Mean Percent elongation ± S.D	Mean Folding endurance ± S.D	Mean (%) ± S.D	Mean disintegration time (sec) ± S.D
F1	18.21 ± 0.86	0.210 ± 0.012	0.798 ± 0.521	1.62 ± 0.82	99.33 ± 7.67	99.27±0.15	32 ± 0.85
F2	27.23 ± 0.54	0.243 ± 0.017	0.690 ± 0.532	1.82 ± 0.78	95.66 ± 6.23	99.94±0.32	34 ± 1.46
F3	34.86 ± 0.59	0.250 ± 0.022	0.633 ± 0.420	2.24 ± 0.69	103.33±9.87	99.95±0.41	37 ± 0.42
F4	19.01 ± 0.02	0.224 ± 0.024	0.739 ±0.620	1.75 ± 0.67	98.41±5.88	98.95±0.39	33 ± 1.51
F5	27.58 ± 0.32	0.246 ± 0.021	0.660 ± 0.612	1.98 ± 0.57	93.66±8.12	97.02±0.47	35 ± 0.35
F6	35.38 ± 0.91	0.295 ± 0.014	0.612 ± 0.580	2.43 ± 0.59	105.25±4.56	97.85±0.59	38 ± 1.78
F7	18.51 ± 0.44	0.240 ± 0.019	2.12 ± 0.210	2.67 ± 0.62	122.35±6.45	99.41±0.15	37 ± 2.52
F8	27 .77 ± 0.53	0.269 ± 0.019	1.45 ± 0.20	4.21 ± 0.93	128.66±5.87	98.05±0.32	39 ± 0.89
F9	35.10 ± 0.61	0.268 ± 0.026	0.971 ± 0.65	5.56 ± 0.53	111.02±8.55	99.54±0.23	47 ± 1.45
F10	19.10 ± 0.09	0.257 ± 0.014	1.84 ± 0.182	2.34 ± 0.81	120.66±5.29	100.1±0.23	34 ± 0.78
F11	28.02 ± 0.51	0.272 ± 0.023	1.23 ± 0.38	4.78 ± 0.87	125.66±7.55	99.75±0.23	41 ± 1.57
F12	36.67 ± 0.66	0.270 ± 0.018	0.912 ± 0.52	5.94 ± 0.88	110.2±9.45	101.10±0.39	48 ± 1.62
F13	19.01 ± 0.48	0.260 ± 0.022	2.59 ± 0.42	4.35 ± 0.66	114.33±8.33	98.63±0.63	78 ± 0.85
F14	27.82 ± 0.49	0.374 ± 0.019	1.97 ± 0.15	3.9 ± 0.91	117.33±8.23	97.26±0.39	109 ± 1.45
F15	36.52 ± 0.49	0.450 ± 0.025	0.93 ± 0.25	2.89 ± 0.45	105.12±8.10	99.98±0.26	210 ± 0.52
F16	19.52 ± 0.49	0.268 ± 0.016	2.35 ± 0.56	4.29 ± 0.67	112.33±5.88	97.85±0.23	79 ± 0.64
F17	28.23 ± 0.21	0.397 ± 0.020	1.49 ± 0.35	3.21 ± 0.21	101.21±6.21	99.19±0.21	110 ± 0.18
F18	36.92 ± 0.21	0.467 ± 0.010	0.79 ± 0.35	2.21 ± 0.24	103.40±5.12	100.52±0.50	230 ± 0.68

Data represents Mean ± Standard deviation, n=3

Weight variation and thickness: The Weight variation and thickness were measured respectively for all the formulations and the results were given in the table 5. Weight variation ranges from 18.21 ± 0.86mmg to 36.92 ± 0.21mmg and thickness ranged from 0.210 ± 0.012 to 0.467 ± 0.010 mm. From the results it was concluded that as the polymer concentration increases, weight and thickness also increased.

Mechanical properties of cpm oral fast dissolving films: Mechanical properties i.e. tensile strength and percent elongation were measured and the results were given in the **table 5.** Tensile strength values ranged from 0.612 ± 0.580 to 2.59 ± 0.42 Kg/mm^2 and percent elongation ranged from 1.62 ± 0.82 to 5.94 ± 0.88. From the results it was observed that the films made of HPMC E6 were shown good film strengths.

Folding endurance: Folding endurance test results were given below in the table 5. The folding endurance of all the oral fast dissolving formulations was ranging from 93.66 ± 8.12 to 128.66 ± 5.87. From this study it was observed that the formulations containing PEG 400 were showing good results and the formulations containing HPMC E6 (F4 – F6) were showing better results compared to other formulations.

Physical appearance and texture analysis: These studies were conducted manually by visual inspection. This study shown that the films made of PEG 400 were shown good physical appearance and texture when compared with the films formulated by using propylene glycol.

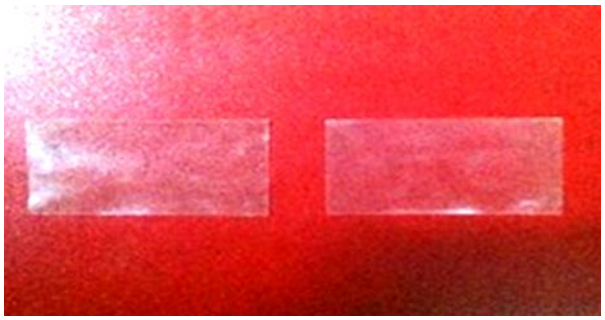
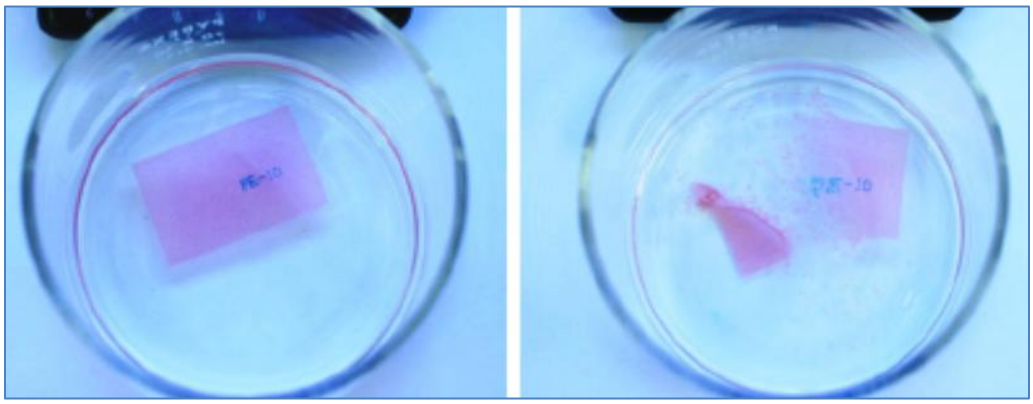


FIGURE 2: APPEARANCE OF THE FILM

Assay and in *vitro* disintegration time: The results were given in the table 5. The assay values of all the formulations were ranging from 97.02 ± 0.47 to 101.10 ± 0.39 % and the mean disintegration time values were ranging from 32±0.85 to 230 ± 0.68 sec. From the results, we can conclude that the formulations containing low viscous polymers with low polymer ratios showed faster disintegration.



Initial Time Disintegrated Film

FIG.3: DISINTEGRATION OF THE FILM

***In vitro* release studies of prepared formulations:** *In vitro* dissolution of CPM oral fast dissolving films was conducted and the results were given below from **table 6 to table 8.**

***In vitro* drug releases for F1 to F6 formulations:** *In vitro* dissolution study of formulations F1, F2, F3, F4, F5 and F6 were conducted and the results were given in the table 6. From this study it was observed that the cumulative % drug release ranged from 85.45±1.31 to 99.53±1.80 % within 10min. Among all formulations F2 showed good dissolution properties when compared with others.

TABLE: 6 *IN VITRO* DRUG RELEASES FOR F1 TO F6 FORMULATION

Time (min)	Cumulative percent drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	47.69±1.85	50.05±1.22	42.89±1.17	46.75±1.11	48.99±1.53	40.42±1.43
4	58.02±1.96	65.21±1.56	52.78±1.09	55.49±1.19	60.62±1.34	51.22±1.22
6	69.58±1.65	78.56±1.72	60.54±1.22	64.65±1.72	75.23±1.75	58.32±1.72
8	77.82±1.47	82.46±1.98	71.27±1.45	74.65±1.65	79.25±1.36	68.44±1.64
10	95.63±1.33	99.53±1.80	90.83±2.27	94.76±2.43	98.05±1.74	85.45±1.31

Data represents Mean ± Standard deviation, n =3

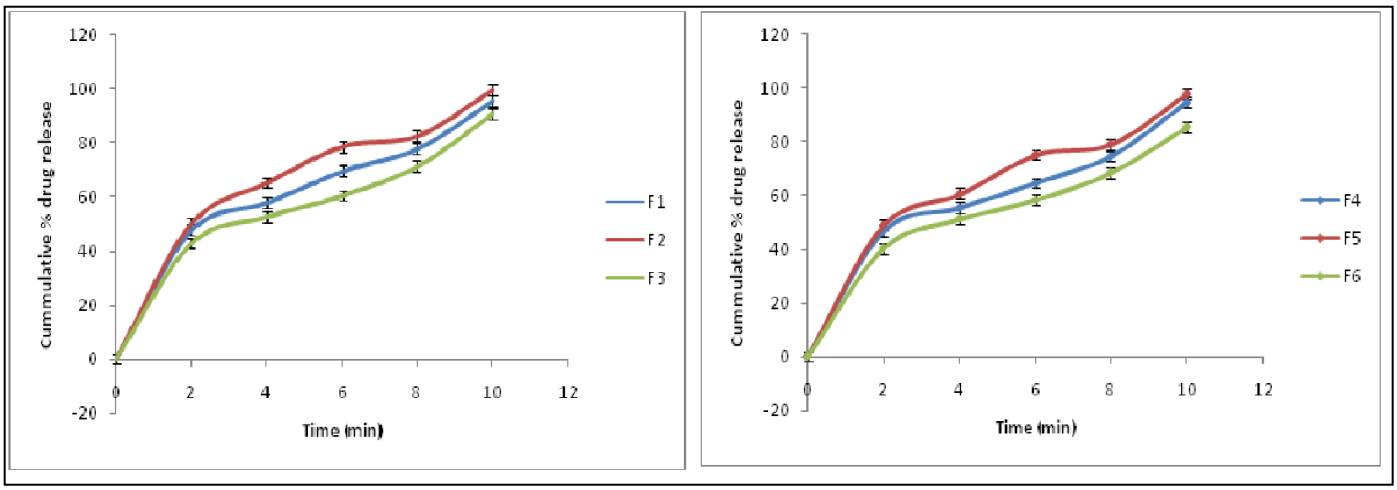


FIG. 4: PLOT FOR *IN VITRO* DRUG RELEASE FOR F1 TO F6 FORMULATIONS

***In vitro* drug releases for F4 A to F6 B formulation:** *In vitro* dissolution study of formulations F7, F8, F9, F10, F11 and F12 were conducted and the results were given in the **table 7**. From this study, it was observed that the cumulative % drug release ranged from 85.73±1.82 to 99.48±1.37 % within 16 min. Among all formulations F2 showed good dissolution properties when compared with others

TABLE: 7 *IN VITRO* DRUG RELEASES FOR F7TO F12 FORMULATIONS

Time (min)	Cumulative percent drug release					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
2	30.72±1.15	32.16±1.36	24.16±1.11	28.35±1.44	30.45±1.12	23.27±1.33
4	36.18±1.44	41.42±1.45	32.54±1.54	35.48±1.72	42.52±1.18	30.51±1.72
6	48.11±1.27	52.18±1.11	46.8±1.19	46.74±1.35	50.74±1.21	45.7±1.46
8	65.9±1.54	68.8±1.41	56.06±1.33	59.80±1.22	65.38±1.10	55.24±1.15
10	82.1±1.31	84.2±1.42	78.2±1.24	80.52±1.10	83.78±1.47	75.4±1.12
12	89.63±1.33	92.53±1.80	85.83±1.27	85.76±1.43	89.05±1.74	80.45±1.31
14	96.42±1.74	98.47±1.52	92.46±1.54	94.85±1.57	95.25±1.58	90.52±1.45
16	95.19±1.39	99.48±1.37	90.70±1.78	93.41±1.42	98.95±1.64	85.73±1.82

Data represents Mean ± Standard deviation, n =3

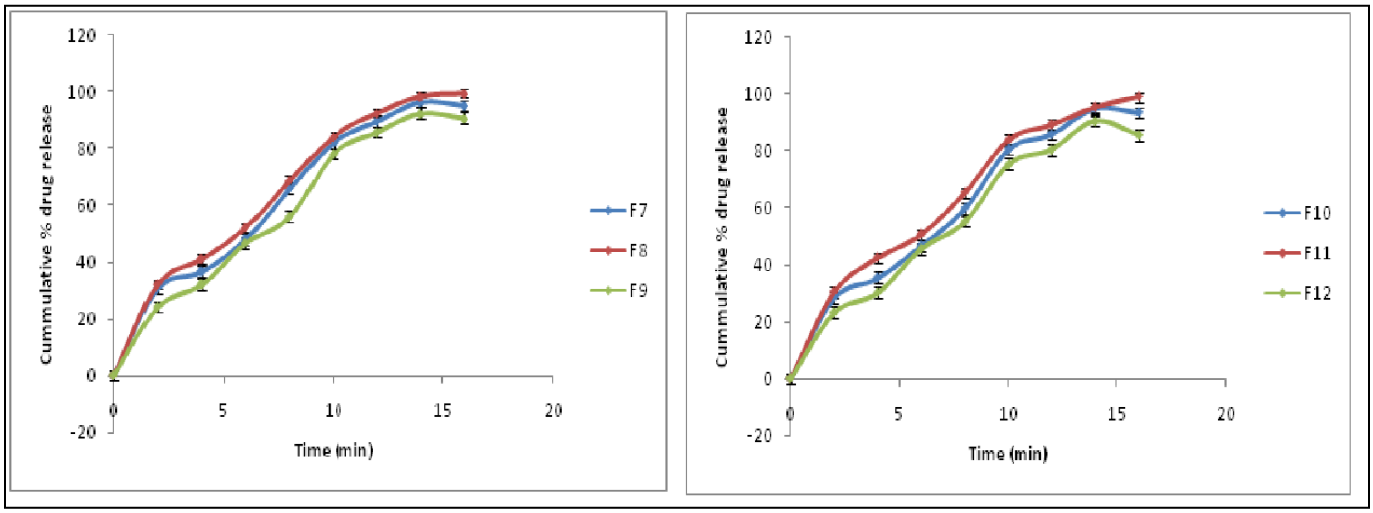


FIG. 5: PLOT FOR *IN VITRO* DRUG RELEASE FOR F7TO F12 FORMULATIONS

***In vitro* drug releases for F13to F18 formulation**

In vitro dissolution study of formulations F13, F14, F15, F16, F17 and F18 were conducted and the results were given in the **table 8**. From this study, it was observed that the cumulative % drug release ranged from 90.45±1.73 to 102.23±1.48% within 22min. Among all formulations F2 showed good dissolution properties when compared with other F13 and F18 formulations.

TABLE: 8 *IN VITRO* DRUG RELEASES FOR F13 TO F18 FORMULATIONS

Time (min)	Cumulative percent drug release					
	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0
2	13.79±1.21	15.11±2.1	10.53±2.1	9.89±0.9	13.21±1.2	8.77±1.28
4	21.54±1.3	25.98±2.3	19.09±1.5	11.64±1.8	14.21±1.5	10.03±1.6
6	35.79±1.4	40.33±1.1	32.29±1.4	28.21±1.5	33.1±3.1	22.53±1.98
8	59.9±1.6	62.12±1.4	55.03±1.8	45.98±1.4	50.74±1.9	44.59±1.9
10	72.4±1.32	74.85±1.6	70.03±1.2	69.48±1.7	73.84±1.8	67.44±1.7
12	77.82±1.45	82.46±1.98	71.27±1.45	74.65±1.65	79.25±1.36	68.44±1.64
14	83.1±1.38	85.2±1.45	79.2±1.58	81.52±1.10	84.78±1.46	76.4±1.12
16	88.63±1.33	92.53±1.80	83.83±1.27	84.76±1.43	90.05±1.74	79.45±1.31
18	96.92±1.74	98.75±1.52	92.77±1.54	94.43±1.57	95.55±1.58	90.73±1.45
20	93.76±1.39	98.48±1.37	89.11±1.78	92.40±1.42	97.82±1.64	84.72±1.82
22	96.29±1.47	102.23±1.48	92.52±1.84	95.46±1.78	100.76±1.56	90.45±1.73

Data represents Mean ± Standard deviation, n =3

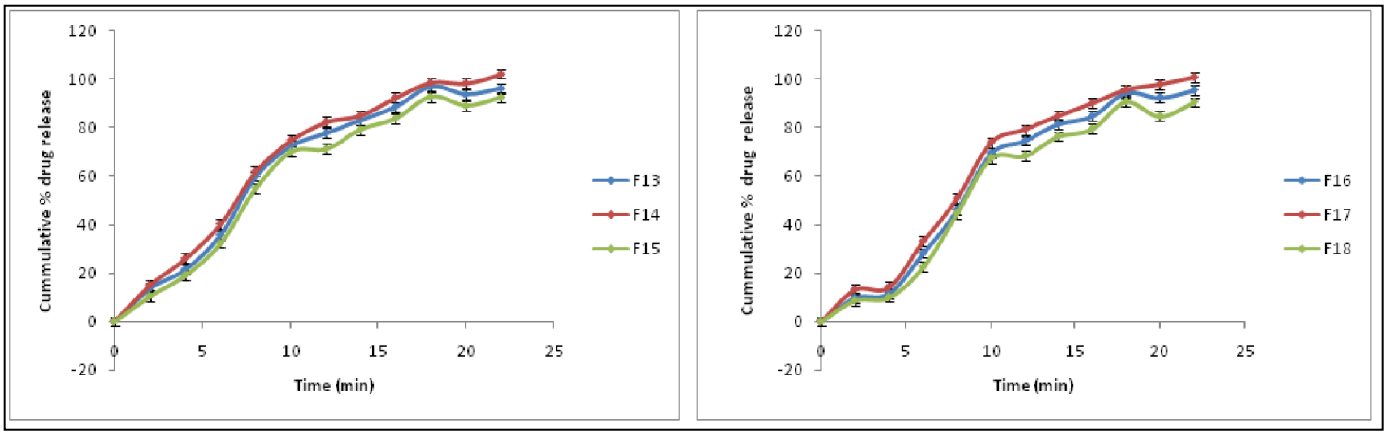


FIG. 6: PLOT FOR *IN VITRO* DRUG RELEASE FOR F13 TO F18 FORMULATIONS

IN VITRO DRUG RELEASES FOR F2, F8, F14 AND MARKETED FORMULATIONS

In vitro dissolution study of formulations F2, F8, F14 and Trofil were conducted and the results were given in the table 19. From this study it was observed that the cumulative % drug release varied from 68.81±2.1 to 99.53±1.80 % within 10min. Among all formulations F2 is showed good dissolution properties when compared with others.

TABLE 9: *IN VITRO* DRUG RELEASES FOR F2, F8, F14 AND MARKETED TABLET FORMULATIONS

Time (min)	Cumulative percentage drug release			
	F2	F8	F14	Marketed tablet
0	0	0	0	0
2	50.05±1.22	32.16±1.36	15.11±2.1	11.54±2.2
4	65.21±1.56	41.16±1.45	25.98±2.3	20.41±2.5
6	78.56±1.52	52.18±1.11	40.33±1.1	40.20±1.9
8	82.46±1.98	68.8±1.41	62.12±1.4	52.52±2.4
10	99.53±1.80	84.2±1.42	74.85±1.1	68.81±2.1

Data represents Mean ± Standard deviation, n =3

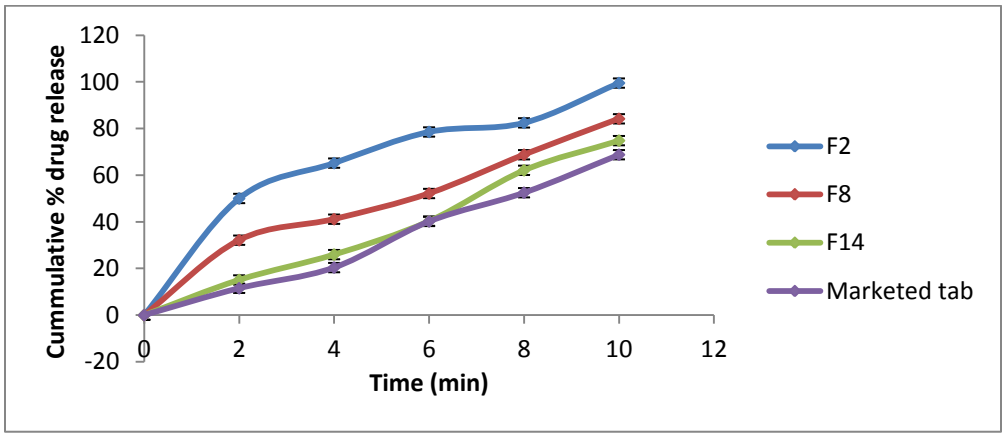


FIG. 7: PLOT FOR *IN VITRO* DRUG RELEASE FOR F2, F8, F14 AND MARKETED 4MG TABLET

Compatibility studies:

Fourier transforms infrared (FTIR) spectroscopy studies

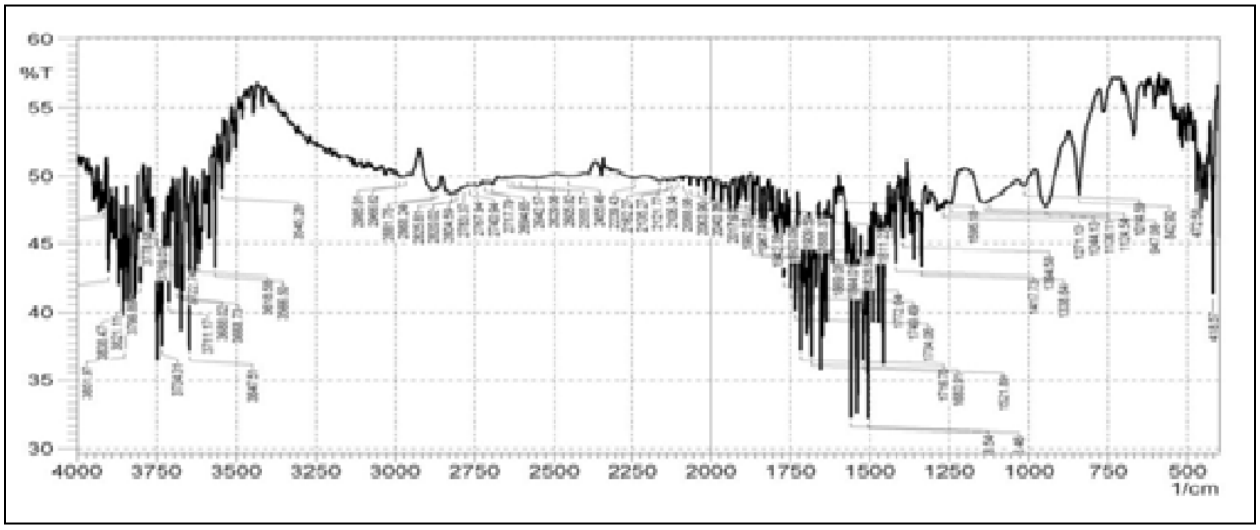


FIG. 8: FTIR SPECTRUM OF CPM

TABLE 10: VIBRATIONS AND FREQUENCY FOR SPECTRUM OF CPM

S. No.	Type of vibrations	Frequency(cm^{-1})
1	N-H Stretching in (amines)	3545.28
2	N-H Stretching	3545.28
3	C-H Stretching in methyl or aromatic	2985.91
4	C-H Stretching	2966.62
5	C=C Stretching in aromatic nuclei	1683.91
6	C=C Stretching	1595.18
7	C-H deformation in methyl	1417.73
8	C-H deformation in –CH3	1394.58
9	C-N Stretching	1124.54
10	C-N Stretching	1014.59

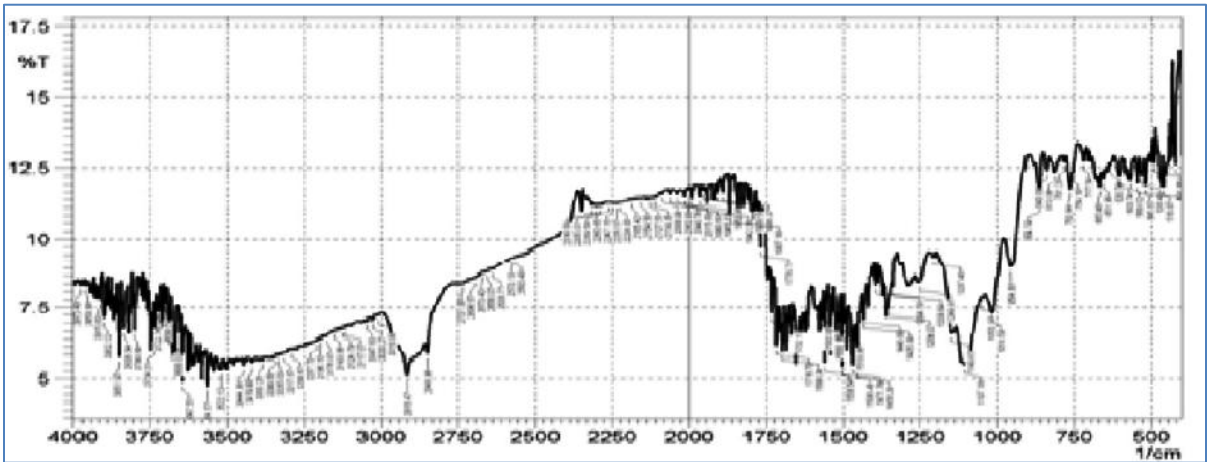


FIG. 9: FTIR SPECTRA OF CPM WITH HPMC E3

TABLE 11: VIBRATIONS AND FREQUENCY FOR SPECTRUM OF CPM AND HPMC E3

S. No.	Type of vibrations	Frequency(cm^{-1})
1	N-H Stretching in (amines)	3522.13
2	N-H Stretching	3444.98
3	C-H Stretching in methyl or aromatic	2916.47
4	C-H Stretching	3010.96
5	C=C Stretching in aromatic nuclei	1699.34
6	C=C Stretching	1583.6
7	C-H deformation in methyl	1435.09
8	C-H deformation in –CH3	1394.58
9	C-N Stretching	1149.61
10	C-N Stretching	1014.59

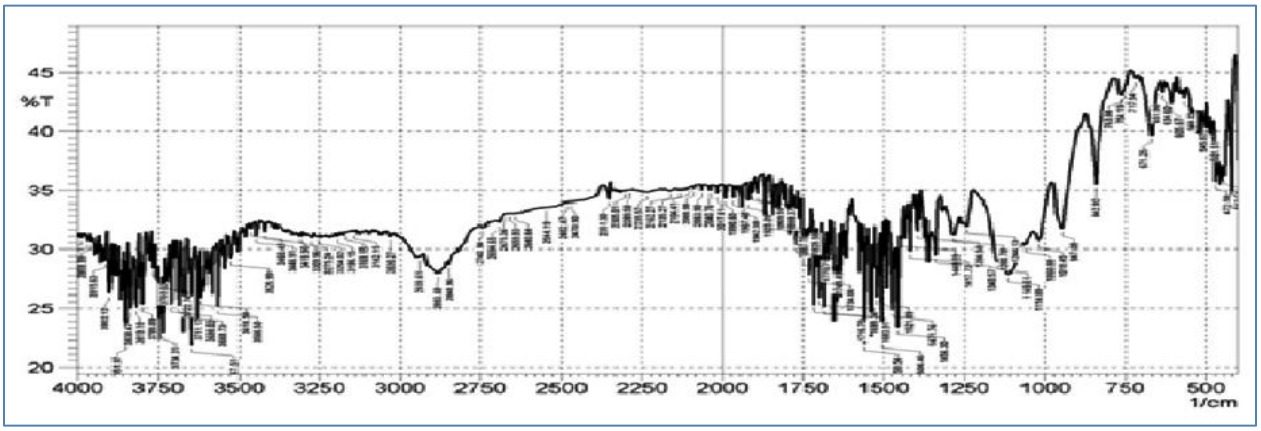


FIG. 10: FTIR SPECTRA OF PHYSICAL MIXTURE (FORMULATION 2)

TABLE 12: VIBRATIONS AND FREQUENCY FOR SPECTRUM OF PHYSICAL MIXTURE (FORMULATION 2)

S. No.	Type of vibrations	Frequency(cm^{-1})
1	N-H Stretching in (amines)	3525.99
2	N-H Stretching	3460.41
3	C-H Stretching in methyl or aromatic	2939.61
4	C-H Stretching	3030.27
5	C=C Stretching in aromatic nuclei	1683.91
6	C=C Stretching	1521.89
7	C-H deformation in methyl	1417.73
8	C-H deformation in –CH3	1394.58
9	C-N Stretching	1149.61
10	C-N Stretching	1018.45

The characteristic absorption peaks of CPM was found at 3545cm^{-1} (N–H stretch in amines), 2985cm^{-1} (C-H stretch in methyl aromatic), 1683cm^{-1} (C=C stretch in aromatic), 1417cm^{-1} (C-H deformation in methyl), 1149 cm^{-1} (C–N stretch). The FT-IR study indicated that the characteristic peaks of CPM which was also present in physical mixture. It showed that there is no interaction between drug and excipients which was further confirmed by DSC analysis.

DIFFERENTIAL SCANNING COLORIMETRY:

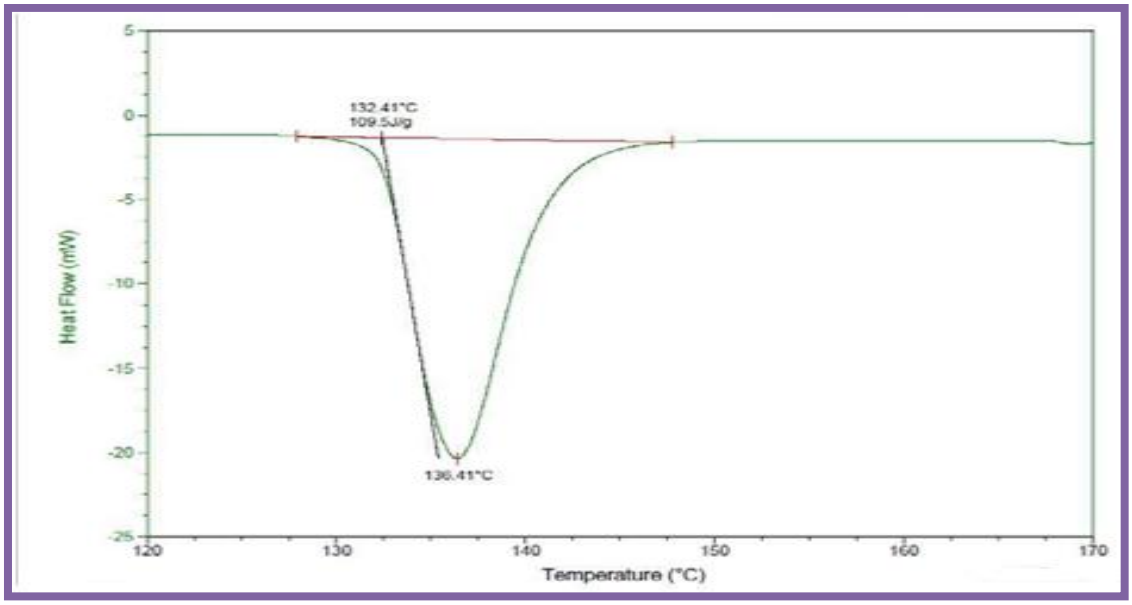


FIG. 11: DSC SPECTRUM OF CHLORPHENIRAMINE MALEATE

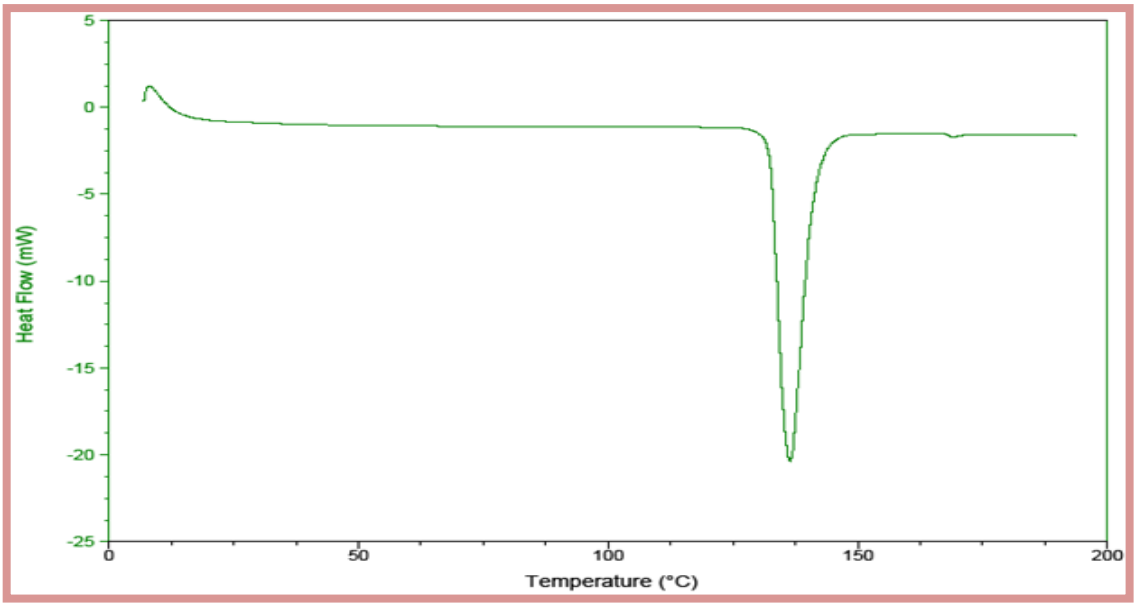


FIG 12: DSC SPECTRA OF PHYSICAL MIXTURE

The DSC spectrum of chlorophenaramine shows sharp endothermic peak at 136°C which is the identity for melting point of drug (**Figure 11**). The DSC spectrum of the selected formulation also shows similar peak (**Figure 12**) which proves that there is no possible physical or chemical interaction between the drug and exicipients.

Scanning Electron Microscopy: Surface morphology of CPM oral film was performed using scanning electron microscopy (SEM) to study differences between upper and lower sides of films and to determine the uniform distribution of active pharmaceutical ingredient. The image of scanning electron microscopy of the formulation F2 was depicted in **figure 13**. The electron intensity creates the image contrast that reveals the topography or surface morphology of films ind the image in figure 13 reveals that the surface morphology of the formulation F2 film has a smooth texture and uniform distribution of active pharmaceutical ingredient.

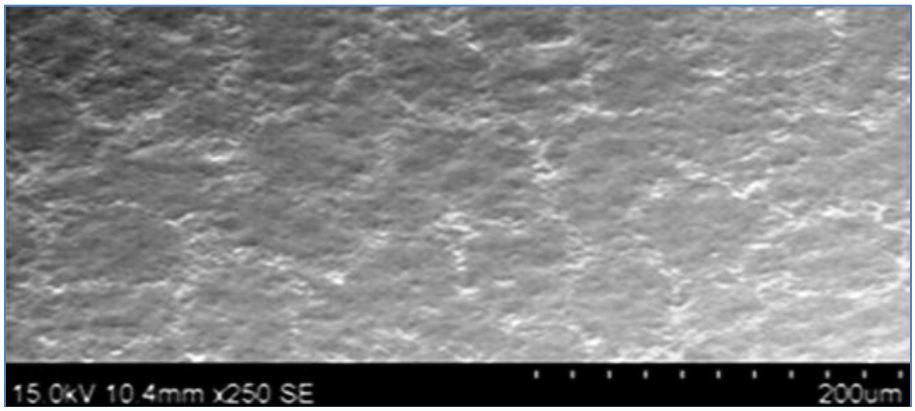


FIG. 13: SCANNING ELECTRON MICROSCOPY IMAGE OF FORMULATION F2

Accelerated stability studies of the optimized batch: The samples were observed for changes on films surface. It was observed that film surface was devoid of any change in color or appearance. It was also noted that film was free of microbial or fungal growth or bad odor. The results are tabulated in **Table 13**. The formulation F1 to F18 was found to be stable in terms of drug content and thickness and *in--vitro* release profile as shown in Table 13. The *in-vitro* release profile of F2, F8 and F14 initially and after 3 months is almost the same and there is not much difference observed. Thus the developed formulation is found to be stable for storage conditions as per the ICH guidelines.

TABLE 13: CHARACTERISTICS OF THE FILMS DURING STABILITY STUDIES

Evaluation	Storage condition $40^0C \pm 2^0C$ / 75±5 % RH			
Parameters	**Initial**	**1st month**	**2nd month**	**3rd month**
Disintegration time (sec)	34 ± 1.46	34±0.52	34±0.14	34±0.48
Thickness (mm) ± S.D	0.243±0.017	0.242±0.058	0.242±0.058	0.242±0.058
Mean weight(mg) ± S.D	27.23 ± 0.54	27.23 ± 0.52	27.23 ± 0.52	27.23 ± 0.52
Mean Tensile strength (Kg/mm^2) ± SD	0.690±0.532	0.690±0.535	0.690±0.535	0.690±0.535
Percent Elongation	1.82 ± 0.78	1.82 ± 0.80	1.82 ± 0.80	1.82 ± 0.80
Folding endurance	95.66 ± 6.23	95.66 ± 6.20	95.66 ± 6.20	95.66 ± 6.20
Drug content uniformity (%)	99.94 ± 0.32	99.94 ± 0.30	99.95 ± 0.10	99.94 ± 0.20
% Cumulative drug release (10min)	99.53±1.80	99.53±1.80	99.53±1.80	99.53±1.80

ACKNOWLEDGEMENT: I express whole-hearted gratitude to my guide Mr. G. Prasad Associate Professor, Department of Pharmaceutics for suggesting solution to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

It is with fathomless gratitude that I express my benevolent thanks to my reverent teacher Prof. Dr. B. Vijay Kumar Principal and Head of the Department, Pharmaceutics, JIPS, Yeshwanthapur, Jangaon for providing invigorate undeterred support, scholastic guidance and conductive environment to pursue this research work with great ease. I feel privileged, fortuitous having been his student in my pursuit knowledge.

CONCLUSION: The present study was undertaken with an intention to develop Oral fast dissolving films (OFDFs) of Chlorpheniramine maleate as an antihistaminic drug and to provide a convenient means of administration to those patients suffering from difficulties in swallowing such as pediatric and geriatric patients. These films were prepared using HPMC (E3, E6, and E15) polymers by solvent casting method. FTIR and DSC showed that there is no interaction between drug and excipients.

All the formulations prepared were evaluated for various parameters like thickness, percent elongation, drug content uniformity, weight variation, disintegration time, folding endurance and in vitro drug release and were showed satisfactory results. Disintegration time of the films was increased with increase in the concentration of the polymer. Content uniformity study showed that the drug is uniformly distributed in the films. Small differences were observed in dissolution of drug from the film for all the formulations.

Present study reveals that maximum all formulated films showed satisfactory film parameters. Formulation with HPMC E3 has shown better *in* vitro dissolution profile compared with other formulations. Finally oral fast dissolving films of Chlorpheniramine maleate were prepared by solvent casting method. From the present investigation it can be concluded that oral fast dissolving film formulations can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

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How to cite this article:

Kanth NP, Prasad G and Kumar VB: Oral Dissolving Films Of Chlorpheniramine Maleate. *Int J Pharm Sci Res* 2014; 5(5): 1859-73.doi: 10.13040/IJPSR.0975-8232.5 (5).1859-73