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Formulation development and characterization of chlorpheniramine maleate mouth dissolving films

Pamula Reddy B.[1*], M. Mohan Varma[1], Sudheer Betha[1], D. Basava Raju[1], Ramu Mecha[1] and J. Vijaya Ratna[2]

[1]Department of Pharmaceutical Technology, Shri Vishnu College of Pharmacy, Bhimavaram, Andhra Pradesh, India
[2]A U College of Pharmaceutical Sciences, Andhra University, Vishakhapatnam, India

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ABSTRACT

Chlorpheniramine Maleate (CPM) is a first generation alkylamine antihistamine used in the prevention of the symptoms of allergic conditions such as rhinitis and urticaria. The purpose of the present study was to formulate and evaluate mouth dissolving films of Chlorpheniramine Maleate (4mg). The films were prepared with various water soluble polymers such as HPMC (3cps and 5cps), Methyl Cellulose (MC E 15), and Kollicoat IR with suitable plasticizers like PEG 400 and glycerin. Citric acid was used in this study as saliva stimulating agent. Superdisintegrant was also included in the formulation to improve the release characteristics. Chlorpheniramine Maleate films were prepared with different ratios of water soluble polymers and plasticizers by solvent evaporation technique. The prepared films were evaluated for vitro dissolution studies. The release of CPM from Kollicoat IR films was 100% in 5mins in the dissolution medium of (pH 6.8 phosphate buffer). The release profiles of films were analyzed by using the UV- Visible spectrophotometer at 223nm. In vitro parameters like thickness, disintegration, folding endurance, assay and weight of the films were evaluated. Preformulation studies of CPM like compatibility studies with polymers, using Fourier transform infrared spectroscopy (FTIR), X ray diffraction (XRD) and Scanning electron microscopy (SEM) were carried out. The drug and polymers were found to be compatible with each other. These results strongly suggested that the water soluble polymers were suitable for the formulation of mouth dissolving films of CPM.

Keywords: Mouth dissolving films, water soluble polymers, CPM, dissolution rate.

INTRODUCTION

A variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication [1- 3]. Oral route of drug administration is considered to be most effective and acceptable form due to its better therapeutic efficacy. Peroral dosage forms can be distinguished as solid or liquid oral dosage forms in which the prior fall in the category of pills, capsules, granules and powders [4, 5]. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, moth dissolve or melt dosage forms [6-8].Among the delivery routes, the oral route is the most acceptable from the patient compliance aspects. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue. It is interesting to note that the permeability of buccal mucosa is greater than that of the skin, but less than that of the intestine [9-11]. It is also reported that the permeability of the buccal mucosa is approximately 4-4000 times greater than that of the skin [12]. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive

tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films [13]. Numerous oral disintegration (OD) dosage forms have been developed, with tablets taken with water being the most widely utilized. OD tablets absorb saliva and immediately disintegrate in the oral cavity. After disintegration, the drug and the insoluble components, such as the disintegrated material incorporated in the OD tablet, remain on or around the tongue. This dosage form, however, may not be easy to swallow, so the development of new forms for patients who have difficulty in swallowing the regular tablets is desirable. Recently, fast dissolving films (Fdfs) have attracted interest as an excellent dosage form, not only for oral care, but also for patients with aphagia or dysphagia [14, 15]. The Fdfs are generally prepared from a polymer base and a plasticizer such as sorbitol, fatty acid and PEG [16-18]. The advantages of oral films include larger surface area, enhanced safety, and high precision during dose administration compared to liquid forms, high levels of patient compliance, and quicker relief [19].

MATERIALS AND METHODS

Drug used in this study was purchased from Vijaya Scientifics limited, Hyderabad. HPMC (3cps and 5cps) was gifted from RA Chem Pharma Limited, Hyderabad. All the other materials and reagents used were of analytical grade.

Preparation of mouth dissolving films

The mouth dissolving film of CPM using polymers were prepared by solvent evaporation method. An aqueous solution of the polymers was prepared in distilled water. CPM was added to the aqueous polymeric solution. This was followed by addition of plasticizers like PEG 400 and glycerin. Citric acid was also mixed with it. The solution was casted on a Petridish and dried at room temperature for 24hrs. The film was carefully removed from the Petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose per strip.

Weight Variation

The $4cm^2$ film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation was observed.

Thickness

The thickness of the film was measured using a micrometer screw gauge at five points (centre and four corners) on the film to ensure the uniformity of the film thickness and the mean thickness was evaluated [20].

Folding Endurance

The folding endurance was measured manually for the prepared films. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance [21].

In *vitro* Disintegration

The film as per the dimensions $4cm^2$ required for dose delivery was placed on a stainless steel wire mesh placed in a Petridish containing 10ml of distilled water. Time required for the film to break was noted.

In vitro Dissolution Studies

According to previous studies, dissolution studies were performed using USP 23 apparatus, paddle over disc method. As the paddle over disc apparatus was not available, USP apparatus 1 (basket) (Lab India Model No: DISSO-2000) was used for this study. Three hundred millilitres of phosphate buffer (pH 6.8), which is a prescribed media for Chlorpheniramine Maleate was maintained at 37±5°C while the basket was set at 50 rpm. A film sample of $4cm^2$ was cut and taken into the basket. The five millilitres of dissolution samples were withdrawn at different time intervals, and the same amount was replaced with the fresh buffer. The withdrawn samples were filtered and analysed using a UVspectrophotometer at a wavelength of 223 nm. The percentage drug release was calculated. The relationship between time and percentage release was plotted to determine when the maximum amount of drug is released. The dissolution studies were carried out in triplicate (n=3).

Characterization Studies

IR ***(Infra-red) spectroscopy analysis***

The FT-IR spectroscopy (BRUKER Optics FTIR spectrophotometer, Model Alpha 200218) was employed as analytical tool to check the drug-polymer interaction, using the KBr disc method. The FTIR spectra were scanned and recorded between 400 and 4000 cm^{-1}.

Scanning Electron Microscopy (SEM)
The surface morphology of the film was studied by using SEM (Jeol, Model-JSM 6610 LV).

X-ray Diffraction of film
The X-ray Diffraction of the drug loaded film was recorded (Panalytical, Model-Xpert Pro).

RESULTS AND DISCUSSION

In this present work, efforts have been made to prepare the mouth dissolving films of Chlorpheniramine Maleate using the water soluble polymers such as HPMC (3cps and 5cps), KollicoatIR and MC using PEG-400 and glycerin as a plasticizer by the solvent evaporation method. The prepared films were evaluated for the physicochemical properties and the in vitro drug release studies. The proper selection of the polymer produces clear, uniform, flexible films with the desired thickness for the mouth dissolving films of CPM. The CPM films were prepared with sodium CMC (M9-M12) showed poor dissolution rate release, when compared with other polymers. The prepared formulations were evaluated for different physicochemical characteristics such as thickness, folding endurance, drug content, weight variation and disintegration. In vitro dissolution studies were carried out in pH 6.8 phosphate buffer. The disintegration, thickness, weight variation, assay values were in the official limits, folding endurance varied from10 to 215 times, pH of films ranged from 6to 7.

IR (Infra-red) Spectroscopy Analysis
When we observe the Fig.1 of FTIR spectra, the drug, exhibited the peaks at 2967.00 cm^{-1},2925.27 cm^{-1} for C-H aromatic stretching, 650.34 cm^{-1}, 944.87 cm^{-1} for C=C characteristic peaks , 3420.60 cm^{-1} for O=H stretching for Maleate salt, 1703.38 cm^{-1} for C=O and 752 cm^{-1} for C-Cl bending. The same peaks of the drug were observed in the drug-Kollicoat IR, M15 physical mixture, there by ruling the absence of drug- polymer interaction.

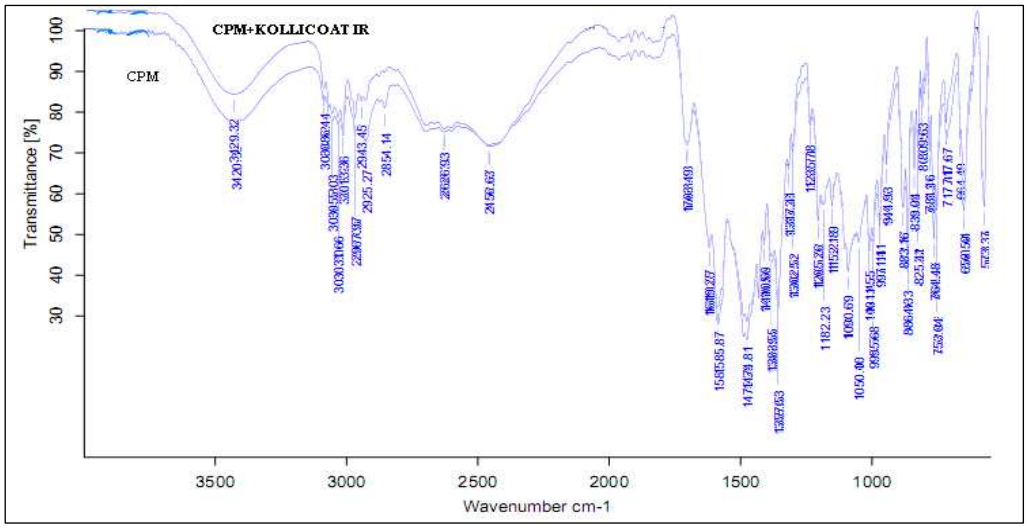

Fig 1: FT-IR spectra of the Drug and Drug+KollocoatIR Physical Mixture.

The FT-IR studies (Fig: 1) all the spectra of drug and drug with polymer mixture at the same wave number, indicated no modifications or interaction between the drug and the excipients. From this it can be concluded that the drug has maintained its identity without losing its characteristic properties.

SEM Studies
Scanning electron microscopy has been extensively employed to study the morphology of the film. The morphology of the selected film was examined by SEM (Jeol, Model-JSM 6610 LV).

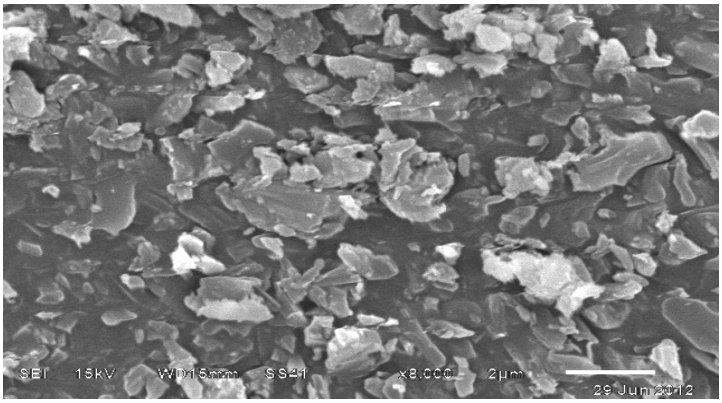

Fig 2: SEM image of Drug+KollocoatIR thin film (Formulae M15)

The surface morphology of the film (SEM image) of the thin film is shown in Fig-2. It conforms that the particle size was in between 340-630nm.

X-ray Diffraction of Film

To investigate the crystallographic properties of the observed particles in the drug loaded oral films X-ray diffraction was used. The X-ray Diffraction of the drug loaded film was recorded (Panalytical, Model-Xpert Pro).

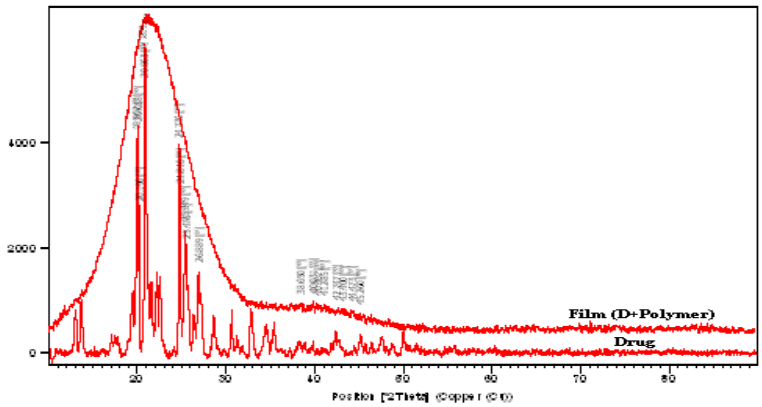

Fig 3: X ray diffractogram of Pure Drug and Film (Formulae M15)

The XRD results revealed that the Fig3 showed the pure drug in sharp crystalline peaks. However, the crystalline peaks completely absent in the drug loaded film (M15), this indicating that the drug present in the amorphous form in the film.

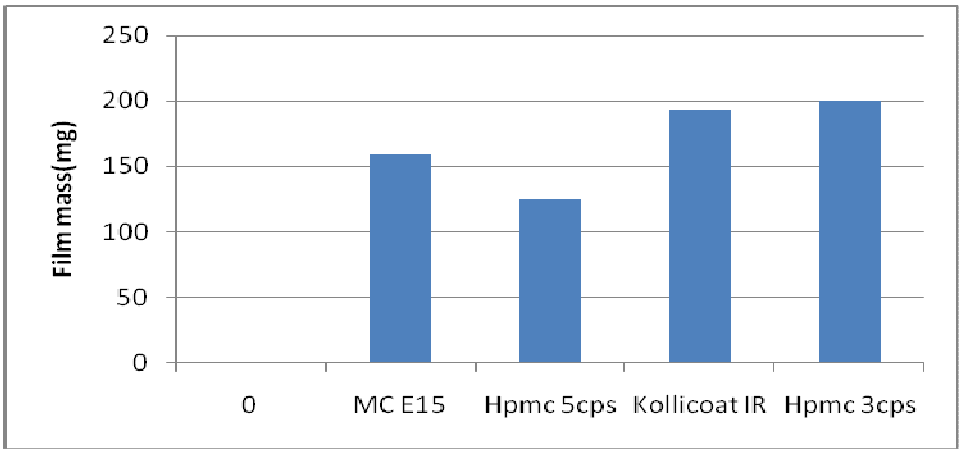

Fig 4: Weight variation of the CPM mouth dissolving films

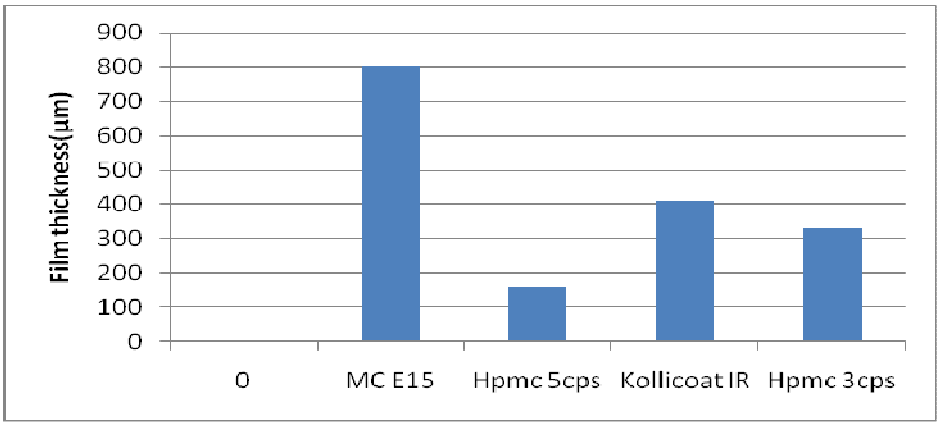

Fig 5: Thickness of the CPM mouth dissolving films

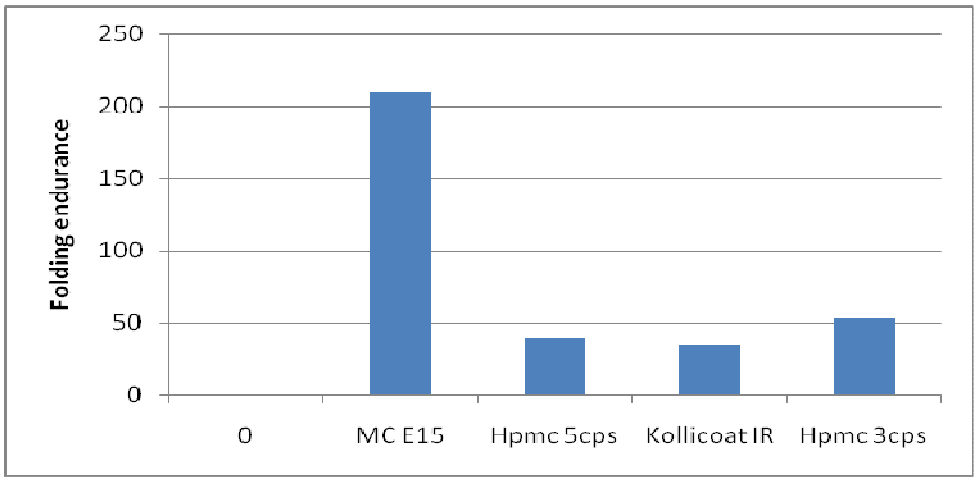

Fig 6: Folding endurance of the CPM mouth dissolving films

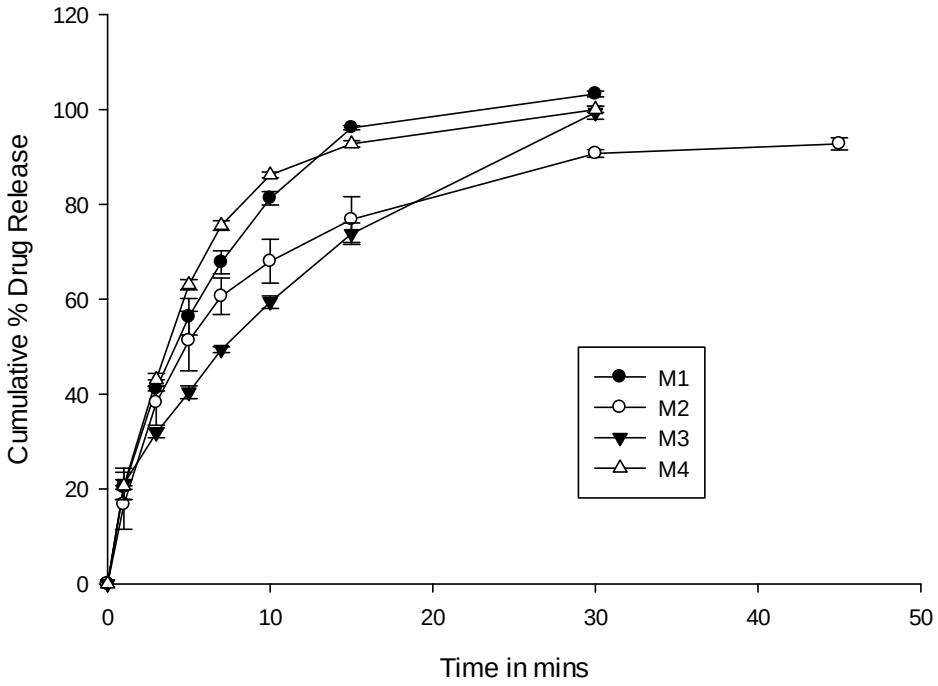

Fig 7: *In vitro* drug release from films containing CPM and MC E15

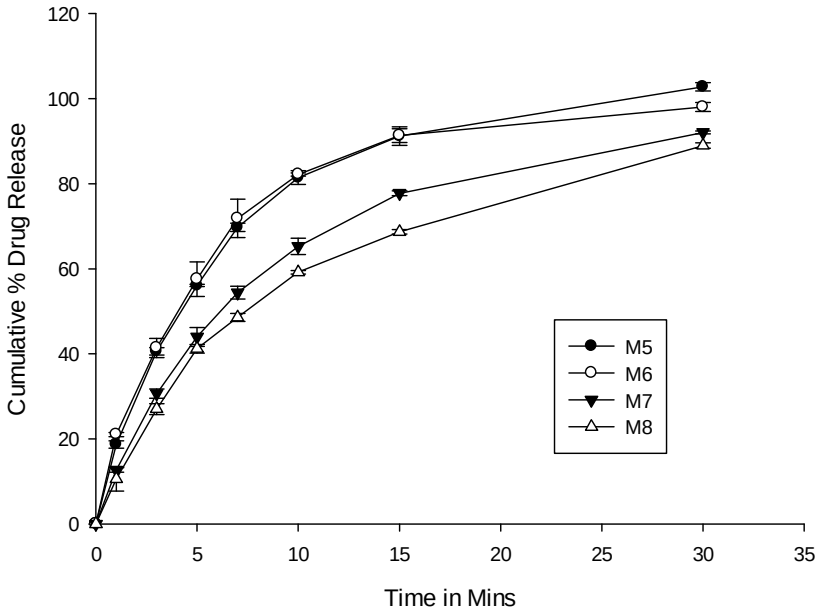

Fig 8: *In vitro* drug release from films containing CPM and HPMC 5cps

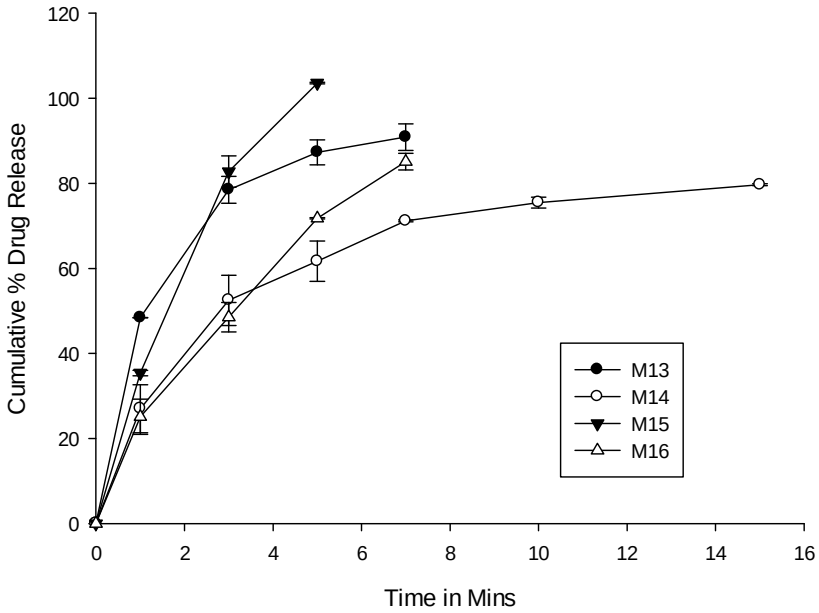

Fig 9: *In vitro* drug release from films containing CPM and Kollicoat IR

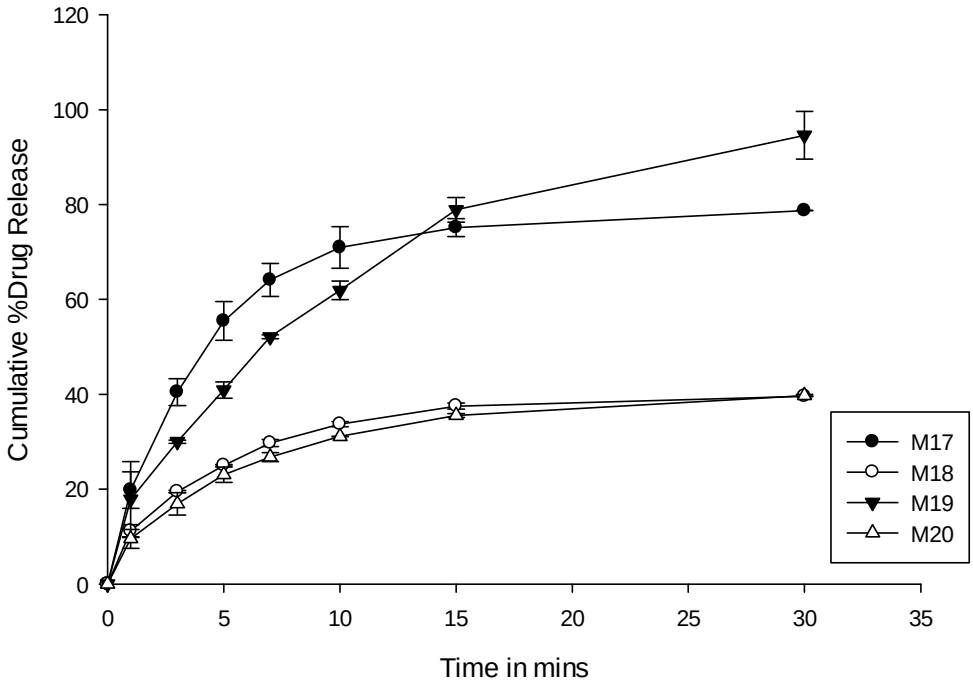

Fig 10: *In vitro* drug release from films containing CPM and HPMC 3cps

Kinetic Studies

Zero Order

The zero order describes the systems where the drug release rate is independent of its concentration. Figure no: 8 shows the for zero order plot of M15.

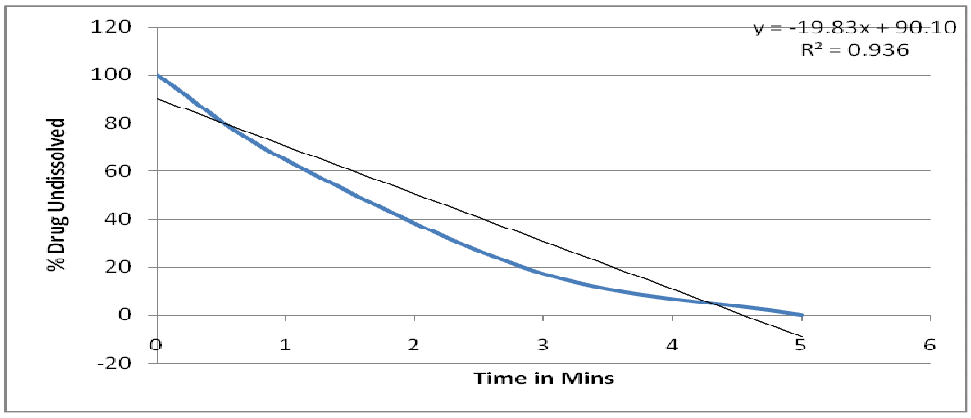

Fig 11: Zero order model for mouth dissolving film of CPM (M15)

First Order

First order describes the release from the systems where the release rate is concentration dependent. Figure no: 9 shows the first order plot of M15.

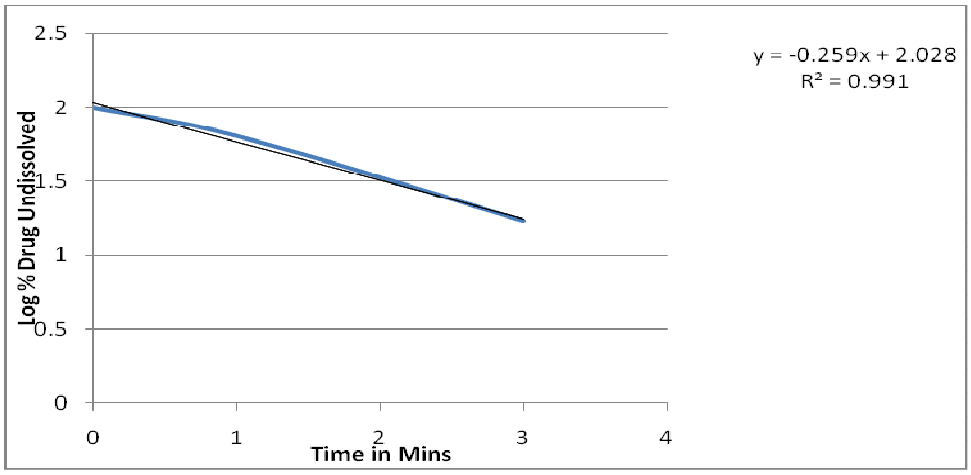

Fig 12: First order model for mouth dissolving film of CPM (M15)

It was found that the *In vitro* drug release of formulated moth dissolving films of M15 was best explained by first order kinetics as the highest linearity of 0.991 was observed; therefore the drug release rate was concentration dependent.

CONCLUSION

The prepared mouth dissolving films of Chlorpheniramine Maleate using different polymers such as HPMC (3cps and 5cps), Kollicoat IR and MC E15 had shown good promising results for all the evaluated parameters such as thickness, folding endurance, weight variation, pH and disintegration time. Based on the rate of drug release, among all the formulations, the formulation M15 containing drug and Kollicoat IR was concluded as an optimized formulation, which produced 100% of drug release in 5mins.

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