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Research Article

FORMULATION AND EVALUATION OF ORAL THIN FILM OF PROCHLORPERAZINE

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A B S T R A C T

The main objective of the present study was to prepare and evaluate the instant release oral thin films of Prochlorperazine, in order to enhance the bioavailability of the drug and to provide rapid onset of action thereby improving patient compliance. The instant release oral thin films of Prochlorperazine were prepared by solvent casting method using film forming polymer like Hydroxypropyl Methylcellulose E-15. The film was evaluated for various physicochemical parameters that include thickness, weight variation, folding endurance, tensile strength, drug content and *in vitro* drug release studies. No differences were observed in *in vitro* dissolution of drug from the formulated film F1-F9 as the film instantly gets wet by dissolution medium. The drug release for F3 formulations was about 97.8%. The accelerated stability studies for the optimized film formulations F3 were performed that indicates that the formulated instant release oral thin films were unaffected after initial and 3 months storage under accelerated conditions.

INTRODUCTION

Oral thin film is a dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"[1]. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients' turn the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc.) has the problem of accurate dosing mainly and parenteral are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the highest bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using super disintegrants and hydrophilic ingredients. Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for Pediatric and Geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms[2-3]. The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane[4].

Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia)[5].

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Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within a minute in the oral cavity after the contact with saliva without chewing and no need of water for the administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin[5]. OTFs also have an established shelf life of 2-3years, depending on the API but are extremely sensitive to environmental moisture[6]. The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules[7]. The oral thin-film technology is still in the beginning stages and has a bright future ahead because it fulfills all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology[8]. Oral thin films, a new drug delivery system for the oral delivery of the drugs, were developed based on the technology of the transdermal patch. The delivery system consists of 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. It then rapidly disintegrates and dissolves to release the medication for oral mucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of lyophilizates, the rapid films can be produced

by a manufacturing process that is competitive with the manufacturing costs of conventional tablets.

Oral mucosal delivery via Buccal, sublingual, and the mucosal route by use of OTFs could become a preferred delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. Dissolvable oral thin films (OTFs) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products[9].

MATERIALS AND METHODS

Prochlorperazine (Aurobindo Pharma Ltd, Hyderabad, India), Hydroxy propyl methyl cellulose, Propylene glycol, Mannitol, Aspartame, Ethanol, Citric acid, (SD Fine Chemicals Ltd., Mumbai), water.

Calibration Curve of Prochlorperazine

Prochlorperazine was dissolved in pH 6.8 phosphate buffer to get 100 µg/ml solution. Serial dilutions were made to get 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml of the final solution. The absorbance was measured at 254 nm by using UV Visible spectrophotometer.

Preparation of Blank Film

Polymer, Hydroxy Propyl Methyl Cellulose E15 (HPMC E15) of different weight were taken i.e., 200 mg, 300 mg, 400 mg, 500 mg…...900 mg, kept aside for soaking for half an hour and dissolved in the solvent separately in a glass beaker. The solution was stirred for 15 min to obtain a homogenous solution. With a time interval of 10-15 mins, other excipients were further added in the order. The solution is kept for stirring for approximately 1-2 hours on the magnetic stirrer. Then the solution is kept aside for few mins to remove any air bubbles entrapped. The mixture is poured into a glass ring which was kept on glass slide evenly as shown in figure 1 and left for drying for 24 h or dried in a hot air oven (Figure 2). The accurate volume of polymer in the film is chosen based on the film properties as observed in figure 3.

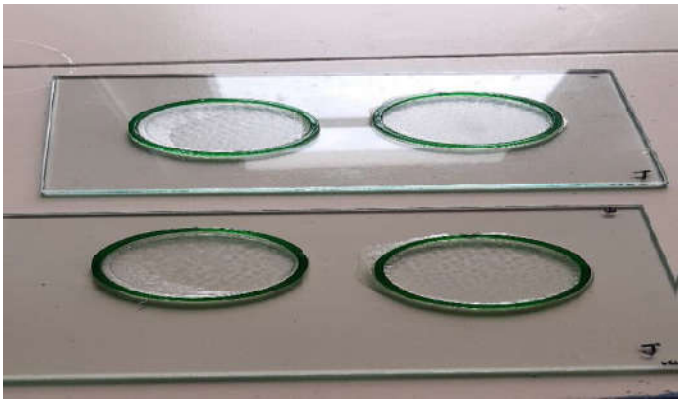

Fig 1 Film casting method of preparation on Glass slide

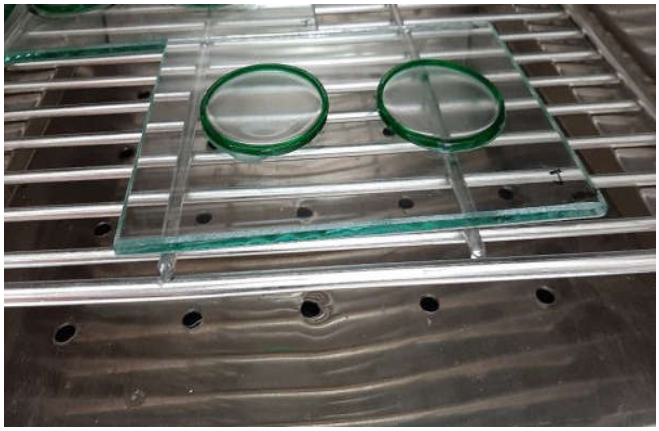

Fig 2 Glass slide placed in hot air oven for drying

Fig 3 Blank films

Preparation of Prochlorperazine Oral Thin Films

The oral thin film was prepared with the solvent-casting technique. In a beaker required quantity of ethanol was taken, the polymer was soaked in ethanol for about half an hour. The solution is agitated on a magnetic stirrer for half an hour. The drug (prochlorperazine) is dissolved in the polymeric solution and stirred for 15 min. Later, with an interval of 5-10 min the excipients, aspartame, mannitol, propylene glycol (PG), and citric acid were added. Eight formulations, F1 to F8 were prepared as shown in table 1 with increasing concentration of HPMC and all other ingredients concentration kept constant. After one hour of mixing the polymeric solution and other excipients, a homogenous solution was obtained. Then the solution is kept aside for 30 min to extract any air bubbles entrapped. The solution was then poured in a 27.3 cm^2 glass ring and are kept for drying either for 24 h at room temperature or put under 40-50 ^oC for 20 min in a hot air oven. The rings were then carefully removed and the films are separated. For further evaluations, the films that were transparent and clear were selected and cut into 4 cm^2 (2 x 2) and carefully placed in parchment paper and held in desiccators[11].

Evaluation of Oral Thin Films

Weight Variation

This test ensures the uniformity of the formed film. Each film was cut from the castfilms in 4 cm (2 x2). Per film was weighed and each films weight difference was estimated[9].

Film Thickness

The thickness of a single film was measured by a micrometer at three different places, an average of three values was

calculated. The thickness of the film is direct to the accuracy of the dose in the film. Samples with air bubbles, nicks or tears, and those having mean thickness variations greater than 5% were excluded from analysis[9].

Surface pH

The pH value was determined by dissolving oral film in 10 ml purified distilled water and measuring the pH of the obtained solution. The films must have a uniform pH value[9].

Folding Endurance

Flexibility of oral thin films is important as the key to the administration of film without breaking. A strip of 2x2cm was subjected by folding the film repeatedly at 180at the same place until a visible crack was observed and the values were noted. The number of times that the film could be folded at the same place without breaking gives the value of folding endurance[7].

Appearance

Each film was checked visually for its transparency, presence of air bubbles, strength, thickness[9].

Drug Content Uniformity

Films we retransferred into graduated flasks containing 100ml phosphate buffer pH 6.8 and continuously stirred with the help of a magnetic stirrer for 2 h. The solution was filtered, suitably diluted, and analyzed spectrophotometrically at 254nm and the drug content was calculated. Three pieces, each 1 cm^2 (1 ×1 cm), were cut from the whole patch, and assayed for drug content[10].

In vitro Disintegration Studies

Petri dish method was used for disintegration studies. The film was placed in the glasspetri dish containing 20ml of purified distilled water and stirred at every 10sec time interval and time taken by the film to disintegrate was recorded[9].

In vitro Dissolution Studies

The phosphate buffer pH 6.8 is taken as the dissolution medium to determine the drug release. USP dissolution testing apparatus-1 (basket type) containing 900ml of phosphate buffer pH 6.8 is used. The film is placed at the bottom of the basket, maintained at 37 ± 0.5 ºC and the agitation speed was 50 rpm. Aliquots (5ml) of the dissolution medium were withdrawn at 5,10,15,20 and 30min time intervals and the same amount was replaced with fresh medium. Drug content in the samples was determined spectrophotometrically at 254nm and the cumulative percent drug release was calculated[9].

Stability Studies

These studies were carried out to know the stability of the drug, effect of temperature and humidity. The formulation F3 films were stored at 45±2°C / 75±5% RH for 3 months. The initial and third-month study was done for the films. Initially film was wrapped in butter paper and placed in aluminum foils and later placed in aluminum pouches which are sealed by heat. These oral thin films were evaluated for disintegration time and cumulative percent drug release[9].

RESULTS AND DISCUSSION

Calibration Curve of Prochlorperazine

Calibration curve was carried out as per the procedure. Prochlorperazine in pH 6.8 phosphate buffer shows linearity in the concentration range of 0-10 µg/ml with a correlation coefficient of 0.998 and the slope was found to be 0.88 (Figure 4).

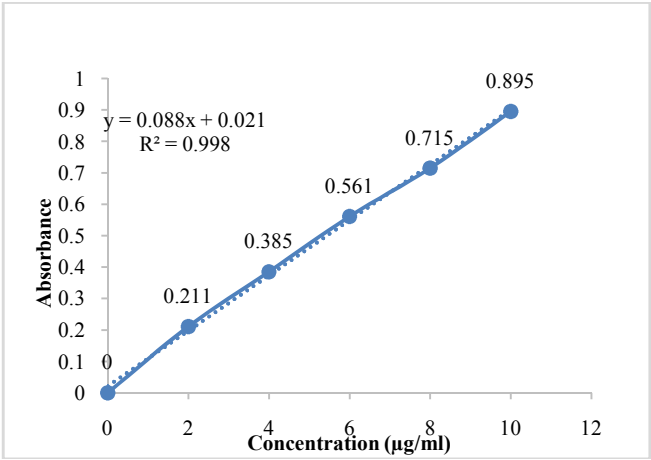

Fig 4 Calibration curve of Prochlorperazine in pH 6.8 phosphate buffer

Preparation of Prochlorperazine Oral Thin Film

Based on results obtained in the preparation of blank films, the composition was finalized to prepare drug containing films. Film casting method was followed to prepare films and glass slide with glass ring was tried unlike petri dishes. This method was successful as films were obtained without any practical problem as shown in figure 5.

Fig 5 Oral thin films containing Prochlorperazine

Evaluation of Oral Thin Films

Weight Variation

This test ensures the uniformity of weight in the formed film. Each film was cut from the cast films in 4 cm^2 (2 x 2) and weight was found to be uniform[9].

Film Thickness

The thickness of films was detected within the range of 0.10 and 0.20. The thickness was measured at three different spots of the film and averages were taken. It was observed that as the polymer concentration increases the thickness of the film also increases as shown in table 2 [11].

Surface pH

The surface pH value of films was found to be within the range of 6.4 to 6.8 which is similar to saliva pH as depicted in table 2.

Folding Endurance

The endurance of the oral thin films was found within the range of 6 to 20. The folding endurance was measured manually. Folding endurance increases with increase in polymer concentration. The no of times the film fold until it broke was reported. All the formulation (F1 to F8) films were shown good folding endurance (Table 2). Folding endurance is also a measurement of plasticizer concentration, but here all formulations have the same concentration of plasticizer, so the polymer concentration effect was easily studied in this research work[11].

Appearance

Each film was checked properly for its transparency but formulations F1 and F2 are not transparent (Table 2) may be the poly is not sufficient. All the films were devoid of air bubbles confirming that the method of preparation was ideal.

Drug Content Uniformity

The drug content uniformity was performed by taking 3 films in every formulation trial and therefore the average drug content was calculated. The results of the drug content of all the films were mentioned in table 3. The prepared film formulations were analyzed for drug content and it was observed that all the formulation found to contain an almost uniform quantity of drug as per content uniformity studies indicating reproducible technique[11].

In vitro Disintegration Studies

The disintegration time of the prepared oral films was found to vary between 14 to 35 sec. The average result of disintegration time is mentioned in table 3, The disintegration time was high for formulation F8, might be because of higher amount of polymer[11]. F3 formulation showed lowest disintegration time along with good folding endurance property. This parameter gives the idea of mouth dissolving time.

In vitro Dissolution Studies

Formulation F1-F8 was prepared and all showed good drug release within 30 min. Compared to all formulations, with formulation F3 more than 95 % of the drug release was observed within 20 min. time. As the disintegration time is also less for this formulation (F3) it was selected as best formulation among all and stability test was conducted for the same.

Stability Studies

These studies are carried out to know the stability of the drug, effect of temperature and humidity. The results of stability studies were shown in table 3.The disintegration time and cumulative percent drug release didn't change before and after stability studies indicating films were stable.

CONCLUSION

Fast dissolving oral film is an innovative dosage form that is having great importance in emergency situations like nausea and vomiting where an immediate onset of action is required[12]. The fast release oral thin films of Prochlorperazine were formulated by solvent casting method. The films were thin and as the concentration of the polymer increases the thickness also increases. All the films prepared were found to be flexible and transparent. Disintegration time was less for formulation F3. *In vitro* dissolution tests for formulations F1 to F8 were performed by USP Type -I dissolution apparatus and the results revealed that the formulation F3 showed high dissolution profile. The stability studies for the optimized film F3 formulations were performed and were unaffected after initial and 3 months storage under accelerated conditions. From this research it was concluded that F3 formulation of Prochlorperazine oral thin films were good.

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Conflict of interest (If any)
None

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