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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING FILMS BY USING PROPRANOLOL HYDROCHLORIDE AS A MODEL DRUG

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ABSTRACT

Propranolol is a nonselective beta-adrenergic blocker and is almost completely absorbed following oral administration. However, most of the drug is undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. The present study investigated to development of novel fast dissolving oral films of Propranolol HCl which was by pass first pass metabolism, provide rapid onset of action and increasing the bioavailability of the drug. The fast dissolving films were prepared by solvent casting method by using HPMC E15 as film forming polymer, due to their hydrophilic nature and palatable taste. All the film formulations (F1-F6) were evaluated for their weight variations, thickness, surface pH, folding endurance, tensile strength, percentage elongation, in-vitro disintegration, drug content and in-vitro drug release studies. Formulations F3 and F4 composed of HPMC E15 at different composition (150mg and 175mg) and releases 100.96±1.55% and 99.35±2.16% of drug respectively at the end of 10 minutes.

KEY WORDS

Propranolol HCl, HPMC E 15, fast-dissolving film, beta-adrenergic blocker.

INTRODUCTION

Fast-dissolving drug-delivery systems were first developed in the late 1970's as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid dosage forms. In response to this need, a variety of orally disintegrating tablet formats were commercialized. Most orally disintegrating products were formulated to dissolve in less than one minute when exposed to saliva to form a solution that could then be more easily swallowed[(1)].

The orally fast-dissolving film is new drug delivery system, which satisfies the unmet needs of the market. It was developed on the basis of technology of the transdermal patch. Fast-dissolving film is easy to handle, administer, maintenances and keeping in convenient packaging. It is also eliminates unpleasant taste and is straight forward to manufacture. The thin film is placed on the top or the floor of the tongue or any oral mucosal tissue. It is wet by saliva the film rapidly hydrates without water or chewing and retained at the site of application and rapidly releases the active agent for local or systemic absorption.

Oral fast dissolving film (FDF) is one of the novel approaches to increase patient acceptance by virtue of rapid dissolution. The need for non-invasive delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management[(2)].

Propranolol (1-(isopropylamino) - 3-(1-naphthyloxy)-2-propanol) is a nonselective beta-adrenergic blocker that interacts with β1 and β2 receptors of the autonomic nervous system with equal affinity. It lacks

intrinsic sympathomimetic activity (negative inotrophic effect) and does not block α-adrenergic receptors. Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Propranolol is a highly lipophilic substance and is almost completely absorbed following oral administration. However, most of the drug is metabolized in the liver during its first passage through the portal circulation; on average, about 25% reach the systemic circulation.

Propranolol is extensively metabolized to 4-hydroxyl-propranolol followed by conjugation with glucoronic acid [3]. The elimination half- life ($t_{1/2}$) of propranolol has been reported to range from between 3 to 6 hours or approximately 3.9 hours [4].

Propranolol has a large volume of distribution (4 L/kg) and readily enters the CNS. Approximately, 90% of the drug is bound to plasma proteins. The drug is used in the treatment of hypertension, hyperthyroidism, cirrhosis, angina pectoris, migraine and glaucoma. The adverse effects of propranolol are bronchoconstriction and disturbance in metabolism[5]. The present study investigated to development of novel fast dissolving oral films of Propranolol HCl which was by pass first pass metabolism, provide rapid onset of action and increasing the bioavailability of the drug.

MATERIALS AND METHODS

Propranolol HCl was obtained as a gift sample from Dr. Reddy's Labs, Hyderabad, India. HPMC E 15 was obtained from Qualikem's fine chem ltd, Vadodara, India. Propylene glycol was purchased from S.D. Fine Chem. Ltd., Mumbai, India and distilled water was prepared in laboratory using all glass distillation apparatus. All other materials like aspartame and other reagents were of analytical grade and procured from commercial sources.

Formulation of fast dissolving films

Fast dissolving films of Propranolol hydrochloride were prepared by solvent casting technique using film forming polymer. Required amount of HPMC E15 was weighed accurately and soaked aside for 1hour for swelling of polymer. Simultaneously Propranolol hydrochloride was weighed accurately and dissolved in 5ml of distilled water in another beaker (**Table 1**). Then drug solution was added to the polymer solution and propylene glycol was added as plasticizer and sodium saccharine as sweetener and was mixed thoroughly with the help of magnetic stirrer. Entrapped air bubbles were removed by applying vacuum. Flat aluminium foil coated glass mould (petridish) having diameter 9cm was placed over a flat surface and the resulting 10 ml solution with the help of measuring cylinder was transferred into petridish slowly drop by drop and was spread uniformly. Funnel was inverted and placed over the petridish to have uniform evaporation. The petridish containing polymeric solution of drug was kept for 24hours at room temperature for drying. After drying the films were removed by peeling from the moulds then cut into a square dimension of 2.5× 3.0 cm^2.[6,7]

Table 1: Formulation of Fast dissolving films of Propranolol hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6
Propranolol hydrochloride	40	40	40	40	40	40
HPMC E 15	100	125	150	175	200	225
Propylene glycol	100	100	100	100	100	100
Aspartame	25	25	25	25	25	25
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

*All units are measured in milligrams

EVALUATION OF ORAL FAST DISSOLVING FILMS

Weight variation

For weight variation three films of every formulation were randomly selected and weighed individually on digital balance then average weight was calculated.[8]

Film thickness

The thickness of each film was measured using micrometer screw gauge at different positions of the film and the average thickness was calculated. This is ascertaining uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.[9]

Surface pH

The surface pH of fast dissolving film was determined in order to find out the possible any *in-vivo* side effects. The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition. The procedure was performed in triplicate and average with standard deviation was determined.[10]

Folding endurance

The folding endurance was determined by repeatedly folding one film 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 the folding endurance.[11]

Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as described in the equation.[12]

Tensile strength = (load at breakage/film thickness × film width) × 100

Percent elongation

When stress is applied, a film or 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.[13]

% Elongation = (increase in length/ original length) × 100

Disintegration time

This test was performed using disintegration test apparatus. 5cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate to achieve equivalent to thirty times a minute. Time required by the film to achieve no trace of film remaining above the gauze was noted. Although, no official guidance is available for oral fast disintegrating films strips.[14,15]

Drug content

A film of 2.5 × 3.0 cm^2 diameter was cut and placed in 100 ml of phosphate buffer solution (pH 6.8). The contents were stirred by using magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (100 ml). The absorbance of the solution was measured against the corresponding blank solution at 288 nm. As the absorbance noted above 1ml of the stock was further diluted to 10 ml of phosphate buffer solution (pH 6.8) and absorbance was measured at 288 nm. The determination was carried out in triplicate for all the formulations.[16, 17]

In-vitro dissolution studies

In-vitro dissolution of propranolol hydrochloride fast dissolving film was carried out in USP paddle dissolution test apparatus using 500 ml phosphate buffer pH 6.8 as the dissolution medium. The temperature was maintained at 37±0.5^{o}C throughout the experiment. 5ml Sample was withdrawn at 2.5min intervals and the same quantity was replaced with phosphate buffer of pH 6.8. The cumulative percentage of drug released was determined using UV visible spectrophotometer at 288 nm.

RESULTS AND DISCUSSION

Weight variation

All the prepared films were found to be non tacky. Three films each of 1 cm^2 were cut at three different places from the casted film and weight variation was

determined. **Table 2** shows the results of weight variation varies from 268±0.04 to 283±0.06 mg.

Film thickness

As all the formulations contain different amount of polymers, the thickness was gradually increased with the increasing amount of polymers. Table 2 shows all the film formulations were found to have thickness in the range of 0.15±0.03 mm to 0.27±0.05 mm.

Surface pH

The surface pH of the films was ranging from 6.75±0.03 to 6.85±0.06.The surface pH of the films was found to be neutral. There will not be possible any kind of irritation to the mucosal lining of the oral cavity.

Folding endurance

The folding endurance of film was found to be in the range of 235±2.25 to 283±3.76. Folding endurance increases with increase in the concentration of polymer. The number of time the film fold until it broke is reported in the **Table 2**.

Tensile strength and Percent elongation

A suitable FDF requires moderate tensile strength and acceptable percentage elongation. **Table 2** shows the comparative mechanical properties of various formulations prepared during the study. The tensile strength was found to increase with increased concentration of HPMC (E15).The tensile strength of formulations was found be 1.33 to 1.96. The percentage elongation of all the batches ranges from 9.98-12.96.

Disintegration time

It was observed that *in-vitro* disintegration time varies from 20 to 65 sec for all the formulations (table 2). *In vitro* disintegration time of FDFs containing varying amount of HPMC E-15 as polymer, it was affected by the thickness of the film and i*n-vitro* disintegration time of the films was found to be increased with increase in the amount of the polymer.

Formulations F1 and F2 has least weight variation, thickness, folding endurance, tensile strength, percent elongation and disintegration time and not met all the satisfactory mechanical properties. Formulations F3 and F4 has good mechanical properties with *in-vitro* disintegration time.

Drug content

The prepared film formulations were assayed for drug content. **Table 2** shows the percentage drug content of all the formulations were found in the range of 99.13 to 99.98 of propranolol HCl and results of drug content showed the uniformity of the drug.

Table 2: Evaluation of physico-mechanical parameters of fast dissolving film of propranolol hydrochloride

F code	Weight variation (mg)	Film thickness (mm)	Surface pH	Folding endurance	Tensile strength	Percent elongation	Disintegration time(sec)	Drug content (%)
F1	268±0.04	0.15±0.03	6.82±0.05	235±2.25	1.33	9.98	20	99.95
F2	270±0.02	0.18±0.02	6.75±0.03	245±2.32	1.49	10.23	26	99.95
F3	272±0.08	0.20±0.04	6.85±0.06	250±3.13	1.55	10.55	35	99.98
F4	276±0.06	0.23±0.05	6.82±0.05	265±3.65	1.63	11.53	46	98.69
F5	278±0.04	0.25±0.04	6.78±0.05	274±3.89	1.75	12.08	55	99.13
F6	283±0.06	0.27±0.05	6.82±0.06	283±3.76	1.96	12.96	65	99.25

In Vitro Dissolution Studies

The percentage drug release of each film by *in-vitro* release studies was shows differences depending on their composition. Formulation F1, F2 and F3 composed of HPMC E15 at different composition (100mg,125mg,150mg) and releases 99.16±1.65%, 99.35±1.45% and 100.96±1.55% of drug respectively at the end of 5, 7.5 and 10 minutes. Formulation F4, F5 and F6 each contains 175mg, 200mg and 225mg of HPMC E 15 and releases 99.35±2.16%, 101.76±2.05%

and 98.55±1.25% of drug respectively at the end of 10, 15 and 20 min. A decrease in the drug release was observed when increasing the concentration of polymer.

The drug release was rapid in all the film formulations was observed by the dissolution test, in which formulation F3 shows maximum 100.96±1.55% of propranolol HCl dissolved within 10 min. It was also observed that HPMC (150mg) showed highest drug releases are shown in **Figure 1.**

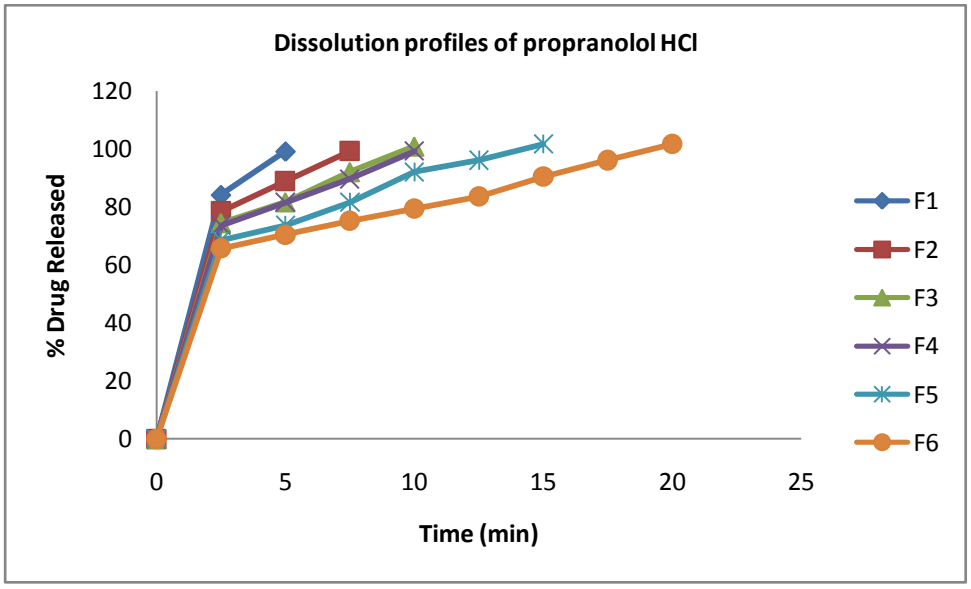

Fig 1: Dissolution profiles of formulations F1 to F6

CONCLUSION

In conclusion, Propranolol HCl fast dissolving films were prepared with varying concentrations of HPMC E15 and the results of the present study indicated that HPMC E15 could be used as a film forming polymer. The prepared films were clear, homogenous, devoid of particulate matter, showed good folding endurance and all the prepared bathes were showed good mechanical properties with *in-vitro* disintegration time. On the basis of data obtained from *in-vitro* dissolution studies that F3 and F4 are formulation suitable for the immediate release of Propranolol HCl.

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