



Formulation of Propranolol Hydrochloride Oral thin films for Migraine Prophylaxis

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ABSTRACT

The aim of present work deals with formulation of Propranolol hydrochloride oral thin films for migraine prophylaxis. Propranolol hydrochloride is a non-selective beta-adrenergic antagonist and completely absorbed from the gastrointestinal tract. On the other hand, nearly 75% of drug undergoes pre-systemic metabolism by the liver, thus bioavailability is reduced to 25%. The purpose of developing this dosage form is to reduce the dose by bypassing its first pass metabolism. Films were prepared from F1-F6 by solvent casting technique. Pullulan was selected as polymer because of its good water solubility and propylene glycol as plasticizer. Polyvinyl pyrrolidone was selected as disintegrant, citric acid as saliva stimulating agent, mannitol as sweetening agent and menthol was used as flavoring agent. The compatibility of the drug in the formulation was confirmed by FT-IR and DSC. Formulated films were subjected to various evaluation parameters. Based on the evaluation parameters, F4 has disintegration time of 47 sec and showed promising drug release of 93% after 20 min. Scanning Electron Microscopy (SEM) of F4 showed smooth surface and little pores. The stability study proved that the formulation F4 was found to be stable in both refrigerator and room temperature. *Ex vivo* permeation study of F4 showed 91% of drug permeation through goat oral mucosa: hence formulation F4 was selected as best formulation.

Keywords: Migraine prophylaxis, Propranolol hydrochloride, first pass metabolism, oral thin films, Pullulan, propylene glycol.

INTRODUCTION

Oral route is the most acceptable route for the patient.¹ But some patients, especially pediatrics and geriatrics experiences difficulty in swallowing solid dosage forms like tablet and hard gelatin capsules. Due to the fear of choking, they are unable to take these dosage forms. In order to overcome this, several fast dissolving drug delivery systems (FDDDS) were designed.²⁻⁴ Buccal route is the most commonly applicable route of drug administration since it by-passes the hepatic first pass metabolism. Nowadays, pharmaceutical companies carried out their research activity in reformulating existing drugs into new dosage forms. One such new developed dosage form is fast dissolving oral thin films.⁵⁻⁷ It is a thin oral strip prepared using hydrophilic polymer that rapidly dissolves when come in contact with saliva.⁸ They can easily disintegrate (in seconds) to release the medication without drinking and chewing.^{9, 10} As the mucosa is highly enriched with blood supply, it provided quick absorption and instant bioavailability of drugs.^{11, 12} The instant bioavailability results from bypassing first pass metabolism. So, they are generally designed for the drugs having high first pass metabolism for achieving better bioavailability.^{13, 14}

Migraine is a neurological disorder represented by persistent moderate to severe headache frequently with a number of autonomic nervous system symptoms that affect only one side of the head. Migraine is usually treated as acute (abortive) and preventive (prophylactic).¹⁵ Propranolol hydrochloride, a beta

adrenergic blocker is the drug of choice for the migraine prophylaxis. Propranolol hydrochloride was chosen because of unavailability of film dosage form in the market, to reduce the dose by bypassing the first pass metabolism in the liver and to have a rapid onset of action in migraine prophylaxis.¹⁶

Pullulan is a natural polymer secreted by the fungus, *Aureobasidium pullulans*. Films made from pullulan are highly water soluble, colourless, odourless, transparent and flexible. They provide excellent mechanical properties and high oxygen-impermeability. Due to its excellent properties, it is the best film forming agent.¹⁷

MATERIALS AND METHODS

Materials¹⁸

Propranolol hydrochloride was procured from Loba chemicals Pvt Ltd, Mumbai. Pullulan was obtained as a gift sample from Gangwal chemicals Pvt Ltd, Mumbai. Rest of chemicals used were of analytical grade.

Methods¹⁹

Pre-formulation Studies

Pre-formulation studies are the first step in the development of a dosage form. It helps to determine the physicochemical properties of drug substances so as to develop a safe and effective dosage form (Physical appearance, Solubility Analysis, pH determination, thin layer chromatography).

Drug-Excipient Compatibility Studies¹⁹



FTIR interaction studies

FTIR Spectroscopy of pure drug (Propranolol) and the polymer (Pullulan) were carried out to determine their interactions.

Differential scanning microscopy

DSC of drug, polymer and physical mixture of both were carried out to determine the thermal properties. Initially, samples were placed in 50 μ l perforated aluminium pans and sealed. Each sample were heated from 5-300 $^{\circ}$ C, using nitrogen as purging gas.

Construction of Calibration¹⁹**Preparation of standard stock solution**

10mg of Propranolol hydrochloride was accurately weighed and dissolved it in 100ml of phosphate buffer (6.8).

Determination of λ_{max}

Stock solution was scanned from 200-400nm by UV spectrophotometer.

Calibration curve of Propranolol hydrochloride

From the above stock solution 2ml, 4ml, 6ml, 8ml and 10ml were pipette out and made up to 10ml by using phosphate buffer 6.8 in six separate 10ml standard flask to produce 20, 40, 60, 80 and 100 μ g/ml respectively. The absorbance was measured at 289nm in a UV spectrophotometer using phosphate buffer (6.8) as blank. The datas are tabulated. The concentration was plotted against the absorbance to obtain standard graph.

Formulation of fast dissolving films²⁰**Table 1:** Composition of Oral Thin Films containing Propranolol hydrochloride

	F1	F2	F3	F4	F5	F6
Propranolol hydrochloride (mg)	40	40	40	40	40	40
Pullulan (mg)	400	400	500	500	600	600
Propylene glycol (ml)	0.25	0.2	0.25	0.2	0.25	0.2
Polyvinyl pyrrolidone (mg)	100	-	100	-	100	-
Citric acid	200	200	200	200	200	200
Mannitol (%w/v)	10	10	10	10	10	10
Menthol(mg)	10	10	10	10	10	10
Purified Water (ml)	20	20	20	20	20	20

Propranolol hydrochloride and pullulan were accurately weighed and dissolved in distilled water. This solution was mixed well followed by the addition of plasticizers and superdisintegrant. Then the resultant homogeneous solution was poured into a petridish (diameter 6cm) and dried in an oven at 60 $^{\circ}$ C for 24 h. The film was carefully removed from the petridish and cut into desired size (2 \times 2cm²).

Evaluation of Fast Dissolving Films²⁰**Weight variation**

Films were taken and the weight was checked on digital balance.

Film thickness

The thickness of each film was determined using a micrometer screw gauge and the average was calculated.

Tackiness

Films from different formulations were taken and pressed against the fingertips and the results were recorded.

Folding endurance

It gives an index about brittleness of the film. The films were randomly selected and repeatedly folded at the same place until it broke and the values were reported.

Percent elongation

Films were taken and the initial length was measured. Then, it was stretched to a lesser extent and the final length was measured.

$$\% \text{ Elongation} = \frac{[L - L_0] \times 100}{L_0}$$

L = Final Length, L₀= Initial Length

Film softening upon storage

Films were stored in desiccator for 48 hours and softening was determined.

Surface pH

pH of the film may cause irritation when placed in mouth. If the pH of the film is too acidic or alkaline, it may cause irritation. So it's important to determine surface pH of the film. Surface pH of the film should be neutral i.e., 7 or should be close to 7. A combined pH electrode was used to determine surface pH. The film was made slightly wet with water and the electrode was brought in contact with film and the pH reading is noted. This test was applied on at least six films and the average is taken, which is the final value of surface pH.

Percentage Moisture Loss

This test is done to find out the physical stability of the film. To determine the percentage moisture loss of the film, a film of size 2×2 cm² was cut and weighed previously. Then the film is kept in a desiccator containing fused anhydrous calcium chloride for three days. After three days, film is weighed again and the percentage moisture loss is calculated.

$$\text{Percentage Moisture Loss} = (\text{Initial Weight} - \text{Final Weight}) / \text{Initial Weight} \times 100$$

Transparency

UV spectrophotometer is used to determine the transparency of the film. Film specimen is taken and placed in the spectrophotometer cell and analysed at 600nm. Transparency can be calculated using the following formula:

$$\text{Transparency} = (\log T_{600}) / B = -\epsilon C$$

Where T₆₀₀ is transmittance at 600nm, b is thickness of the film and C is concentration

Drug Content

For this test, a patch of film (size 2.5×2.5cm²) was dissolved in 100ml phosphate buffer (pH - 6.8). It was stirred for six hours with a magnetic stirrer. Later the content is filtered using whattman filter paper and the filtrate sample is analyzed by UV spectrophotometer at 289 nm. Then a calibration curve was plotted and drug content was determined.

In-vitro disintegration Studies

Disintegrating time is defined as the time (seconds) at which a film disintegrate when come in contact with water or saliva.

In-vitro Dissolution Studies

The studies were carried out in phosphate buffer 6.8 at 37°C in a USP paddle apparatus. Five ml of samples were withdrawn at various time intervals of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min and analysed by UV spectrophotometer at 289nm.

Scanning Electron Microscopy (SEM)²¹

Scanning electron microscopy is an important tool to study the surface characteristics of the oral film. Excipients added in formulation affect the surface morphology of film differently which affect various parameters of the film. A film sample is taken and placed in sample holder of SEM and various photomicrographs are taken.

Stability studies²²

It is important to perform stability testing of the formulation prepared to check whether it is a stable product or not. Firstly the formulation is wrapped in a butter paper, and then aluminium foil is wrapped over it and packed in aluminium. The formulation were kept for stability studies for 2 months at room temperature, refrigerator temperature and incubator to determine its physical and chemical stability

RESULTS AND DISCUSSION

Pre-formulation studies

Physical appearance

Propranolol hydrochloride was found to be a white to off white crystalline powder with non-hygroscopic nature.

Melting point

Melting point was found to be between 152-169⁰c.

pH determination

pH of Propranolol was found to be 4.3.

Thin layer chromatography

By iodine chamber method, a single spot was seen, shows that the drug is pure. Rf value was found to be 0.44.

Drug-Excipient Compatibility Studies

FTIR- Spectroscopy

From the obtained spectrum, it is clear that there was no major shifting in the frequencies which confirms that the drug is compatible with all excipients used in the formulation.

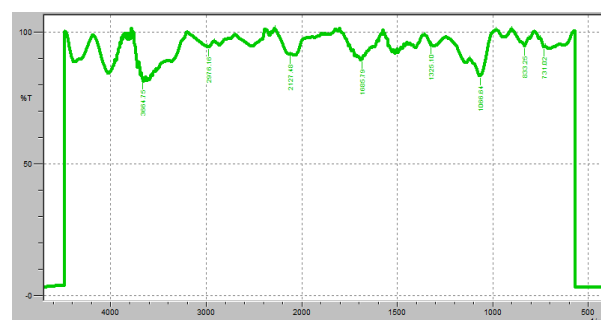


Figure 1: FTIR spectrum of Propranolol oral thin films

Differential Scanning Colorimetry: DSC of drug, polymer and its mixture were carried out and confirms

that there was no change in the melting point when temperature was applied.

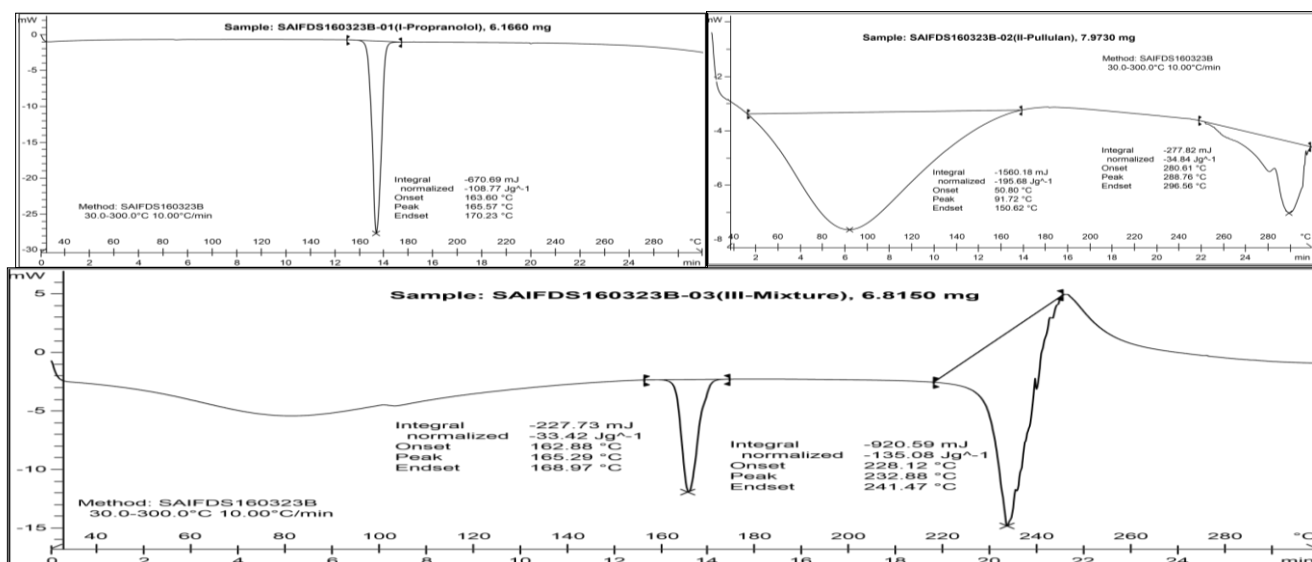


Figure 2: DSC of Propranolol hydrochloride, Pullulan and mixture of both

Table 2: Evaluation of Propranolol hydrochloride

Formulation	F1	F2	F3	F4	F5	F6
Film forming capacity	Bad	Bad	Very good	Very good	Good	Good
Peel ability	Non-peel able	Non-peel able	Peel able	peel able	peel able	peel able
Tackiness	Tacky	Tacky	Non-tacky	Non-tacky	Non-tacky	Non-tacky
Weight variation(mg)	52±0.15	53±0.85	66±0.49	65±0.35	78±0.28	76±0.21
Film thickness(mm)	0.16±0.005	0.15±0.005	0.18±0.088	0.17±0.005	0.19±0.091	0.19±0.091
Surface pH	6.75±0.03	6.82±0.06	6.78±0.05	6.85±0.06	6.86±0.07	6.72±0.02
Folding endurance	228±2.51	225±1.15	244±1.52	247±2.01	263±1.51	261±3.05
Percentage moisture loss (%)	5.62±0.22	3.61±0.266	4.29±0.21	3.15±0.08	3.54±0.26	2.72±0.10
Film softening upon storage	Softening	Softening	No film softening	No film softening	No film softening	No film softening
Percent elongation (%)	30	20	30	10	20	35
Disintegration time(sec)	38sec	35sec	51sec	47sec	54sec	52sec
Transparency	-5.3	-6.4	-6.82	-8.2	-5.71	-6.07
Drug content (%)	87%	90%	91%	94%	92%	93%

Calibration curve of Propranolol hydrochloride

Determination of λ_{max}

The stock solution was scanned between the range of 200-400nm by UV spectrophotometer. From the graph, it was concluded that the λ_{max} of propranolol hydrochloride is 289nm.

In-vitro Dissolution Studies

The dissolution profile of propranolol hydrochloride with different concentration of pullulan is shown in figure 3. F4 formulation was showed greater release than other formulations.

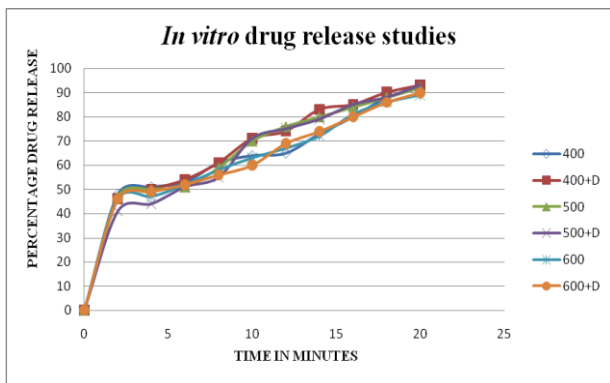


Figure: 3 Drug release profile of F1 to F6 formulations

Scanning Electron Microscopy (SEM)

Morphology of FDF is studied by SEM. The electron microscopy showed that the optimized formulation (F4)

are clear, colourless with smooth surface and little pores, without any scratches on the films.

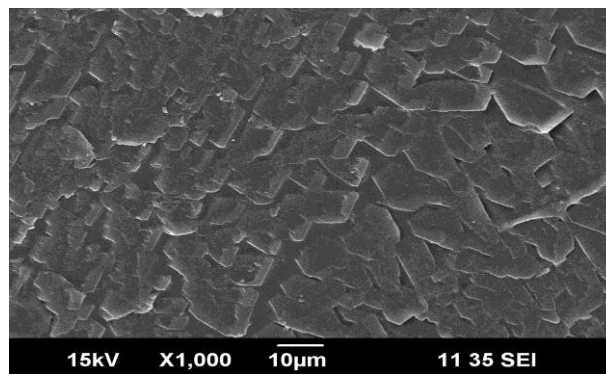


Figure 4: Photographs of the scanning electron microscopy of optimized formulation F4



Figure 5: Formulated oral thin dissolving films

Table 3: Stability studies

S.No	Time (Days)	Appearance	In-vitro disintegration time (sec)	%drug release
1	Initial (0days)	Transparent and Acceptable	51±2.1	88%
2	1 month (30days)	Transparent and Acceptable	48±3.1	92%
3	2 months (60days)	Transparent and Acceptable	48±1.2	95%

CONCLUSION

A migraine is usually a neurological disorder felt as a throbbing pain⁵⁵. Propranolol hydrochloride is the first line agent for migraine prophylaxis. Propranolol is a non-selective beta-adrenergic antagonist undergoes hepatic first pass metabolism, thus bioavailability is reduced to 25%. The first pass metabolism in the liver can be avoided by developing oral thin films of propranolol hydrochloride, and dose can be reduced in migraine prophylaxis. Oral thin films of propranolol hydrochloride were prepared successfully using pullulan as polymer by solvent casting method. The developed formulations showed satisfactory results for peel ability, tackiness, weight variation, surface pH, folding endurance, percentage moisture loss, film softening upon storage, percent elongation, disintegration time, transparency and drug content. The prepared films were disintegrated within 60 sec. Films with 500mg of

polymer and the 0.2ml plasticizer (F4) showed faster release rate than the others.

It can be concluded that the oral thin film is a potential new dosage form for paediatrics, geriatrics and other populations. Hence oral thin films of Propranolol hydrochloride were found to be better formulation for the treatment of migraine prophylaxis.

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