

FORMULATION AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF PAROXETINE HYDROCHLORIDE FOR TREATMENT OF DEPRESSION

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ABSTRACT

Objective: Oromucosal route could be an alternative over the conventional route for paroxetine hydrochloride (PXH) as it offers direct systemic delivery, by avoiding extensive first-pass metabolism, which results in poor systemic absorption. The film dissolves quickly when placed in mouth without need of water thus helpful in providing rapid onset of action.

Methods: Fast dissolving film of PXH was prepared using Pullulan in various combinations of 3² full factorial design by solvent casting technique. Prepared films were subjected to mechanical, *in vitro*, and *ex vivo* characterization.

Results: The physicochemical characteristics such as mass uniformity, thickness, surface pH, and folding endurance were found satisfactory. The formulation (F3) containing 4% w/v Pullulan showed maximum release 94.31% and *ex vivo* permeation 92.67% through goat oral mucosa in 15 min. Uniform drug loading was observed in all the batches with disintegration time <25 s. Fourier transform infrared spectroscopy study revealed the compatibility of drug with polymer. Scanning electron microscopy revealed that there was uniform mixing of all ingredients. Optimized batch F3 was found to be stable for 1 month as no significant changes were observed in % cumulative drug release and weight of film.

Conclusion: Pullulan a natural biodegradable polymer allocates good physical property to film. Hydrophilic nature of polymer imparts fast disintegrating property to film.

Keywords: Fast dissolving film, Paroxetine hydrochloride, Pullulan, Solvent casting.

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INTRODUCTION

Research work on oral drug delivery has led to the progress of solid oral dosage forms in the form of fast dissolving films (FDF). FDF can be defined as a dosage form that employs a water-soluble polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly wet, adhere, and dissolve to release the drug when placed on the tongue or in the oral cavity for oromucosal absorption [1]. The geriatric, paediatric, mentally ill and non-cooperative patients often find difficulty in swallowing tablets and capsules. Also when patients travel, there are circumstances when water is not available with them, during such conditions FDF is one of the good approach for curbing such problems.

It is the most preferred formulation due to ease of administration, preparation, handling, transportation, palatability, and dose uniformity. FDF is highly accepted for oral delivery of various potent drugs (e.g., analgesics, anti-histamines, anti-asthmatics, cardiovascular drugs, and neuroleptics) in contrast to immediate release orodispersible tablets (ODT). Although ODT was designed for fast disintegration in mouth, their risk of choking and non-compliance for certain patients can still exist, while FDF formulation can resolve the problem of swallowing thus improves patient compliance. FDF has the benefit of large surface area for rapid dissolution and hence consumer-friendly. Various hydrophilic polymers are used as film formers for FDF such as Pullulan, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, maltodextrin, and Kollicoat® IR [2].

Pullulan is a natural biodegradable-biocompatible, non-ionic water-soluble extracellular film-forming polysaccharide, obtained from the fermentation medium of the black yeast such as *Aureobasidium Pullulan*. Pullulan based films show low oxygen permeability, are oil and grease

resistant, being a natural one are superior over synthetic polymers. Pullulan films are non-toxic, non-immunogenic, non-mutagenic, non-reducing, hydrophilic, tasteless, colorless, resistant to oil, heat-stable, and impermeable to oxygen [2]. Based on these properties and advantages of Pullulan, it was used as a film former in present investigation.

After sublingual administration, the drug substances are rapidly absorbed into the reticulated vein underneath the oral mucosa, and transported through the facial veins, internal jugular veins, and brachiocephalic vein and then drained into systemic circulation thereby avoiding the hepatic first-pass effect [3]. In terms of the permeability sublingual area of the oral cavity is more permeable than other mucosal area. Sublingual films have been developed for certain condition, for example, migraines, bipolar mania, and other mental illness for which rapid onset of action is desired.

According to the World Health Organization, major depression has become the second most prevalent cause of illness-induced disability worldwide [4]. Paroxetine hydrochloride (PXH) is a potent and selective inhibitor of (5-HT, serotonin) 5-hydroxytryptamine uptake used in the treatment of obsessive-compulsive disorder, panic disorder, and social anxiety disorder/social phobia. PXH is well absorbed after oral dosing and undergoes extensive first-pass metabolism thus results in poor oral bioavailability 31±15% [5]. It is available as conventional oral film-coated tablets (20 mg), mouth dissolving tablets (10 mg) in the market. This justifies the need for the development of other effective alternative such as FDF formulation as the mouth dissolving tablet has its own limitations.

Hence, based on the justification and background of Pullulan and PXH, the aim of the present investigation was to formulate and

evaluate palatable Pullulan based FDF of PXH following optimization of process factors. The proposed formulation has potential to improve compliance and quick onset of action in depressed patients than the available tablets of PXH. This PXH loaded Pullulan based FDF presents numerous advantages over its marketed oral dosage forms such as ease of administration without water, easy to formulate, simplicity to handle, and carry away.

MATERIALS AND METHODS

Materials

PXH was obtained as a gift sample from Sun Pharmaceutical Industries Ltd., Mumbai. Pullulan was obtained from Gangwal chemicals, Mumbai. Polyethylene glycol (PEG) 600, citric acid, and sucralose were procured from Loba Chemie Ltd., Mumbai, India. All other reagents used were of analytical grade. Purified water was used for study.

Preformulation studies

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical, and mechanical properties of new drug substances, to develop stable, safe, and effective dosage forms. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form is also considered [6].

Calibration curve of PXH in phosphate buffer (pH 6.8)

A stock solution of PXH of concentration 100 µg/ml was prepared in phosphate buffer (pH 6.8). The above stock solution was further diluted to get concentration in the range of 10–80 µg/ml, and standard calibration curve was plotted. The absorbance of the prepared solutions was observed at λ_{\max} 293 nm using UV-visible spectrophotometer (Jasco UV Model V-630) [5,6]. The calibration curve was used for the estimation of drug content in formulation and for *ex vivo* diffusion studies [6].

Drug excipient compatibility study

Excipients are important components of almost all pharmaceutical dosage forms. The successful formulation of a stable dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug, and protect it from degradation. PXH along with excipients in 1:1 ratio was kept in the stability chamber at 40°C±2°C temperature and 75±5% relative humidity (RH) for 1 month. The samples were withdrawn at the end of a month and evaluated for compatibility studies by differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR).

Drug-excipient compatibility study by FTIR

FTIR study was performed by KBr powder mixing method using FTIR spectrophotometer (Shimadzu Corporation, Japan, 8101A) and the spectrums were recorded in the wavelength region of 4000–400 cm⁻¹.

Drug-excipient compatibility study by DSC

DSC analysis of PXH and its physical mixture (PM) with polymer was performed using Shimadzu DSC 60 Plus and thermal data obtained were processed using TA60 software System. Thermal behavior was studied by heating 2 mg of sample in crimped aluminum pans at a scanning rate

of 5°C/min in the atmosphere of nitrogen gas flow 100 ml/min over the temperature range of 30–300°C [5,6].

Formulation design of oral FDFs

Preliminary trial

Different plasticizers such as PEG 400, glycerol, and PEG 600 were screened with Pullulan film by considering three parameters, i.e., disintegration time (DT), folding endurance, and appearance [6].

Experimental design

The objective of the present investigation was to observe the combined effect of the concentration of polymer as well as the concentration of plasticizer on the DT, *in vitro* % drug release and folding endurance for obtaining the optimized FDF. The experimental design was generated by Design-Expert® software (Version 11, Stat-Ease Inc., USA). In this work, a 3² factorial design was used for the optimization of FDF. A 2-factor was evaluated each at three levels, and experimental trials were performed on all nine combinations. A statistical model incorporating interactive and polynomial terms were used to evaluate the response using the equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1 . The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1 and X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity. The above equation indicates a coefficient with the negative sign which shows that there is an increase in response when factor level is decreased from higher to lower level, and the factor with higher absolute value of coefficient and lower value “p” has major effect on the response variables. A 3² randomized full factorial design was utilized to study systematically the effects of two independent factors on the characteristics of the film [6].

Preparation of PXH loaded Pullulan based FDF

FDF of PXH was prepared using Pullulan in various combinations as per 3² full factorial design by solvent casting technique. Required quantity of citric acid (saliva stimulator) was added in aqueous Pullulan solution to minimize recrystallization of PXH. It was allowed to stir for few minutes using magnetic stirrer (Labman Scientific Instruments, India) until it dissolved. On its dissolution, 175 mg of accurately weighed PXH (Electronic balance, AUX 120, Shimadzu, Japan) was added with stirring. When the solution was clear, smooth and homogeneous, accurately weighed 300 mg of PEG 600, needful quantities of sucralose and mint flavor (5 mg) were added to the preparation with stirring to get clear homogeneous preparation. The solution was allowed to stand for ½ h to remove air-bubble if any. The formulation was casted on a suitable platform using a film-forming machine (VJ Instruments, Lat., India) and dried at 45–50°C to form a film. The film was then carefully removed and cut into suitable size, i.e., 2 cm×2 cm and stored in aluminum sachets at 2–8°C until further studies. The composition of FDF is shown in Table 1.

Table 1: Composition of FDF

Formulation code	Drug (mg)	Pullulan (%w/v)*	PEG 400 (%w/v)*	Sucralose (mg)	Citric acid (mg)	Mint flavor (mg)
F1	10	4	1	10	50	5
F2	10	4	2	10	50	5
F3	10	4	3	10	50	5
F4	10	5	1	10	50	5
F5	10	5	2	10	50	5
F6	10	5	3	10	50	5
F7	10	6	1	10	50	5
F8	10	6	2	10	50	5
F9	10	6	3	10	50	5

*All the ingredients were added in weight (g)/volume (ml). Total volume of the polymer solution including drug and plasticizer was 6 ml. FDF: Fast dissolving films

Dose calculation

The dose of PXH is 10 mg. Therefore, amount of PXH required in 4 cm² of the film is 10 mg.

$$\text{Area of film} = 7 \times 10 = 70.00 \text{ cm}^2$$

$$\text{Area of film} = 2 \times 2 \text{ cm} = 4 \text{ cm}^2$$

$$4 \text{ cm}^2 \text{ contains } 10 \text{ mg}$$

$$(70.00) \text{ cm}^2 \text{ contains } = 175 \text{ mg of PXH [6,7].}$$

Characterization of FDF

This parameter was checked simply by visual inspection of films and evaluation of texture by feel or touch. FDFs of PXH were evaluated for their weight, thickness, pH value, folding endurance, drug content, DT, and *in vitro* dissolution. All studies were carried out on films of 2×2 cm² area in triplicate, and average values were reported [8].

Physical and mechanical properties

Uniformity of weight and thickness of the films were estimated using digital weighing balance and Vernier caliper (MGW Precision tools, India), respectively. Folding endurance was ascertained by repeatedly folding one film at the same place until it ruptures. The counting of folding made before the film ruptured was denoted as the mean folding endurance. All determinations were performed in triplicate [9].

Surface pH

Surface pH was determined using a digital pH meter (Equiptronics, EQ-611, Mumbai, India) to check whether the film causes irritation to the oral mucosa. Films were placed in closed Petri plate containing 5 ml distilled water. After moistening pH probe was placed in close contact with the wetted films, and the surface pH was identified in triplicate. It is necessary that films should have nearly uniform and neutral pH value [9].

Drug content and % moisture content

To evaluate the uniformity of drug content, the films were dissolved in 100 ml phosphate buffer (pH 6.8), suitably diluted and analyzed using UV-Visible spectrophotometer at 293 nm. The drug content was determined as mean of three determinations using standard calibration curve. Percentage moisture content was determined in triplicate for each batch since moisture in the film could be crucial as it affects the mechanical strength, adhesive properties, and friability of film [10].

Disintegration time

For disintegration, the required size of films was placed in the beaker containing 10 ml of pH 6.8 buffer to mimic saliva. The DT was noted for each film at which film started to break apart. All the studies were performed in triplicate for each batch [10].

***In vitro* % drug release**

The film samples were subjected to *in vitro* dissolution studies using USP Type I dissolution apparatus (Electrolab, India) at 37±0.5°C and 50 rpm speed in 300 ml dissolution medium which was phosphate buffer (pH 6.8). Films were submerged into the dissolution media, and appropriate aliquots were withdrawn at 2, 5, 8, 10, and 15 min time intervals. The samples were filtered through Whatman filter paper and analyzed spectrophotometrically at 293 nm [11].

***Ex vivo* permeation studies through goat buccal mucosa**

Permeation studies were carried out for optimized batch using the modified Franz diffusion cell of an internal diameter of 2.5 cm. Goat oral mucosa was used as the model membrane. The membrane was stabilized before mounting to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 27 ml of isotonic phosphate buffer of pH 6.8 which was maintained at 37°C±0.2°C, and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. Previously weighed film was placed in intimate contact with

the mucosal surface that was previously moistened with a few drops of simulated saliva. The donor compartment was filled with 1 ml of simulated saliva of pH 6.8. Samples were withdrawn at suitable interval, replacing the same amount with the fresh medium to maintain the sink condition. The percentage of drug permeated was determined spectrophotometrically at 293 nm [12,13].

Scanning electron microscope (SEM)

For this study, a small section of the optimized film was cut and then mounted onto stubs using double-sided adhesive tape. Then, the section was determined using SEM (ZEISS EVO 18 Germany) [14].

Physical stability

Stability studies on the optimized formulation were carried out to determine the effect of temperature and humidity on the stability of the drug. The film (optimized batch) was stored in the stability chamber (REMI Elektrotechnik Ltd., Vasai, India) at 40°C±0.5°C and 75±5% RH for 2 months. The samples were withdrawn after 2 months and subjected for DT, weight of film and *in vitro* % drug release studies [14].

RESULTS AND DISCUSSION**Exploration of the plasticizers for the formulation of oral FDF**

Different plasticizer, namely, Glycerol, propylene glycol, and PEG 600 was used for the formulation of FDF. All these films were evaluated for appearance, DT, and folding endurance, as shown in Table 2.

Effect of plasticizer

All the trial batches were formulated using various types of plasticizer. Plasticizer affects the film separation property of the film. When the concentration of PEG 600 was increased, it also increased the flexibility of the film as compared to the glycerol and propylene glycol films which showed poor flexibility and mechanical strength due to high moisture retaining nature of glycerin, while propylene glycol yields brittle film with moderate flexibility. Furthermore, PEG 600 resulted in better film separation than propylene glycol. The plasticizer affects the flexibility of the films hence folding endurance also got affected. The PEG 600 showed good effect on folding endurance and disintegration time and hence selected as a plasticizer for further batches of the films.

Standard calibration curve of PXH

The standard calibration curve of PXH was plotted as absorbance versus concentrations. The λ_{max} of PXH in phosphate buffer pH 6.8 was found to be 293 nm. The standard calibration curve of PXH was plotted between 10 and 80 µg/ml, as shown in Fig. 1.

Drug-excipient compatibility by FTIR

The IR absorbance peak for characteristic functional groups of PXH at 3331.89 cm⁻¹ (N-H stretching), 1521.14 cm⁻¹ (aromatic C-C stretching), 1222.91 cm⁻¹ (C-O stretching), and 2915.16 cm⁻¹ (C-H symmetric

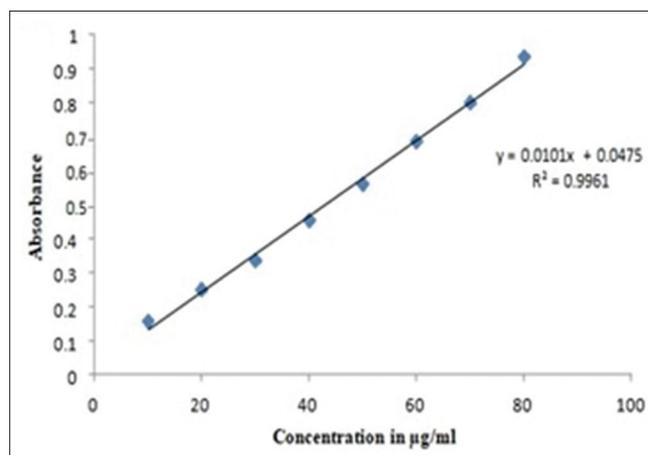


Fig. 1: Calibration curve of paroxetine hydrochloride in phosphate buffer pH 6.8

stretching) was observed in IR spectra of plain drug. The peaks observed were retained in PM, as shown in Fig. 2a. This indicates that there was no interaction between drug and excipients.

Table 2: Evaluation of trial batches of Pullulan with different plasticizer

S. No.	Batch	Disintegration time (s)	Folding endurance (Number of times)	Appearance of film
1.	R1	21	42	Transparent
2.	R2	26	33	Transparent
3.	R3	15	49	Transparent

Drug-excipient compatibility by DSC

PXH showed a sharp endothermic peak at 121.30°C corresponding to its melting point. Similarly, the PM of PXH with Pullulan showed a peak at 120.23°C. There was slight shifting of melting endotherm of PXH in the PM which indicated that there was no interaction between drug and the excipients, as shown in Fig. 2b.

FTIR and DSC studies suggested that the drug, PXH is compatible with the excipients. From these, it can be concluded that the drug has maintained its identity without losing its characteristic properties. It will not show any adverse effect in action of the formulation and helps to study the desired parameters in the study.

Table 3: Physicochemical characteristics of PXH FDF

Batch code	Disintegration time (s)	Folding endurance (Number of times)	In vitro drug release (%)	Thickness (mm)	Drug content (%)	% Moisture content	Weight variation (mg)
F1	11.31±1.51	92.23±1.03	81.55±0.16	0.03±0.01	92±0.48	12.30±0.07	29.6±1.52
F2	12.13±1.49	98.31±1.04	88.58±0.13	0.03±0.02	95±0.51	10.44±0.16	40±2.00
F3	13.33±1.52	105.32±1.06	94.31±0.15	0.05±0.01	97±0.57	10.11±0.33	40.6±1.52
F4	15.26±1.47	91.35±1.08	78.15±0.12	0.02±0.04	88±0.36	13.01±0.12	36.3±1.54
F5	17.34±1.39	97.34±1.06	75.48±0.15	0.04±0.03	86±0.53	15.15±0.27	27.6±1.51
F6	18.29±1.44	102.37±1.02	69.75±0.14	0.03±0.02	87±0.23	14.23±0.58	34±2.02
F7	21.31±1.33	91.33±1.05	65.06±0.12	0.02±0.04	89±0.35	13.24±0.12	32.3±1.49
F8	22.32±1.38	99.36±1.11	60.70±0.11	0.03±0.01	89±0.46	14.13±0.40	36±1.00
F9	24.29±1.43	104.32±1.13	62.08±0.13	0.03±0.02	87±0.67	14.92±0.49	33±2.04

Data represent mean±standard deviation, n=3. PXH: Paroxetine hydrochloride, FDF: Fast dissolving films

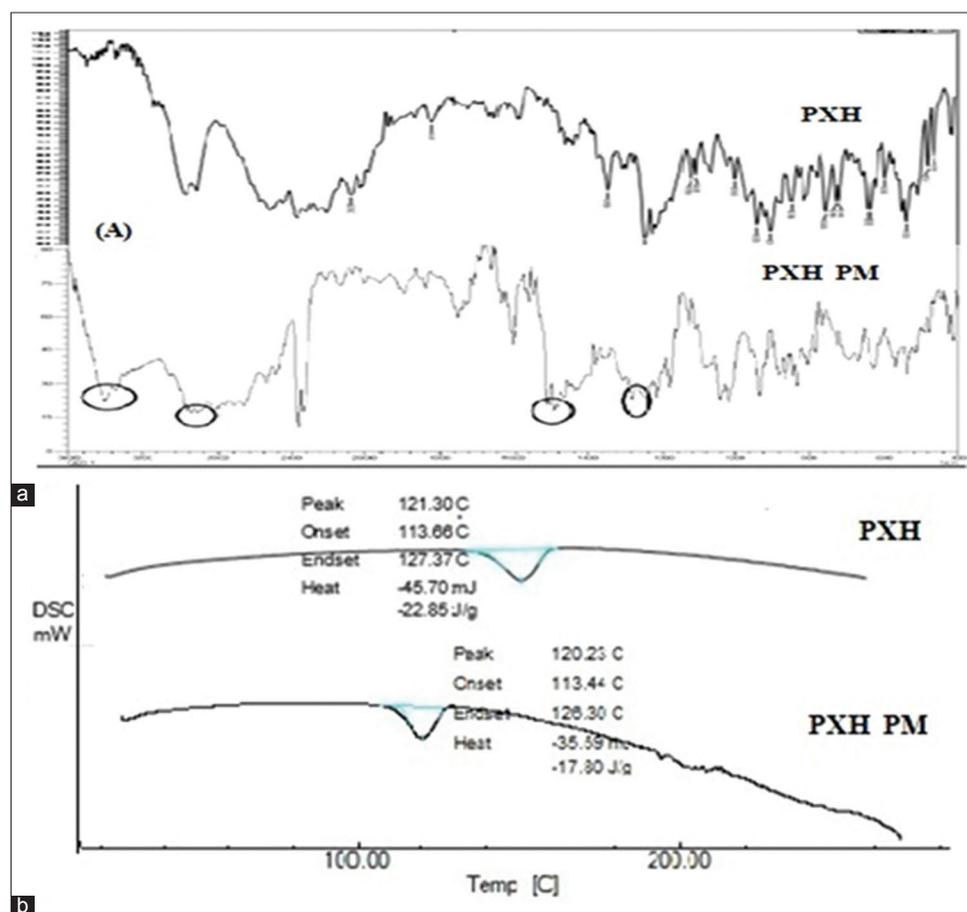


Fig. 2: (a) IR spectra of paroxetine hydrochloride (PXH) and PXH PM (b) differential scanning calorimetry thermogram of PXH and PXH PM

Physicochemical evaluation of FDF

PXH films were designed with the objective of immediate release of the drug for improved patient compliance and better bioavailability. Therefore, rapidly water-soluble natural polymer such as Pullulan¹ was chosen for the formulation. Physicochemical characteristics of the PXH films are shown in Table 3.

Appearance

The prepared films were found to be smooth, uniform in thickness, mass, drug content without any visible cracks or folds. The physical appearance was checked with a visual inspection of films and texture by feel or touch. Appearances of all the films were transparent, all were having smooth surface and were elegant enough for appearance.

Film thickness

As all the formulations contain a different concentration of PLN (4–6% w/v) and PEG 600 (1–3% w/v), the thickness gradually increased with the amount of polymers. All the film formulations were found to have a thickness in the range of 0.023±0.04–0.05±0.01 mm.

Weight variation

Three films each of 4 cm² were cut at three different places from the casted film, and weight variation was determined. Weight variation varies from 29.66±1.52 to 33±2.04 mg.

Table 4: Experimental and predicted response of optimized batch F3

S. No.	Parameters	Predicted result	Experimental result
1.	Disintegration time (s)	17	13.33
2.	<i>In vitro</i> % drug release	89.97%	94.31%
3.	Folding endurance (Number of times)	112	105

Table 5: Stability studies of optimized formulation F3

Parameter	Initial	After 1 month	After 2 months
Description	Transparent and smooth	Transparent and smooth	Transparent and smooth
DT (s)	13.33±1.52	14.19±0.18	16.13±0.26
Weight of film (mg)	40.66±1.52	41.25±1.33	45.36±1.78
<i>In vitro</i> drug release (%)	94.31±0.91	92.67±0.23	89.54±0.63

Data represent mean±standard deviation, n=3. DT: Disintegration time

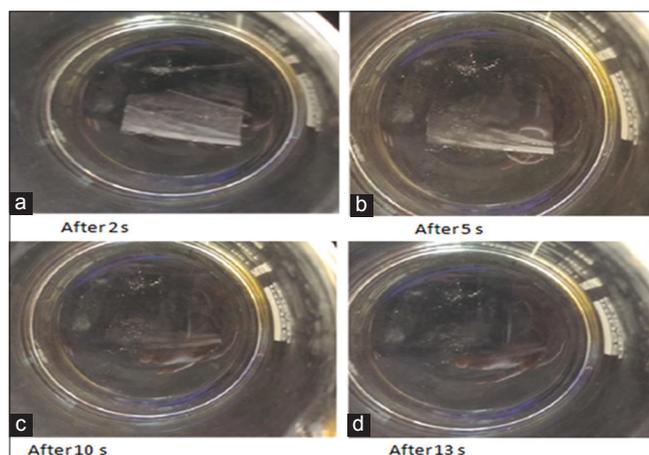


Fig. 3: Disintegration of optimized batch at different time point. (a) After 2 s, (b) After 5 s, (c) After 10 s, (d) After 13 s

Folding endurance

It helps in determining the mechanical strength of films. Higher the value of folding endurance, higher is the mechanical strength of film. All the medicated films had satisfactory folding endurance >90 indicating that they were strong and flexible enough during handling and application. The highest folding endurance was found to be 105.32±1.06 for F3. It was noticed that, as the concentration of PEG 600 increased, folding endurance of Pullulan film also increased indicating that it affects overall flexibility of film. A direct relation exists between mechanical strength and folding endurance of films. As mechanical strength is governed by plasticizer concentration, so it is clearly evident that plasticizer concentration also indirectly affects folding endurance value.

Surface pH

Since pH of the saliva range from 5.5 to 7, an attempt was made to keep the surface pH of the film within range. The surface pH of all the films varied between 6.2±0.14 and 6.73±0.13, the overall results were near or above 6.5, and hence, this film may not cause any irritation in the oral cavity.

Drug content and % moisture content

The drug content of the film was between 92±0.48 and 86±0.53% w/w, indicating an almost uniform drug loading in all medicated batches. A minimum of 10.11±0.33% moisture content was seen in F3 batch.

DT

All film formulation denotes excellent DT almost <25 s which was attributed to the presence of water-soluble excipients in the film. Amount of saliva in oral cavity is one of the important parameters for rapid disintegration in addition to low thickness of the film. The DT at different time point is shown in Fig. 3.

In vitro drug release study

Being highly water-soluble polymer, it provides rapid disintegration and dissolution of the film. This characteristic helps in the rapid onset of action of the formulation, as the drug quickly diffuses from the oral

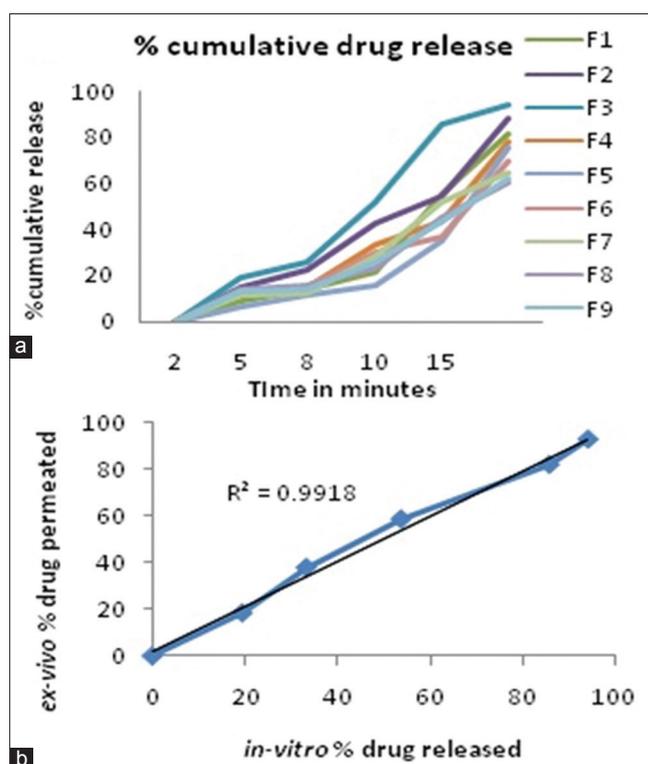


Fig. 4: (a) % *In vitro* release profile of all the batches and (b) correlation between *in vitro* release and *ex vivo* permeation of optimized batch

mucosa and reaches the systemic circulation. The *in vitro* drug release profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition, as given in Table 1. Being the fast disintegrating formulations, the release rates of all the formulations were nearly rapid. Approximately >60% release was observed from all the batches as illustrated in Fig. 4a and highest dissolution of 94.31% was seen in F3 formulation within 15 min. The drug release is governed by polymer content, higher amount of Pullulan resulted in release of drug at slower rate, and it may be due to reduction in the permeability due to change in the morphology of the polymer. Increased polymer concentration may have provided the matrix with lower tortuosity and poor water porosity for diffusion of drug. Moreover, higher polymer concentration would have resulted in viscous environment of the system inhibiting movement of water into the matrix for easy diffusion of the drug [15].

Ex vivo permeation

Ex vivo permeation study on optimized formulation F3 revealed that $92.67 \pm 0.36\%$ of the drug was permeated within 15 min, as shown in Fig. 4b. Good correlation was observed between *in vitro* drug release

and *ex vivo* permeation. This study revealed that drug directly reaches systemic circulation through the oral mucosa bypassing the first-pass metabolism [15].

Comparative results of *in vitro* drug release of films made up of Pullulan and HPMC E3

HPMC is known to be a polymer showing good film-forming properties. Hence, considering HPMC as a standard polymer, *in vitro* % drug release between Pullulan based film was further compared with a film made up of HPMC E3, as shown in Fig. 5. The % cumulative drug release from Pullulan film was better than the HPMC E3 film.

Optimization of FDF by factorial design

The response surface plots were generated using design expert software (Version 11, Stat-Ease Inc., USA), as shown in Fig. 4, so as to observe the effects of independent variables on the response studied such as DT, *in vitro* % drug release and folding endurance, respectively. The response surface plots showed that various combinations of independent variables X_1 and X_2 may satisfy any specific requirement (i.e., DT, *in vitro* % drug release and folding endurance) while taking into consideration the various factors involved in the dosage form.

Using the polynomial equations, the optimized formulation was obtained for the response parameters. In the trial runs, the optimized formulation was arrived using numerical optimization of FDF using design expert software (Version 11, Stat-Ease Inc., USA). After developing the polynomial equations for the responses Y1-Y3 with the independent variables X_1 and X_2 , the formulation was optimized. Optimization was performed to find out the level of independent variables (X_1 and X_2) that would yield a maximum value of FDF.

The DT, *in vitro* % drug release, and folding endurance were evaluated and found within the limits. The formulation F3 was considered for model validation. The values of responses predicted from the obtained model by software and the results obtained by experimentation are shown in Table 4. The close resemblance between observed and predicted response values indicates the validity of the generated model.

The DT was increased with increase in the concentration of Pullulan and a slight change in DT was seen when concentration of PEG 600 increased while keeping Pullulan constant, as shown in Fig. 6a. Increase in Pullulan concentration resulted in decrease in % *in vitro* drug release. Concentration of PEG 600 did not significantly affect the % *in*

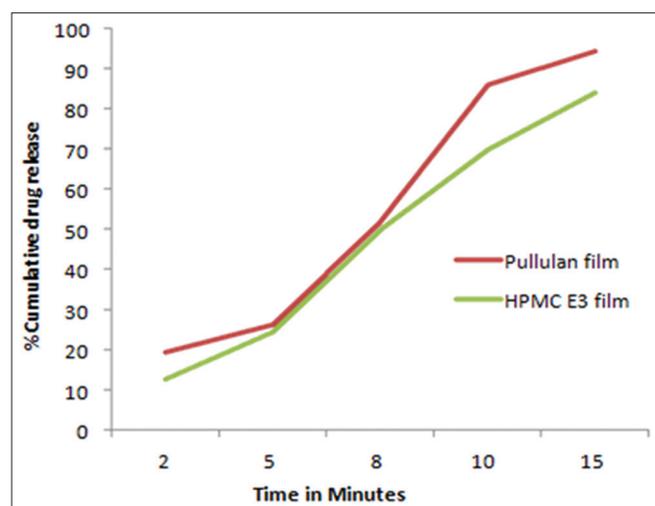


Fig. 5: *In vitro* % cumulative drug release of Pullulan and hydroxypropyl methylcellulose E3 films

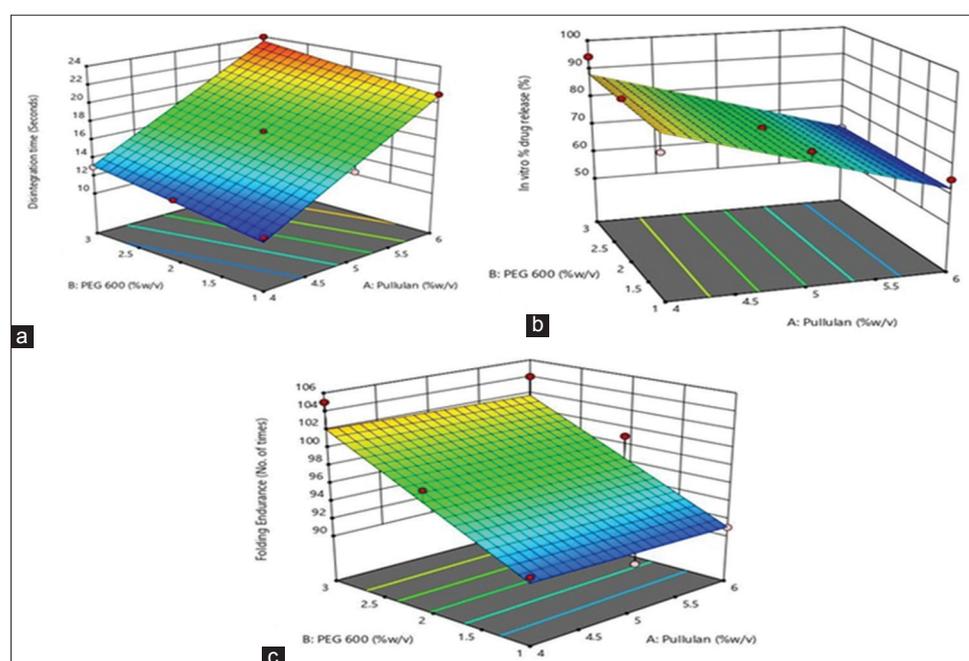


Fig. 6: Response surface plots for (a) folding endurance, (b) disintegration time and (c) *In vitro* % drug release

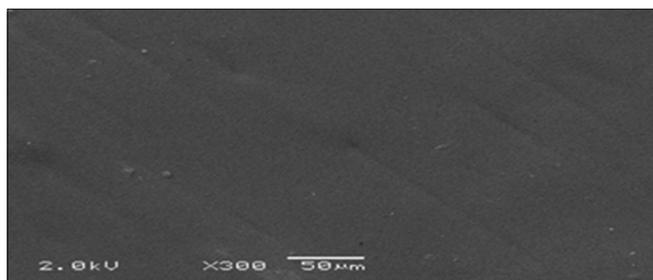


Fig. 7: Scanning electron microscope image of optimized film formulation

in vitro drug release. Maximum % *in vitro* drug release was observed for lower concentration of Pullulan as shown in Fig. 6b. When we increased the concentration of PEG 600 from 1% to 3%, there was increase in the folding endurance from 92 to 105. PEG 600 majorly affected folding endurance than Pullulan, as shown in Fig. 6c.

SEM evaluation

The surface morphology was examined by SEM for optimized F3 film formulations, as shown in Fig. 7. The formulations showed very smooth surface at low magnification. This affirmed the smooth texture of film surface, which is one of the esthetic attributes of films. However, at microscopic level, there was high surface area, which helped in the rapid disintegration of the film. From Fig. 7, it was observed that the surface morphology showed smooth surfaces indicating uniform distribution of formulation ingredients. All the ingredients were also miscible which showed that nature of excipients was hydrophilic that resulted in complete mixing between them [16-18].

Stability study

The optimized formulation F3 was evaluated for stability studies which were stored at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$ for 2 months and were analyzed for physical appearance, DT, weight of film, and *in vitro* % drug release rate after particular time interval. The results are shown in Table 5. The physical appearance of the film was good, smooth, and transparent till the end of duration. It was found that films retained its physical appearance and there was not much significant change in the values. No statistically significant changes were observed in DT of the film, weight of film and *in vitro* drug release (%) after 2 months [19].

CONCLUSION

FDF of PXH using Pullulan as a natural biodegradable film former, PEG 600 as a plasticizer was successfully formulated at lab-scale by solvent casting method. Based on the results, it was found that Pullulan showed potential negative effect on the drug release rate while Plasticizer PEG 600 directly affected mechanical strength of film thus in turn affecting folding endurance. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical applications. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. Pullulan is a natural polymer obtained from non animal origin and does not require chemical modification. Thus, it can be concluded that FDF formulation using Pullulan as natural polymer can be an innovative and promising approach for the delivery of PXH.

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AUTHORS' CONTRIBUTIONS

Farheen Ali: The main researcher, design of problem, experimental study. Rita Wadetwar: Corresponding author, designing of problem, manuscript preparation, and manuscript correction. Pranita Kanojija: Manuscript preparation and manuscript correction.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest. The contents of the paper have not been submitted for publication in any of the journals.

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