

Development of Taste Masked Orodispersible Film Containing Paroxetine Hydrochloride

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ABSTRACT

Aim and Objectives: The present study was to formulate and evaluate orodispersible films to overcome drawbacks of conventional dosage forms such as degradation by first-pass hepatic metabolism, decreased bioavailability and patient non-compliance. In the present work the taste masked Paroxetine HCl was formulated in the form of Orodispersible film. Rationale for formulating the taste masked PXT in ODF form was to increase convenience of paediatric, geriatric, bedridden, psychiatric patients and those who have dysphasia. **Materials and Methods:** The orodispersible films were prepared by solvent casting method using HPMC E-5, Propylene glycol (plasticizer), citric acid (saliva stimulating agent), stevioside (sweetener) and PVP K-30 as superdisintegrant. Paroxetine hydrochloride was taste masked by inclusion complex formation with HP β -CD by freeze drying. The 3 factorial designs was used to study the effect of independent variables viz. concentration of HPMC E-5 (X) and concentration of PG (X) on three dependent variables such as *in vitro* drug release, folding endurance and disintegration time. Optimized formulation was evaluated for physical appearance, thickness, moisture content, weight uniformity, surface pH measurement and taste masking ability by human gustatory sensation test. **Results:** The optimized batch (F3) showed 99.94% drug release with 72 as folding endurance and disintegration time of 24 sec. *Ex vivo* permeation, oral mucosa sensitivity test, release kinetics and accelerated stability studies confirmed that developed formulation exhibited flash drug release and was stable, non-irritant and therapeutically effective. **Conclusion:** Taste masked complex of paroxetine hydrochloride with HP β -CD could be successfully formulated into orodispersible film.

Key words: Paroxetine hydrochloride, Hydroxy Propyl Beta Cyclodextrin, Taste-masking, Freeze-drying, Oral films.

INTRODUCTION

Development of drug delivery to any molecule is based on market needs, product differentiation and patient compliance. In the present scenario, there is an ever increasing demand for more patient-compliant dosage forms. One important innovation in this direction is fast dissolving/disintegrating dosage forms. These have been proved ideal for the geriatric and paediatric populations, bedridden or travelling patients, people suffering from dysphasia, clinical conditions in which water intake is limited and situations in which water is not available. Rapidly disintegrating/dissolving dosage forms are further categorized as Orodispersible

Tablets (ODTs) and Orodispersible Films (ODFs). Most ODTs are fragile and brittle, need special package for protection during storage and transportation. However, films are flexible; they are not as fragile as ODTs, easy for transportation, handling and storage.¹

ODF is a dosage form that employs hydrophilic polymer which allows the dosage form to quickly hydrate by saliva and / or adhere to mucosa, disintegrate within a few seconds, dissolve and releases medication for oromucosal absorption when placed on the tongue or oral cavity.² The oral mucosa is relatively permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of

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drugs due to high blood flow.³ ODF was developed based on the technology of transdermal patch and is specially designed for the drugs which have extensive first pass metabolism and low dose. There are many methods for formulation of rapidly disintegrating/dissolving films. Practically reviewing these methods with respect to the ease of preparation and cost-effectiveness, the solvent casting method was found to be the best option.⁴ Cyclodextrins (CD) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. On account of their relatively hydrophobic interiors, CDs have the ability to form inclusion complexes with a wide range of substrates (Loftson *et al.* 1996). This complex forming ability of CD have been widely exploited in the pharmaceutical field for various applications, including taste-masking of bitter drugs.^{5,6} Paroxetine hydrochloride (PXT) is a BCS Class-II drug with very bitter taste. Paroxetine hydrochloride is a SSRI drug generally indicated for the treatment of depression and anxiety and it is extensively metabolized, predominantly due to hepatic metabolism. At present, there is no ODF in the market; the drug is marketed as conventional tablets, sustained-release tablets, oral suspensions. Formulation of taste masked ODF of PXT will show rapid onset of action and avoid hepatic metabolism.^{6,7}

MATERIALS AND METHODS

Materials

Paroxetine hydrochloride was a generous gift from Zydus Cadila Healthcare Ltd. (Ahmedabad, India). Hydroxy Propyl β -cyclodextrin (HP β -CD) was purchased from Loba Chemicals (Mumbai, India). HPMC E-5, PG, PVP K-30, Vanilla flavour and Citric acid were procured from Research Lab Fine Chemicals (Mumbai, India). Stevioside was purchased from Desle Agro export (Pune, India). All reagents were of analytical grade. Double distilled water was used for all the experiments.

Taste masking of Paroxetine HCl using inclusion complexation

Phase solubility studies were carried out at room temperature and in triplicate.⁸ An excess amount of paroxetine hydrochloride was added to double distilled water containing various concentrations of HP β -CD (0.002-0.1 M) in a series of stoppered conical flasks and then shaken for 3 days on a rotary flask shaker. The suspensions were filtered through Whatman filter paper and assayed for Paroxetine hydrochloride using a UV spectrophotometer (Jasco, Japan) at 292.5 nm

against blank prepared using same concentration of HP β -CD in double distilled water. The association constant (K_a) was calculated from the slope of the linear portion of the phase solubility diagram. According to Equation (1),

$$\text{DPPH radical scavenging effect (\%)} = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control} \times 100} \quad (1)$$

Preparation of solid complexes by freeze-drying method

Physical mixture of paroxetine hydrochloride and HP β -CD in a molar ratio of 1:1 were added to double distilled water and stirred for 5 hr using magnetic stirrer. The suspension was freeze-dried (Labconco® Freeze Dryer). The freeze-dried complex was pulverized and sieved through (<38 μm).⁵

Evaluation of taste of complexes

The sample of drug-HP β -CD complex (1:1 molar ratio) underwent gustatory sensory evaluation by a panel of five members; the evaluation was performed by classifying the bitter taste into the following five classes-Class 5: Very strong bitter, Class 4: Strong bitter, Class 3: Moderately bitter, Class 2: Slightly bitter, Class 1: No bitter taste/ tasteless.

The pure drug was used as a standard control, with a mean bitter taste of class 4. Each of the members was given the control, i.e., 10 mg of pure drug and complex (equivalent to 10 mg PXT) to be held in the mouth for 5–10 s then spat out and the bitterness level was recorded.⁵ The members of the panel were asked to gargle and wait for 20 min before another sample was given to them. The mean bitterness value of each complex was calculated based upon the level of bitterness sensed by each individual member of the panel.

Characterization of drug and HP β -CD complex

Evaluation of taste masked drug and HP β -CD complex prepared by freeze dried method was done using following techniques.

Drug content

A drug- HP β -CD complex equivalent to 10 mg of the drug was stirred with 100 ml of acetate buffer pH 4.5 for 60 min. The solution was then filtered and treated as a stock solution (100 $\mu\text{g}/\text{ml}$ of the drug). From this stock solution, the concentration of 10 $\mu\text{g}/\text{ml}$ was prepared. Drug content was determined using calibration curve of the pure drug in acetate buffer pH 4.5 spectrophotometrically at 292.5 nm.⁵

In vitro dissolution study

Table 1: Composition of taste masked PXT orodispersible film

Sr. No.	Name of excipients	Formulation Code Concentration (%w/w)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	HPMC E-5 LV	59	59	59	61	61	61	63	63	63
2	PG	32	34	36	32	34	36	32	34	36
3	PVP K-30	10	10	10	10	10	10	10	10	10
4	Citric acid	3	3	3	3	3	3	3	3	3
5	Stevioside	10	10	10	10	10	10	10	10	10
6	Vanilla flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Dissolution study of inclusion complex was performed using USP type II apparatus (Electro lab) in 500 ml of acetate buffer pH 4.5. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$ and rotation speed was 50 rpm. Samples were withdrawn at time intervals of 2, 4, 6, 8, 10 and 30 min and analyzed spectrophotometrically at 292.5 nm

Infrared Spectroscopy

Infrared (IR) spectra of pure drug, HP β -CD and complex were obtained by using IR spectrophotometer (Jasco, Japan) with KBr pellets. The scanning range used was 4000 to 400 cm^{-1} .

X-ray Diffractometry

Drug (Paroxetine HCl) and complex of drug with HP β -CD were subjected to powder X-Ray Diffraction (XRD).

Differential scanning calorimetry (DSC)

DSC was performed to confirm the complexation between drug and HP β -CD. Wherein small amount of sample (5.09 mg) was hermetically sealed and analyzed using DSC 60 (Shimadzu, Japan). Thermograms of complex and pure drug were compared for confirmation of complex formation.

Preparation of orodispersible films

Accurately weighed freeze dried complex of PXT+HP β -CD (equivalent to 110.73 mg of PXT) was dissolved in 10ml of distilled water using magnetic stirrer for 30 min. Further required quantity of PVP K-30, Citric acid and Stevioside were added with constant stirring into same solution. HPMC E-5 LV was dissolved in 10 ml of cold DW separately (since HPMC dissolves in cold water) for 2-3 hr. Both the solutions were mixed together followed by addition of propylene glycol (33-35% w/w of polymers) using magnetic stirrer (Equip-Tronics, Mumbai) with constant stirring for 10-15 min. This solution was sonicated for 30 min. The resultant clear, bubble-free solution was casted on glass Petri plate and allowed to dry in hot air oven at 40°C

Table 2: Coded and Actual levels of variables in ODF formulations

Batch No.	Coded levels		Actual level	
	Factor 1 (X_1)	Factor 2 (X_2)	Factor 1 (Conc. of HPMC E-5)	Factor 2 (Conc. of PG)
F1	-1	-1	59	32
F2	-1	0	59	34
F3	-1	+1	59	36
F4	0	-1	61	32
F5	0	0	61	34
F6	0	+1	61	36
F7	+1	-1	63	32
F8	+1	0	63	34
F9	+1	+1	63	36

for 12 hr.⁹ Finally, dried film was cut into the size of $3\text{ cm} \times 2\text{ cm}$, with total surface area of 6 cm^2 . Samples were packed in aluminium foil and stored in amber colored glass container at room temperature and 60% RH.¹⁰

Design of experiments

A 3^2 randomized full factorial design was applied to the experiments. Concentration (%) of HPMC E-5 LV and plasticizer PG were selected as independent variables, whereas dependent variables are % drug release in 20 min, folding endurance and disintegration time.^{11,12} Formulations F1 to F9 were prepared using three different levels of HPMC E-5 and PG concentration Shown in Table 1. The responses of the dependent variables were evaluated. The polynomial equations were generated for each responses using Design Expert Software (7.1.4) and intensive grid search was performed over the experimental domain to locate five optimum formulations (S1–S5). These five formulations were then formulated and used to validate the obtained polynomial equation model. The summary of the formulations is shown in Table 2.

Physical appearance and surface texture of film

Films of each formulation were randomly selected and visually inspected for texture by feel or touch.²

Thickness and Weight uniformity

Thickness of film was assessed using a Micrometer screw gauge with a least count of 0.01 mm at different spots of films. Thickness was measured at five positions (central and the four corners) and the mean thickness was calculated for three randomly selected films. Each film was weighed individually on an analytical balance (Contech, CB-50) and the average weight was calculated.¹¹

Surface pH measurement

Surface pH of 3 randomly selected films was determined to check whether the film causes irritation to oral mucosa using pH meter (Equip Tronics, EQ-614, India). In this method pH probe was placed in close contact with the wetted film surface and pH was recorded.¹⁰

Moisture content

The prepared films were weighed individually and kept in desiccators containing calcium chloride at room temperature for 24hr. The films were weighed again, until constant weight is achieved. The % moisture content was calculated as a difference between initial and final weight with respect to final weight.¹³

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \quad (2)$$

Disintegration time

Disintegration time is calculated manually by dipping film in 10 ml of Acetate buffer pH 4.5 in a beaker with swirling every 10 sec. at $37 \pm 2^\circ\text{C}$. When film starts to break or disintegrates, time was noted.

Folding endurance

Folding endurance of films was determined manually by repeatedly folding a film at the same place until it breaks. The experiments were performed in triplicate and average values were reported.¹²

Tensile strength

Tensile strength is defined as the maximum stress applied to a point at which the film specimen breaks and can be calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{N}{\text{mm}^2} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}} \quad (3)$$

Tensile strength of 400 mm² randomly selected film was checked by Universal tensile strength testing machine

(LS5, Lloyd Instruments Limited, UK). The force of the film at the point when the film broke was recorded.¹⁴

Drug content uniformity

This was determined by standard assay method described for the PXT HCl in USP 28. Content uniformity was determined by estimating the API content (10 mg) in individual strip. Limit of content uniformity is 85-115%.

In vitro drug release studies

USP dissolution apparatus type II was used to study drug release from film under sink conditions at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A single film was placed in 500 ml dissolution media containing pH 4.5 Acetate buffer.⁵ Samples (10 ml) were withdrawn at suitable time interval of 2, 4, 6, 8, 10 and 20 min and replenished with fresh dissolution medium. The amount of PXT was determined by UV spectrophotometer at 292.5 nm (Jasco) with the help of standard curve of drug the test was performed in triplicate for each formulation.

Kinetics of drug release

To understand the release patterns followed by drug from film matrix, all formulations were subjected to various mathematical kinetic models like Zero-order, First-order, Higuchi, Korsmeyer-Peppas. The model with the highest correlation coefficient was considered to be the best fitting one.¹⁰

Ex vivo drug permeation studies

The optimized formulation was subjected to permeation studies through the sheep oral mucosa using Franz diffusion cell. PXT being hydrophobic drug has high permeability through oral mucosa and hence no penetration enhancer was incorporated. A 6 cm² film was placed on the oral mucosa. Receptor compartment contained 15.5 ml while donor compartment was filled with 1 ml of acetate buffer pH 4.5. The cell contents were stirred using magnetic bead at $37 \pm 1^\circ\text{C}$. Aliquots of 1 ml were withdrawn at regular intervals (every 2 min) for 30 min and filtered. The amount of drug permeated was quantified using UV spectroscopic method of analysis with the help of standard curve of drug ($y = 0.009x + 0.013$, $R^2 = 0.996$ and range 10-60 ppm) at 292.5 nm. The graph of cumulative amount of PXT (μg) permeated per unit of mucosal surface area (cm²) against time (min) was plotted. Permeation flux (J , $\mu\text{g cm}^{-2}\text{min}^{-1}$), was calculated from this graph as the amount of PXT passing across 1 cm² of the permeation membrane per unit time.¹²

Histopathological study

The final optimized formulation was subjected for oral mucosa sensitivity test. After completion of the diffusion experiment, oral mucosa was collected and repeatedly washed with acetate buffer pH4.5. Small portion of the tissue was fixed in 10% buffered formalin solution and dehydrated. Sections were taken and stained with haematoxylin eosin (HE) and examined under digital microscope (Motic) to evaluate any histological changes in the epithelium and the adjacent connective tissue. Control oral mucosa was also treated and examined similarly.¹⁵

Accelerated stability studies

Stability studies were conducted according to ICH guidelines Q1A. The orodispersible films were wrapped in aluminium foil, packed in glass container and kept in stability chamber, at $40 \pm 0.5^\circ\text{C}$ temperature and $75 \pm 5\%$ RH for 3 months respectively. After 1, 2 and 3 months, oral films were tested for changes in appearance, drug content, disintegration time (sec).

RESULTS AND DISCUSSION

Taste Masking of Paroxetine HCl

Phase solubility profile between PXT and HP β -CD was observed at 37°C . It was observed that as we go on increasing the concentration of HP β -CD there was increase in concentration of PXT which gives linear curve as shown in Figure 1 and this linear curve followed an A_L type system according to Higuchi and Connors showing that soluble complexes were formed. Phase solubility analysis indicated the formation of first order soluble complexes. The stability constant ($K_{1:1}$) 371.08 M^{-1} was obtained which was found to be within the range of 50 and 2000 M^{-1} .

A. Determination of drug content in PXT and HP β CD inclusion Complex

Drug content of freeze dried complex of HP β -CD and PXT was found to be $94 \pm 0.5\%$.

B. *In vitro* dissolution study

Figure 2 indicates that 96.63 % drug release was shown by drug and HP β -CD complex within 30 min. Figure 2

C. Confirmation of complexation

FTIR studies

Freeze dried complex showed prominent peaks of the drug, but there was a reduction in peak intensity which was obscured by HP β -CD peak, conforming the formation of inclusion complexes. Data shown in Figure 3.

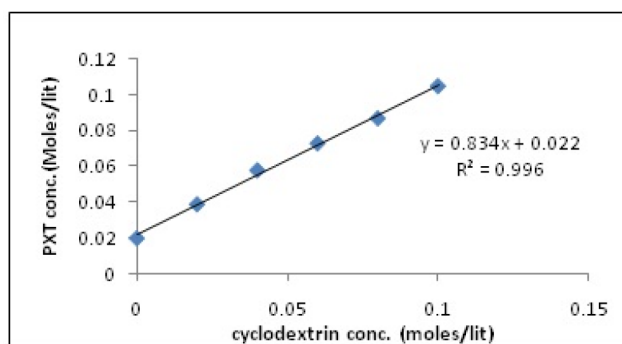


Figure 1: Phase solubility study between PXT and HP β -CD.

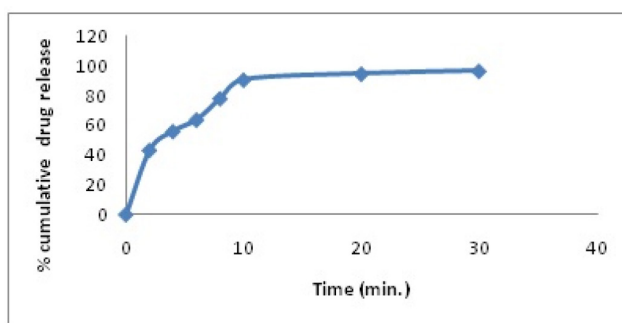


Figure 2: *In vitro* drug release of freeze dried complex of drug and HP β -CD.

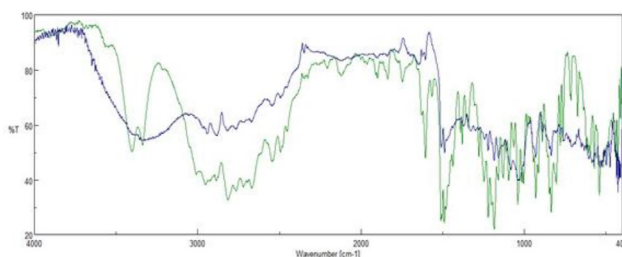


Figure 3: FTIR Overlay of PXT and freeze dried complex of PXT+ HP β CD.

XRPD studies

XRD analysis was carried out to confirm the formation of amorphous solid state (inclusion complex formation). In which it has been observed that the diffraction patterns of inclusion complex are somewhat diffused compared to pure drug. The diffractogram of drug exhibited characteristic peaks, due to its crystalline nature. But in freeze dried complex (Figure 4), no characteristic peaks were observed due to amorphous nature of complex confirming the formation of inclusion complex.

DSC study

Thermogram of the complex showed very less intensity of peak of PXT at 138.5°C and sharp endothermic

peak of HP β -CD at 263.63°C as shown in Figure 5. This indicates successful inclusion complexation of drug with HP β -CD.

Optimization of Formulation

Evaluation of taste masked orodispersible film

Physical Appearance

All films were found to be smooth and elegant with transparent appearance.

Thickness and Weight uniformity

The average thickness of all ODFs ranged from 51-68 μ m as given in Table 3. This depicts that the film cast was uniform. Weight variation values (mg) of different PXT films were found to be in the range of 104-132 mg. Thus there was proportional gain in weight of films with increase in the thickness of films.

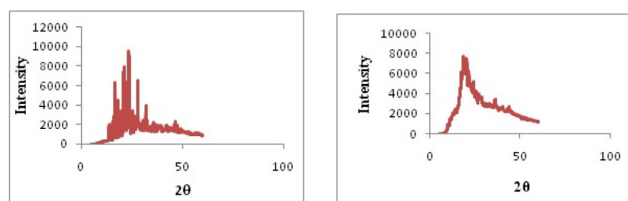


Figure 4: XRD graph of (a) Pure drug (b) Freeze dried complex of PXT and HP β -CD.

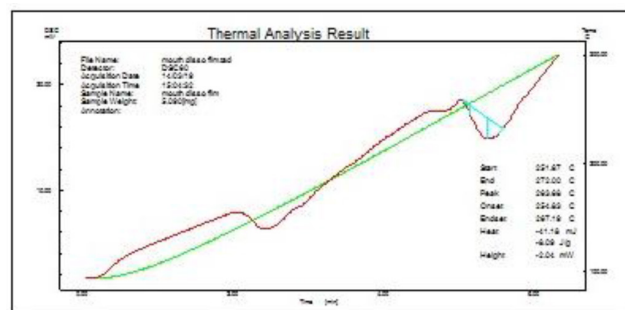


Figure 5: Thermogram of freeze dried drug and HP β -CD complex.

Surface pH measurement

Surface pH of all the films was found to be in the range of that of 4.5- 4.8 (Table 3). Hence no mucosal irritation was expected from these films.

Moisture content

Results showed that moisture content of all films ranges from 3.26 to 5.6.

Folding Endurance

Folding endurance was found to be increased with increasing concentration of PG. This may be due to increase in molecular mobility with the increase in PG concentration which in turns caused a reduction resistance and increase in flexibility.¹⁶

Disintegration time

Disintegration time calculated by simple manual method is shown in Table 4, which indicates that disintegration time of F2 to F6 batches was less than 30 sec. This could be because of less thickness and viscosity of these films containing low concentration of HPMC E-5. On the other hand F7 to F9 formulations containing high concentration of HPMC E-5 showed high D.T. irrespective of the concentration of PG.

Drug Content Uniformity

The percentage drug content was determined using the standard calibration curve. Results are shown in Table 4. As the drug content values of same formulation did not show a significant difference, it can be concluded that the drug was uniformly dispersed in ODF.

Tensile strength

Tensile strength of the film was checked by universal tensile strength testing machine. Typical tensile strength for film should be 1.80 ± 0.20 MPa. Tensile strength of optimized batch F3 was found to be 9.12N/mm²,

Table 3: Evaluation of physicochemical parameters of PXT film

Formulation code	Thickness* (μ m)	Weight uniformity* (mg)	Surface pH*	Moisture content (%)
F1	53 \pm 1.24	118 \pm 0.94	4.48 \pm 0.01	5.4
F2	52 \pm 1.14	109 \pm 0.56	4.38 \pm 0.01	4.58
F3	51 \pm 1.54	106 \pm 0.87	4.38 \pm 0.02	3.26
F4	56 \pm 1.42	104 \pm 0.46	4.36 \pm 0.05	4.31
F5	58 \pm 1.10	115 \pm 0.53	4.36 \pm 0.02	3.5
F6	58 \pm 1.08	114 \pm 1.21	4.37 \pm 0.01	4.2
F7	65 \pm 0.96	124 \pm 0.81	4.37 \pm 0.03	4.87
F8	63 \pm 1.63	118 \pm 0.67	4.36 \pm 0.03	5.6
F9	68 \pm 1.29	132 \pm 0.74	4.37 \pm 0.02	4.54

Table 4: Folding endurance, Disintegration time and drug content uniformity of F1- F9 formulations

Formulation Code (FC)	Folding endurance ^a	Disintegration time (sec.)	Drug content uniformity ^a (mg)
F1	62 ± 0.45	38± 1.53	9.49 ± 0.01
F2	68 ± 1.00	23± 0.81	9.50 ± 0.02
F3	72 ± 1.52	24± 1.2	9.49 ± 0.03
F4	43 ± 1.52	30± 0.88	9.48 ± 0.01
F5	49 ± 1.52	28± 1.89	9.50 ± 0.01
F6	52 ± 1.52	30± 1.54	9.51 ± 0.01
F7	24± 1.52	39± 1.11	9.48 ± 0.03
F8	28 ± 1.08	40± 1.63	9.49 ± 0.01
F9	34 ± 0.51	45± 1.12	9.50 ± 0.02

which means formulation F3 showed good mechanical strength so as to withstand any damage during handling or transportation.¹⁶

In-vitro drug release studies

In-vitro drug release profiles are shown in Figure 6. An immediate drug release was successfully observed for all taste masked orodispersible films of PXT. Optimized batch F3 showed maximum cumulative drug release in 20 min. Minimum drug release was shown by F7 formulation containing high concentration of HPMC E -5 and lowest concentration of PG (Table 5). Thus, *in-vitro* drug release study result showed that as the concentration of plasticizer increases, drug release of mouth dissolving films also increases.

Kinetics of Drug Release

The value of coefficient of regression for different models of optimized formulation (F3) is given in Table 6. The coefficient of regression value was found to be highest for First order model and hence the release mechanism was found to follow first order kinetics.

Ex vivo drug permeation studies

The optimized formulation F3 was subjected to permeation studies through the sheep oral mucosa. Results of *ex vivo* drug permeation studies are shown in Table 7. Cumulative drug release of F3 batch was found to be 65.69 % at the end of 30 min. (Figure 7).

Histopathological study

The final optimized formulation F3 was subjected to oral mucosa sensitivity test. Histopathological evaluation of sections of sheep oral mucosa showed (Figure 8) that cellular membrane was intact and there was no damage to the epithelial layer. Cell necrosis was not observed and hence it can be concluded that, formulation F3 is safe for oral administration of PXT through orodispersible film.

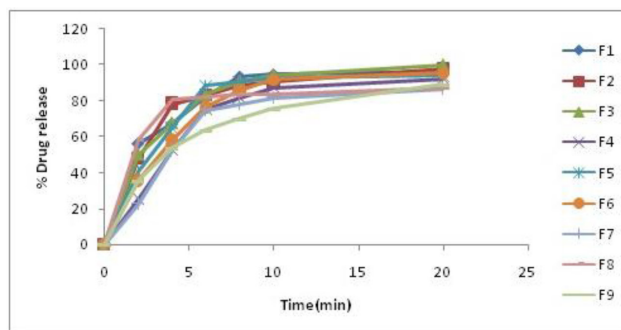
**Figure 6: Comparative *in vitro* drug dissolution profiles of PXT orodispersible films.**

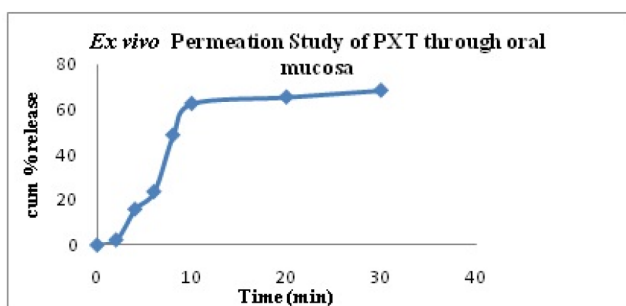
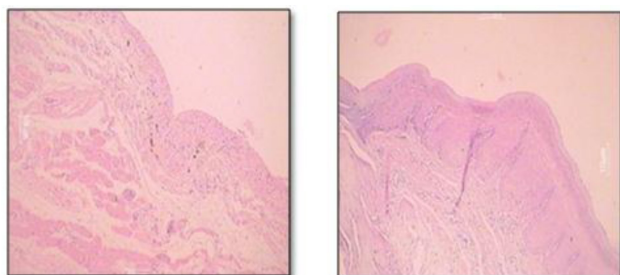
Table 5: Cumulative drug release of F1 to F9 batches of ODF									
Time (min)	Cumulative drug release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	56.18	47.53	50.13	25.73	40.39	35.61	22.70	58.45	35.42
4	67.23	78.27	67.59	53.02	65.02	58.34	52.35	80.57	53.75
6	82.15	83.12	83.47	75.54	88.24	76.64	74.69	82.32	63.49
8	93.58	88.71	91.07	81.93	90.28	85.90	77.86	83.36	69.84
10	94.83	90.28	94.35	87.57	92.65	92.07	81.60	83.51	75.72
20	96.11	97.61	99.94	92.36	94.03	95.40	86.34	87.15	88.93

Table 6: Kinetic parameters of PXT orodispersible film

FC	Zero order	First order	Higuchi	Hixon-crowel	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	N
F3	0.6241	0.9951	0.8835	0.6845	0.9895	0.2059

Table 7: *Ex vivo* permeation of PXT through oral mucosa

Time (min)	cum% drug release
0	0
2	0.00
4	2.30
6	15.97
8	23.70
10	48.86
20	62.81
30	65.69

**Figure 7: *Ex vivo* permeation of PXT through oral mucosa.****Figure 8: Histopathological evaluation of sections of sheep oral mucosa (a) Control (b) Sample mucosa (treated formulation F3).**

Accelerated Stability Studies

The results of stability studies performed on batch F3 are shown in Table 8. After the 3 months study, it was found that there was no change in appearance of the film and negligible change in moisture content. The drug content and % drug release after 20 min. was decreased but not significantly.

Table 8: Stability studies of optimized batch F3 at 40°C±2°C and 75%±5 RH

Parameters	0 day	30 days	60 days	90 days
Appearance	No change	No change	No change	No change
Drug content (mg)	9.38	9.36	9.35	9.31
% Drug release	96.092	95.64	95.32	95.21
Disintegration time(min.)	24	25	25	25

CONCLUSION

Paroxetine hydrochloride a bitter drug could be successfully taste-masked using HP β -CD by freeze-drying method and was incorporated to prepare of oro-dispersible films. Films formulated with HPMC E-5 (59%), PG (36%) and PVP K-30 (10%) as super-disintegrant showed faster disintegration and drug release. The prepared formulation offered significant results in terms of improving taste and bioavailability.

In the final conclusion, taste masked PXT orodispersible films can be successfully formulated, to provide rapid release using HP β -CD as taste masking agent, PVP K-30 as superdisintegrant and makes it suitable for the anxiolytic and depressed patients, those who are suffering from dysphasia and also for bedridden patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

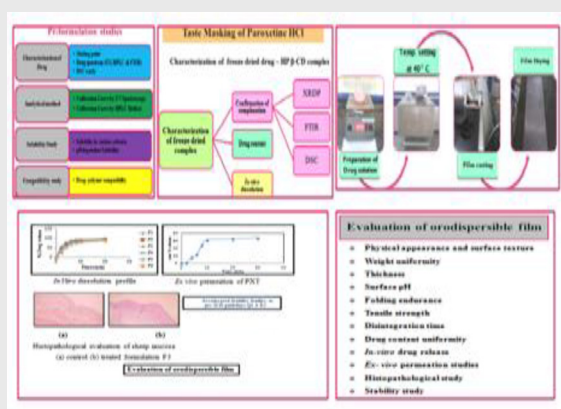
ABBREVIATIONS

ODF: Orodispersible film; PXT HCl: Paroxetine Hydrochloride; DSC: Differential Scanning Calorimetry; ICH: International Conference on Harmonization; FT-IR: Fourier Transformed-Infrared Spectroscopy; HCl: Hydrochloric Acid; HPLC: High Performance Liquid Chromatography; λ_{\max} : Maximum Absorbance; RH: Relative Humidity; UV: Ultra Violet; USP: United States Pharmacopoeia; PVA: Polyvinyl alcohol; HPMC: Hydroxy propyl methyl cellulose; PVP: Poly vinyl pyrrolidone; SSG: Sodium Starch Glycolate; PEG: Polyethylene glycol; HP β -CD: Hydroxy propyl beta cyclodextrin.

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PICTORIAL ABSTRACT



SUMMARY

Bitter taste of PXT was masked by using HP β -CD. Optimization of orodispersible film was carried out using 3^2 factorial design. The final optimized formulation was then tested for oral mucosa sensitivity, the results indicated that the selected formulation batch F3 not showing any irritation effect on oral mucosa of sheep. The stability studies of final optimized formulation revealed that was no significant change in the physical parameters.

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