Orodispersible Films of an Antipsychotic Drug: Development and Physicochemical Characterization

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Summary: To deliver maximum amount of paroxetine in shortest duration of time, the orodispersible films (ODF) were formulated and tested for their suitability as a carrier system. ODF were prepared by using hydroxypropyl methylcellulose and polyvinyl alcohol and different superdisintegrants at a specific proportion. The newly developed ODF were subjected to characterization for folding endurance, weight variations, thickness, disintegration time, drug release pattern and drug content. The surface morphology of orodispersible film was examined by means of scanning electron microscope. Moreover physical compatibility between the drug and excipients was guaranteed in the orodispersible film by Fourier transform infrared spectroscopy. It was found that all films prepared were transparent, smooth and elegant in appearance. ODF showed good folding endurance, uniform thickness, weight and drug content. The surface pH of all orodispersible film was found to be neutral and they disintegrate within few seconds. FTIR spectroscopy supported compatible among all excipients and they can be used together in formulation. It was concluded that stable paroxetine orodispersible films can be made by solvent casting technique with ultrafast dissolution rate.

Keywords: Paroxetine orodispersible films, Solvent casting method, Superdisintegrants, Hydroxypropyl methylcellulose, Poly vinyl alcohol.

Introduction

Various routes of administration such as inhalation, transdermal, parenteral have made tremendous progress as a drug delivery system, but even than oral route has been the most favorable route of administration [1]. Absorption extend through these routes is a primary focus in drug development process because drug must be absorbed before any pharmacological effect can take place. The absorption of some drugs is affected by some unfavorable conditions existing in gastro intestinal tract. Drugs (like paroextine) given by the oral route of administration are absorbed from the GI tract and before reaching the systemic circulation drug undergoes first pass metabolism in the GI tract and in the liver, resulting in a decreased drug bioavailability.

Recent advances in novel drug delivery system aim to enhance safety and efficacy of drug molecule by formulating a dosage form for administration and to achieve better patient compliance. Orodispersible drug delivery system is a new generation delivery system also known as fast dissolving/disintegrating film for the oral delivery of the drugs which came as an alternative to tablets, capsules, syrups and other formulations. Orodispersible films disintegrate rapidly in a matter of seconds when placed on the tongue [2]. The patients suffering from disabilities such as elderly patients, children and patients having difficulty in swallowing, face difficulty in chewing or swelling solid oral formulations. A wide population of these patients has fear of choking and thus they avoid taking these oral solid dosage forms. Thus orodispersible dosage forms are quickly achieving popularity in the pharmaceutical market. These formulations do not need water for swallowing or chewing and rapidly disintegrate or dissolves in the mouth within a matter of seconds. Mostly liquid formulations are used for child patients or in the condition of dysphagia, but it leads to inaccurate dosing. Solid oral formulations have superiority then liquid oral formulation in terms of accurate dosing. In addition, these systems may offer better clinical profiles with superior absorption in the oral cavity, thus they provide high drug bioavailability then the traditional oral formulations available in the market for oral consumption [3].

Paroxetine is an orally administered antidepressant drug belongs to class of selective

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serotonin-reuptake inhibitors. It is absorbed from GI tract rapidly and shows extensive first pass metabolism [4]. The time to reach peak plasma concentration is approximately 5 hrs and its biological half life is 21 hrs. These pharmacokinetic properties of paroxetine make it ideal for the formulation into ODF dosage form that has not yet been developed. ODF will improve absorption from stomach and also reduce subsequent first pass metabolism of paroxetine. Moreover ODF will be more convenient to the geriatric patients for the management of depression with anxiety.

Experimental

Materials

Paroxetine was obtained as gift sample from Popular Chemical Works Pvt. Ltd, Pakistan. Hydroxypropyl methylcellulose E5 (HPMC) was purchased from Alfa Aesar, Germany. Polyvinyl pyrrolidone (PVP) was obtained from Bio Basic, Canada. Polyvinyl alcohol (PVA), Polyethylene glycol (PEG) 400, Crosspovidone (CP), Sodium starch glycolate (SSG), Croscarmellose Sodium (CCS) and Aspartame were provided by Daejung Chemical and Metals co. Ltd. Korea.

Formulation of Paroxetine Containing Orodispersible Films by Solvent Casting Method

Preliminary various orodispersible films were prepared using two hydrophilic polymers (HPMC and PVA) and different plasticizers (Glycerin, Polyethylene glycol and Propylene glycol) were used to analyze film forming capacity, appearance, ease of separation from petri dish without cracking, and folding endurance.

Orodispersible film (ODF) of Paroxetine was prepared by solvent casting method. Hydrophilic polymers and plasticizers was placed in specific proportion of distilled water (10 ml) to make aqueous solution and maintained at 80 ^{o}C and this solution was stirred until a clear solution obtained. Subsequently, required amount of sweetener (aspartame) and superdisintegrants (crosscarmellose sodium, crosspovidone, polyvinyl pyrrolidone and sodium starch glycolate) were added and mixed continually by stirring until it became transparent [5]. Another solution was prepared in which weighed drug was dissolved in methanol and then added in polymeric solution (Table 1). Then this solution was sonicated to remove the air that was entangles in form of bubbles. After the removal of air bubbles, the solution was casted on glass petri dishes of 5 cm^2. Then it was dried for 24 hrs at room temperature and after drying the films were detached from petri dishes carefully and cut into square of 2×2 cm^2. Films with air bubbles or any imperfection were not included in further studies. Then ODF were wrapped in aluminium foils and stored in air tight glass jar [6].

Morphological Properties of Film

Properties such as homogeneity, color, surface smoothness and transparency of paroxetine orodispersible films were visually examined [7].

Weight Variation and Thickness

All films were weighed on electronic weighing balance and average weight was recorded for each formulation. The measurement of each ODF was done for three times and represented as mean ±SD. Thickness was calculated by micrometer screw gauge at different positions of film and average was calculated.

Surface pH

The pH of the film was noted by wetting a piece of film with distilled water in petri dish. The surface of ODF was touched by electrode of pH meter to note its pH value. It is essential to note the pH of the orodispersible film because acidic or basic pH of the film can cause irritation to oral mucosa [8].

Table-1: Composition of various paroxetine ODF formulations.

ODF	Paroxetine (mg)	PVA	HPMC E5	PEG 400	Aspartame	CCS	CP	PVP K30	SSG
F1	20	2	-	15	6	5	-	-	-
F2	20	2	-	15	6	-	5	-	-
F3	20	2	-	15	6	-	-	5	-
F4	20	2	-	15	6	-	-	-	5
F5	20	-	2	15	6	5	-	-	-
F6	20	-	2	15	6	-	5	-	-
F7	20	-	2	15	6	-	-	5	-
F8	20	-	2	15	6	-	-	-	5

*Polymers were in % w/v and all other ingredients were in % w/w of polymer

Folding Endurance

Endurance value is a number of times the film is folded without any breakage. It was performed to determine the brittleness of film and also the elasticity and durability of the film during handling and storage. The ODF was folded repeatedly at 180º angle of plane at the same place till it breaks and the number of times it was folded was observed [9].

Tensile Strength

Tensile strength is defined as maximum stress applied at which the film specimen breaks. This test was performed to determine the mechanical strength of the film. Texture analyzer was used to conduct tensile strength that was equipped with a 5N load cell. Film free from any air bubbles or any imperfection was cut into longitudinal shaped strips and placed between the clamps of texture analyzer. Gauge length was 120 mm and speed was 100 mm min^{-1} [10]. The test was considered concluded when the film breaks. It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

$$Tensile\ strength = [\text{load at failure} / (\text{film thickness} \times \text{film width})] \times 100$$

Percent Elongation (E %)

Strain is actually the deformation of the film divided by the original dimension of the film [11]. Percent elongation is calculated by dividing the extension at the moment of breakage by the initial gauge length of film and multiplying by 100 according to the equation:

$$E\% = [(L - L0) / L0] \times 100)$$

where L_0 = initial length and L = length at the time of breakage

Drug Content

Drug content uniformity of each ODF formulation was determined by cutting the film of size 2×2 cm^2 and putting it into 10 ml volumetric flask containing methanol: phosphate buffer 6.8 pH and kept aside until the film completely dissolved. This solution was filtered through 0.45µm membrane filter. Then 1 ml of this solution was diluted with phosphate buffer 6.8 pH. The drug content was determined by UV spectroscopy at 294 nm [12].

In-Vitro Disintegration Time

In-vitro disintegration time of ODFs was calculated by two methods: drop method and petri dish method. In drop method, the film was placed on a petri dish and placed on a plane surface and a drop of phosphate buffer 6.8 pH was dropped onto the film with the help of pipette. The time at which a hole forms in the film was observed as disintegration time. In Petri dish method, 5ml of the phosphate buffer (6.8 pH) was added in a petri dish and the film was placed in it. The time at which the film breaks into layers was noted as disintegration time [13].

In-Vitro Release Study

In-vitro dissolution study was performed in Paddle dissolution apparatus. Paddle method is difficult to perform because the film starts to float on the dissolution medium. To overcome this problem, the film was fixed to a rectangular slab and placed the bottom of the dissolution vessel. The dissolution medium used was 250 ml phosphate buffer of 6.8 pH and temperature was maintained at 37±1º C and the rotation speed was set at 50 rpm. Samples of 2 ml were withdrawn at 0.5, 1, 2, 3, 5 and 10 min intervals and replaced with same volume of fresh phosphate buffer at 37±1º C. The samples were filtered through 0.45µm pore size membrane filter and analyzed for the determination of concentration of paroxetine released [14].

FTIR Spectroscopy

Drug and drug-excipient interactions have been studied using Agilent Fourier-transform infrared spectrophotometer. IR spectra of pure paroxetine as well as formulations were recorded. Average of 8 scans were taken per sample in the range of 4000-650 cm^{-1} with a resolution of 4 cm^{-1} [15, 16].

Scanning Electron Microscopy

The surface morphology of ODF was examined by means of scanning electron microscope (Model S-4700, Hitachi, Japan) operating at 5 kV. The samples were fixed on a glass stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. The micrographs were recorded to study the morphological and surface characteristics of drug-loaded ODF [17].

Stability of Paroxetine ODF

From all the formulations, the results of thickness, surface pH, % elongation, drug content, disintegration time and drug release, F6 showed the best features due to having low viscosity HPMC and a superdisintegrant CP. On the basis of these results F6 was carried to stability studies. The stability study for fast dissolving film was carried out according to the ICH guidelines at 40±2°C and 75±5% RH for 45 days by storing the aluminum-packed samples in a stability chamber [18].

Results and Discussion

Plasticizer Selection

Selection of plasticizer was carried out on basis of folding endurance. Among various plasticizers PEG 400 with both polymers showed maximum folding endurance Figure 1.

HPMC and PVA have excellent film forming properties and provided transparency and smoothness to films [19]. PEG 400, PG and Glycerol were used as p plasticizers in films and as their concentration increased, the flexibility of the films was improved. The plasticizer affected the flexibility of the films hence folding endurance was also got affected**.** Plasticizer also affected the film separation property of the film [20, 21].

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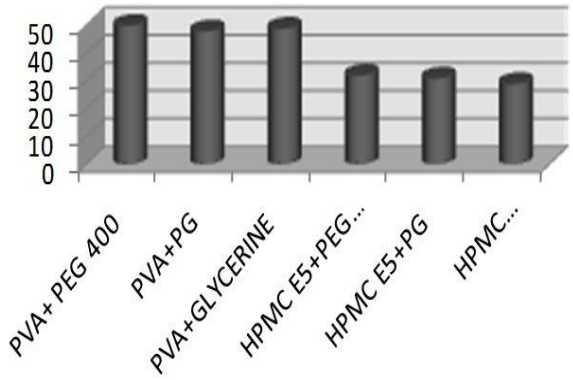

Fig. 1: Folding endurance values PVA and HMPC films with different plasticizers.

Morphological Properties of Film

On visually inspection, it was found that all the films prepared with different polymer were flexible, smooth, transparent, non-sticky, uniform and free from entrapped air (Figure 2), which are essential parameters for the elegant surfacing of films. The appearance of films was found to be transparent because of the hydrophilic nature of film forming polymer while films prepared by PVA are more transparent and more flexible [22]

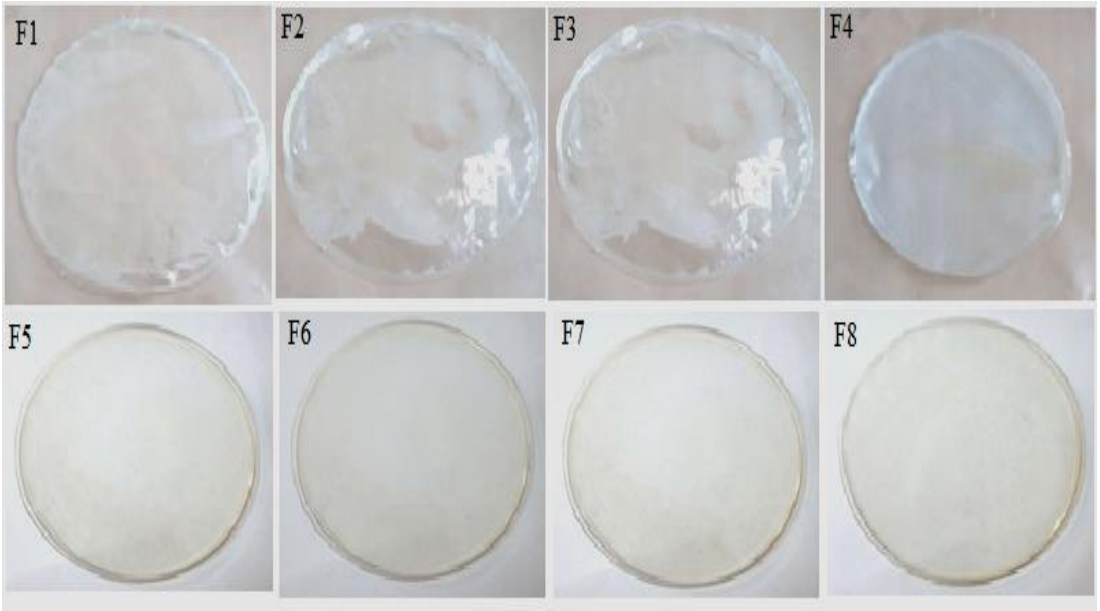

Fig. 2: ODF's of paroxetine having PVA as polymer in F1-F4 and HPMC as polymer in F5-F8.

Chemico-mechanical Properties

Weight variation, thickness, surface pH and % drug content, folding endurance, tensile strength and % elongation are given in Table-2.

A negligible differences weight of ODF was found with constant and uniform amount of drug. The thickness of the films was found to vary from 0.10±0.01 to 0.13±0.02 mm. There was no significant difference in the thickness of the films due to the balanced amount of plasticizer added. Thickness and drug content are directly related and it signified the uniformity of drug content [23-25].

The films were of neutral pH, which indicates that the film will not cause any irritation in oral cavity. The minor difference in pH values among films was due to the different excipients used. PVA and HPMC have pH of 5-6.5 and 5-8 respectively. Superdisintegrants CCS, CP, PVP K30 and SSG have 5-7, 5-8, 5-7 and 5.5-7.5 pH respectively. All these pH are near to neutral and were responsible for pH of surface of film [26].

A higher % elongation and tensile strength were expected for an ideal oral film. The tensile strength and % elongation varied from 3.01±0.172 to 3.23±0.152 (N/cm^2) and 82% to 94%, respectively. From this, it can be observed that the % elongation increased in formulations containing PVA as a polymer due to its flexibility. Films having PVA and PVP K30 as a disintegrant showed more elongation as compared to all other formulations because of combination of most flexible polymers. Formulation containing HPMC and PVP K 30 also exhibited good elongation and less tensile strength as compared to others.

Disintegration Time Release Studies

All ODF disintegrated within 28 seconds by both drop and petri-dish method (Figure 3).The release studies revealed more than 90% release within 2 minutes from all ODF (Table 3).

The disintegration time of formulated ODF was found to decrease by using HPMC as a polymer and CP as a superdisintegrant. PVA has also excellent film forming capacity but it has high viscosity than HPMC. CP relies on both swelling and wicking action, the air present between the particles is being replaced and bonding is also reduced that apart the film into fine particles [27].

SSG follows the swelling mechanism that cause quick immersion of aqueous media volume of granules is expanded and proceeds to breaking of film. Croscarmellose sodium also relies on swelling and wicking action but in contrast to other superdisintegrants like SSG and croscarmellose, CP does not cause gelling at high ratio. All these three superdisintegrants have crosslinked structures except PVP K30 and crosslinking decreases the viscosity of solution [28].

Most of drug released before two minutes from all ODF formulations. Comparison indicated that films containing HPMC release drug more rapidly as compared to PVA. These results indicated that the components of HPMC E5 films promote the dissolution rate of paroxetine than from PVP films and this may be attributed to the lower viscosity of HPMC (4–6 cP) than that of PVP. The disintegrants in polymeric films promoted the quick release of paroxetine by ulta-fast disintegration in dissolution medium [29].

FTIR Spectroscopy

FTIR spectroscopy of pure drug and all formulation F1 – F8 showed that paroxetine is compatible with all excipients and can be used together (Figure 4). Stretching frequency of all functional groups of paroxetine is shown in Table 4.

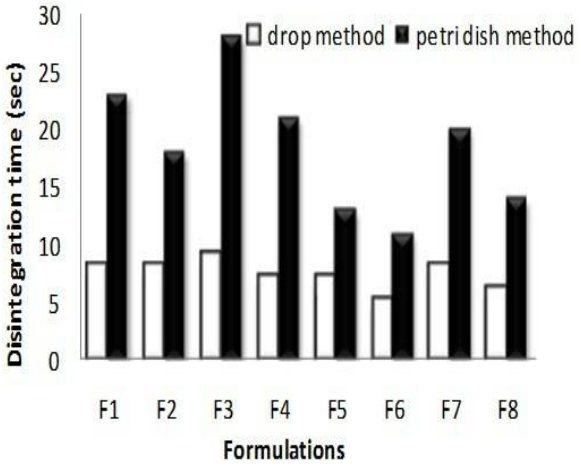

Fig. 3: Disintegration time of formulations in comparison of drop method and petri dish method.

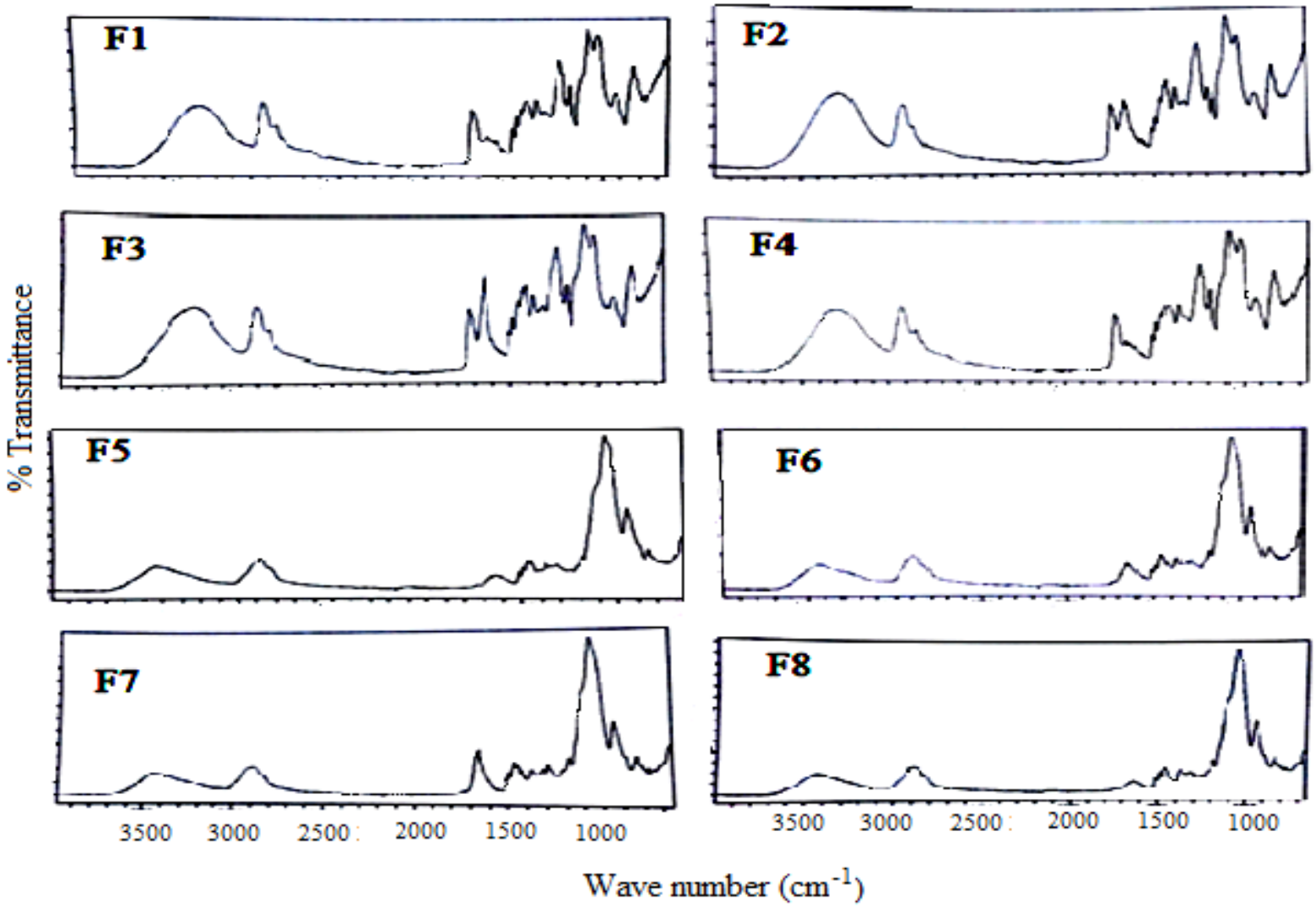

Fig. 4: FTIR of paroxetine loaded ODF with PVA (F1-F4) and HPMC (F5-F8).

Table-2: Chemico-mechanical nature of paroxetine ODF.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Appearance	Transparent and smooth	Transparent and smooth	Transparent and smooth	Transparent and smooth	Transparent	Transparent	Transparent	Transparent
Weight (mg)	122±0.53	121±0.32	122±0.64	122±1.08	121±1.02	122±1.52	121±1.08	121±0.65
Thickness (mm)	0.13±0.02	0.12±0.01	0.13±0.01	0.11±0.01	0.10±0.01	0.12±0.02	0.10±0.02	0.10±0.01
Surface pH	6.8±0.10	6.7±0.25	6.8±0.15	6.8±0.10	6.7±0.23	6.8±0.10	6.7±0.14	6.8±0.12
% Drug content	97.49±0.21	98.59±0.14	97.49±0.22	96.47±0.11	98.36±0.20	99.87±0.10	98.54±0.20	97.56±0.25
Tensile strength (N/cm^2)	3.12±0.130	3.01±0.172	3.23 ±0.152	3.15±0.183	3.21±0.204	3.22±0.43	3.10±0.64	3.12±0.23
% elongation	85.34±2.50	84.23±2.60	94.05±2.34	86.43±2.85	82.76±1.05	89.85±1.95	88.65±2.54	85.65±1.76
Folding endurance	51	49	55	46	32	34	35	29

Table-3: Release studies of formulations at different time interval.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	42.81± 0.001	41.25±0.005	32.66±0.002	45.37±0.005	52.70±0.004	56.72±0.004	50.15±0.001	51.66±0.003
1	62.67±0.003	60.23± 0.003	49.37±0.004	66.98±0.004	72.56±0.005	92.63±0.005	53.51±0.002	69.92±0.001
2	87.56±0.004	89.63±0.002	71.41±0.003	90.71±0.002	98.73±0.005	95.74±0.003	89.36±0.001	82.63±0.002
3	92.40±0.002	93.72±0.001	89.93±0.005	93.41±0.005	98.53±0.002	98.91±0.002	95.56±0.002	96.49±0.003
5	92.41±0.003	93.74±0.0005	95.62±0.004	93.39±0.006	98.93±0.003	98.92±0.002	95.14±0.002	96.43±0.002
7	92.43±0.005	93.76±0.001	95.28±0.001	93.59±0.004	98.93±0.005	98.92±0.004	95.14±0.001	96.49±0.003
10	92.62±0.004	93.76±0.001	95.32±0.002	93.58±0.004	98.93±0.003	98.92±0.004	95.14±0.002	96.49±0.004
20	92.63±0.001	93.76±0.003	95.34±0.004	93.78±0.002	98.92±0.005	98.92±0.004	95.14±0.002	96.49±0.003

FTIR spectrum displayed identification peaks of functional groups in paroxetine. These values were perfectly matched to the standard data of the drug indicating the purity of drug. PVA was used as a film former in F1-F4 so a wide peak shows in these formulations have hydroxyl group stretching that indicated the presence of this polymer. HPMC E5 was used as polymer in F5-F8 and peak appears at 1,045 cm^{-1} (C–O stretch vibration) that is the main absorption band of HPMC. F1 and F5 shows a peak at 1731cm^{-1} represent ester C=O group of crosscarmellose sodium. F2 and F6 displayed a peak of CP at 1643 cm^{-1} C=O stretching band. F3 and F7 showed absorption band at 1658 cm^{-1} that is characteristic of PVP K30. A small peak was observed at 1275$cm^{-1}$of SSG in F4 and F8 which pointed out the compatibility with drug. The combined spectral analysis of drug with other excipients showed all characteristics peaks of drug indicated that the drug was compatible with polymers and superdisintegrants [30, 31].

Table-4: Stretching frequency of functional groups of paroxetine.

Functional group	Frequency stretching (cm^{-1})
Water (O-H)	3404
Aliphatic (C-H)	2924
Ammonium (N^{+}-H)	2817, 2765, 2720, 2540, 2494
Aromatic (C-C)	1600, 1512, 1504, 1490
Ether (C-O-C) Asymmetric	1222
Flouro aromatic (C-F)	1185
Ether (C-O-C) Symmetric	1041
Acetal (C-O-C)	930
Aromatic (C-H)	836

Scanning Electron Microscopy

The surface morphology using scanning electron microscopy of the optimized film formulation of paroxetine depict smooth surface with some little pores (Figure 5), which indicated the uniform distribution of drug particles and that film was enough porous to allow the penetration of surrounding fluid for swelling and dissolutions of drug particles required for the faster drug absorption within the oral cavity [32, 33].

Stability Studies of Paroxetine ODF

Stability parameters of paroxetine ODF are presented in Table 5.

These ODF were stable as no significant change in appearance, thickness, pH, drug content and release rate was observed. Stability at accelerated temperature (40±2°C and 75±5% RH) ensured longer shelf life of ODF at room temperature without any physical or chemical alteration [34].

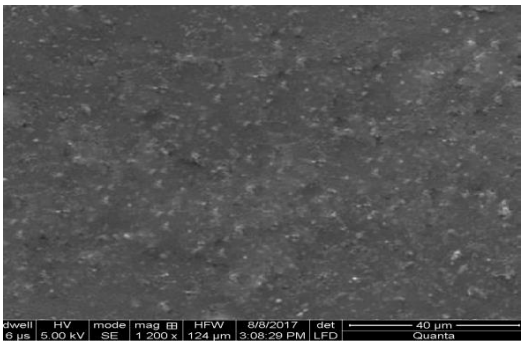

Fig. 5: SEM of paroxetine loaded ODF (F6).

Table-5: Stability parameters of paroxetine ODF.

Time (days)	Appearance	Thickness	pH	Drug content	Drug Release in 3 minutes (%)
0	Transparent	0.12±0.001	6.8	99.87 0.1	98.9
15	Transparent	0.12±0.001	6.8	99±0.01	98
30	Transparent	0.12±0.01	6.8	99.01±0.10	98
45	Transparent	0.11±0.01	6.7	98±0.01	97

Conclusion

The fast-dissolving orodispersible films of paroxetine can be prepared using different film-forming materials by the solvent-casting method. ODF showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Paroxetine was evenly distributed in ODF having fast disintegration and release profile.. Due comparable pH with saliva these ODF will not cause irritation to mucosa. These ODF were stable at accelerated temperature and will be having long shelf life without any degradation.

Therefore, the present orodispersible films containing paroxetine would be potentially useful for treatment of depression where improved patient compliance and convenience is expected.

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Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Aneela Manzoor (manuscript writing and formulation development), Muhammad Naeem Aamir and Zeeshan Javaid (study

designing and publication processing), Hina Hussain (proofreading), Akhtar Rasul (statistical data analysis), Tariq Mahmood (data collection for FTIR) and Khizar Abbas (data collection for SEM).

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