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Neoteric approach of fluoxetine laden orodispersible film for non-compliant paediatric patients of selective mutism and obsessive-compulsive disorder

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Abstract
The objective of present research work was the fabrication, characterization and optimization of fluoxetine laden orodispersible film (ODF), with intent to enhance dosage forms options for paediatric population suffering from incapacitating psychotic disorders of selective mutism and obsessive-compulsive disorder (OCD), which will be ultimately beneficial in enhancing compliance factor and the quality of pharmacotherapy. Solvent casting technique was used to formulate the fluoxetine laden orodispersible film (ODF) formed by natural hydrophilic polymers matrix of HPMC E15 and pullulan. Propylene glycol as plasticizing agent imparted satisfactory tenacity and flexibility to ODFs. FITR studies were done to investigate any potential compatibility and results revealed no potential interaction between fluoxetine and excipients. Developed ODFs were evaluated for physicochemical properties, content uniformity, *in-vitro* disintegration time and *in-vitro* dissolution time studies. The experimental data suggested that different polymer concentration had complex effect on content uniformity, *in-vitro* disintegration time and cumulative percentage drug release from the ODFs. TF7 was found out to be the most optimized formulation with disintegration time of 10.66 sec and 99.37 % drug release within 3 minutes. Further the most optimized fluoxetine ODF was submitted to universal testing machine for tensile strength and percentage elongation determination. It was also further evaluated by thermogravimetric analysis (TGA), scanning electron microscopy (SEM) and X-ray diffraction (XRD). In conclusion, fluoxetine laden ODFs of good pharmaceutical quality can be prepared on small scale. Hereby opening the perspective of using ODFs for individualized pharmacotherapy to ameliorate the compliance issues in selective mutism and OCD paediatric patients.
Keywords: Orodispersible film, fluoxetine, selective mutism, obsessive-compulsive disorder, HPMC E15, Pullulan

Introduction

Pediatric population comprises of heterogeneous age bracket as it encompasses entire population from neonate to adolescence. For decades, complications faced by pediatric population during administration of oral dosage form were not taken into serious account.[1] 90 percentage of total marketed paediatric medicinal products are in liquid dosage forms. However, liquid dosage forms are replete with complications of erroneous dosing, instability, augmented contamination probability and requirement of dedicated utensil for administration.[2, 3] Paediatric patients with disability, mentally challenged state, and psychotic disorder experience slew number of hindrances in oral administration of drug.[4]

Focusing psychiatric disorders, selective mutism and obsessive compulsive disorder (OCD), which are anxiety disorders according to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), inflict paediatric population and sometimes exist concurrently.[5-7] Selective mutism, a complex incapacitating anxiety disorder with onset between 2 to 5 years of age, is typically delineated by perpetual failure to develop verbal communication in distinct social settings where verbal communication is required (e.g., school); however, such children can converse well in domestic backdrop.[8, 9] Similarly, OCD lands up the afflicted children in vitiated social and academic performance.[10, 11]

Selective serotonin reuptake inhibitors (SSRIs), an anti-depressant class of drugs, have been recommended for the treatment of selective mutism and OCD due to their significant efficacy.[12-14] A plethora of studies has reported the well tolerated and effective treatment of OCD and selective mutism with fluoxetine which diminishes the panic attacks and social phobias in paediatric population.[15-17] It is well reported fact that paediatric population experience dysphagia while intake of solid dosage forms.[18] One of the major factors among others might be the smaller dimensions of the children's pharynx and the developing oropharyngeal musculature.[19]

Therefore, for tackling the aforementioned challenges, we aimed to fabricate the fluoxetine laden oral dispersible films (ODF). ODF technology comprises of thin postage stamp sized pliable strip manufactured of hydrophilic film forming polymers and excipients, which release active drug within seconds on contact with saliva in buccal cavity. Needless to mention that excipients incorporated in ODF, such as plasticizer, film stabilizer, saliva stimulating agent, taste masking agent, flavour, and super-disintegrant, must be Generally Regarded as Safe i.e., GRAS listed according to Food and Drug Administration.[20-22] In addition, one of the most salient and crucial components for the formation of ODF is utilisation of polymers. Indeed, the optimal polymer utilisation is vital to impart the required critical characteristics to ODF, for instance solubility, hydrophilicity, pliability, and pleasant mouth feel. In recent times, ODF technology has garnered huge attention for the delivery of active drugs which are prone to deterioration along the GIT due to enzymes and pH variation. Additionally, ODF offers substantial benefits like widened surface area which shortens the disintegration and dissolution time.[20] It ascertains the better accurate and precise dose per film as compared to other dosage form like syrup and drop etc. It is equipped with oral absorbance feature, which leads to accelerated and enhanced bioavailability while offering less frequent dose schedule and consequently lead to enhanced clinical outcomes with minimized side effects.[23] On top of that, ODFs are more palatable than other dosage forms, which assist in enhancing patient compliance.

Moreover, owing to its pliable nature, it is less frangible than orally disintegrating tablet (ODT).[24] It requires no water and no need of swallowing of whole film as it disintegrates in saliva. Further it takes precedence over ODT among patients with fear of choking the tablets, making ODFs ideal for dysphagic patients.[23] While ODFs represent phenomenal advantages, major obstacle to its widespread application is limited drug loading capability of ODFs which only permits the incorporation of low dose high potency drugs into ODFs.[25]

The objective of current research work is formulation, optimization, and characterization of the fluoxetine laden ODFs with the intent to attain faster disintegration leading to faster dissolution and brisk drug absorbance. In addition to this, our work aims to widen the dosage forms options for pediatric patients of selective mutism and OCD and enhance the patient's compliance for achieving the better therapeutic outcomes. Furthermore, the influence of formulation parameters like (polymer, plasticizer) with respect to their concentrations on ODF's evaluation was also investigated.

Materials and Methods

Materials

Fluoxetine was used as an active pharmaceutical ingredient (API) and was generously gifted by Wilshire Labs (Pvt) Ltd. Lahore, Pakistan. Pullulan, a film forming polymer, was purchased from Sigma Aldrich and HPMC low viscosity E15, which is also a film forming polymer and polyvinylpyrrolidone (crospovidone), a super-disintegrant, were purchased from Moringa Pharmaceutical Pvt. Ltd., Lahore, Pakistan. Propylene glycol which is an excellent plasticizer, was obtained from Sigma Aldrich. Citric acid used as saliva stimulating agent and fructose as sweetening agent were obtained from CCL Pharmaceutical Pvt. Ltd., Lahore, Pakistan. Phosphate-Buffer Saline pH 6.8 was obtained from Pharmaceutical research Lab of University of Central Punjab, Lahore, Pakistan. All the chemicals were of analytical grade.

Methods

Solvent casting evaporation method reported in previous literature was minutely tweaked and adapted.[26] Procedure involved solubilisation of required quantity of film forming polymers HPMC E15 and pullulan into distilled water. Further, plasticizer propylene glycol (PG) was also solubilised into same hydro-polymeric solution beaker and placed on magnetic stirrer for 30 minutes. Required quantities of fluoxetine, crospovidone (super-disintegrant), citric acid and fructose were solubilised into distilled water in separate beaker and subjected to mixing by putting on magnetic stirrer for 30 minutes. Previously made plasticizer and polymeric solution was poured into drug- excipients solution and the final volume of each formulation was adjusted to 15ml. Further, final solution was subjected to homogenization under 1000 rpm for 60 minutes by highspeed homogenizer. Homogenized solution was kept aside for one hour to withdraw all entrapped air bubbles. In the next step, homogenized and almost air bubble free solution is casted in petri dishes and placed in hot air oven at 45 °C for 24 hours. After 24 hours, dried film was meticulously peeled off and carved into 2 x 2 cm^2 ODFs and wrapped in aluminium file and stored in desiccator until further use. Trials design and composition is shown in Table 1.

Pre-formulation studies

Fourier transform infrared spectroscopy (FTIR)

FTIR was deployed to inspect the compatibility between fluoxetine and excipients. FTIR of fluoxetine and each individual excipient was performed independently. API and all excipients were in 1:1 blended ratio. Each chemical was individually admixed with KBr and then scanned over the frequency range of 400 to 4000 cm^{-1}.[27]

Post-formulation studies

Physical appearance

Physical appearance of all batches of ODFs was visually investigated considering multiple factors in scrutiny like aesthetic appearance, colour, ODF surface texture and its symmetry, peel ability of ODF from mould (degree of ease in removing ODF from mould without cracks and punctures in its surface), stickiness and its flexibility.

Mechanical Characteristics

Weight variation

Five oral strips from each batch were carved into 4 cm^2 size and weighed individually by utilizing the electronic weighing balance. Average weight of weighed ODFs was calculated and subtracted from individual strip weight. Less variation of resultant value suggests the efficiency of method employed and uniform distribution of API and inactive ingredients across the surface of ODF.[28]

Thickness

Thickness determination of ODF holds great importance in revealing drug's even distribution and appropriate thickness, which facilitates ODF's adhesion capability to tongue. Consistency in thickness of the film validates the accurate dose embodied in the ODF.[28] ODF thickness was measured by utilizing calibrated micrometre screw gauge, at all the four corners and centre point of individual ODF. Further average value and SD was calculated.

Folding fortitude

Folding fortitude manifests the pliability, tenacity, and resilience of ODF. It depicts the capability of ODF to withstand the folding on one plane without rupturing and cracking.[29] This test was performed by repeatedly folding three ODF of each batch at single plane until it cracked, and value was noted as folding endurance value.

Drug content uniformity

Drug content uniformity of fabricated ODFs was probed by adopting the marginally tweaked technique used by El-Setouhy and El-Malak (2010).[30] ODF with area of 4 cm^2 was carved and put into beaker with 50 ml of phosphate buffer of pH 6.8 and subjected to 1 hour stirring on magnetic mixer. Afterwards solution was further processed with filtration via syringe filter of 0.45 µm pore size. Fluoxetine content was determined in the filtrate by UV spectrophotometer at λ max of 263 nm.

Disintegration test

Currently, there is no method for disintegration test specified in pharmacopoeias officially. Among multiple reasons, major and most solution demanding is high volume of disintegration medium used in conventional dosage forms. Because high media volume does not simulate the biological physiological condition of buccal cavity due to limited saliva volume retaining capacity of buccal cavity. In this consideration, several disintegration test techniques have been reported in literature.[31] Considering the popularity and feasibility, petri dish method was opted in which phosphate buffer of pH 6.8 was used as solvent medium for *in-vitro* disintegration test.[32] ODF was cut in 4 cm^2 and placed in petri dish and previously heated 2.5 ml of phosphate buffer of pH 6.8 at 37 °C was poured in petri dish and whirled every 10 seconds. The time (seconds), when ODF start to disintegrate and fragment, was noted as *in-vitro* disintegration time.[33, 34] Disintegration time for three ODFs of same batch was determined and average was calculated.

***In-vitro* dissolution test**

There is no appropriate dissolution method for ODF mentioned in any of the pharmacopoeias. Various published methods in previous research projects of ODF were taken in consideration due to lack of any authentic official method prescribed

and adapted.[35, 36] Hence, *in-vitro* drug release was determined by using USP paddle apparatus type II with 500 ml phosphate buffer of pH 6.8 and temperature set at 37 ± 0.5 °C at 50 rpm. ODF with area 4 cm^2 was carved and placed into the dissolution media and 5ml of samples were taken at 0 min, 0.5 min, 1 min, 1.5 min, 2 min, 2.5 min, 3 min, 5 min, 7 min, 9 min and 11 min immediately replaced with fresh media. Afterwards, samples were filtered through filter syringe of 0.45 µm and examined for absorbance at 263 nm by UV visible spectrophotometer.

Scanning Electron Microscopy

Surface morphology and framework of optimized formulation was scanned and examined by scanning electron microscopy (SEM). ODF was cut in 2 x 2 cm^2 and its surface morphology was scanned with SEM (model JSM5910JEOL, Japan) at voltage acceleration of 10kV with a resolving power of max 2.3 nm.

Tensile strength, Percent elongation and Young's modulus

Mechanical properties in term of tensile strength, percent elongation and Young's modulus were inspected by Universal Testing Machine (UTM) (100-500KN, Testometric Inc. UK).[37] Optimized formulation of 30 x 16 mm^2 was placed between two clamps which were situated at the distance of 2 cm and one clamp was immotile while other clamp moved in the opposite direction at the speed of 1.00 mm/min.[27] At the point of rupturing and cracking, force and elongation values were noted. Tensile strength, percent elongation and young's modulus were computed from the ensuing equations.[27, 38]

$$Tensile\ Strength\ (N/mm^2) = \frac{Force\ at\ rupture\ (N)}{Thickness\ X\ width\ (mm^2)}\ X\ 100$$

$$\%\ Elongation\ at\ break = \frac{Increase\ in\ length}{Initial\ length}\ X\ 100$$

$$Young's\ modulus\ (N/mm^2) = \frac{Force\ at\ corresponding\ strain\ (N)}{Cross\ sectional\ area\ (mm^2)}\ X\ \frac{1}{Corresponding\ strain}$$

X-ray diffractometry

Crystallinity of fluoxetine was studied by X-ray diffractometry in samples. X-ray diffraction of optimized formulation, placebo formulation and pure drug (fluoxetine) was performed. Drug powder and formulations were scanned in 2 theta (Θ) range from 19º to 70º with tube voltage 30 kV and current of 10 mA along with using monochromatic copper radiation Cu Ka (k = 2 Å) with a nickel filter.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) analysis helps the researcher to construe the effect of temperature rise on the mass of sample tested. Sample is subjected to heating and consequent mass variation detection by sensitive balance in controlled environment. Mass variation occurs due to multiple factors like sample chemical atrophy and physical process like drying, vaporization and sublimation. TG analysis was performed for the thermal analysis of optimized ODF and pure drug (fluoxetine) by gradual increase of temperature from 25 up to 300 °C at the rate of 10 °C per minute while continuous exposure to heating by constant nitrogen flow (20 mL/min).

Results and Discussion

The FTIR-spectrums of fluoxetine and blend of fluoxetine with polymers and other excipients were observed and no interaction was detected (not shown).

Physical appearance

Visual inspection revealed that trial formulations with polymer concentration cumulatively up to 40 % were considered as failed batches as trial number TF1, TF2 and TF3 were unable to be detached from petri dish. Because these trial formulations displayed significant adhesiveness presumably because of low percentage of polymer and also higher concentration of PVP (Table 2). This pronounced adhesiveness can be attributed to hydrophilic and hygroscopic nature of PVP which ultimately imparts tackiness that could also be seen in TF5 and TF13 as well. [39] ODF batches with relatively higher pullulan content than that of HPMC, rendered stickiness/tackiness and translucency. ODF batches with low pullulan and HPMC content were semi-transparent as the polymer content mounted up, it imparted the translucency to the formulation. ODF batches with lower content of polymer exhibited wrinkles and curves in ODF batches. Formulation trials TF5, TF7, TF11, TF12 and TF14 exhibited the exceptional characteristics of having the smooth and intact surface with minimum or no wrinkled edges and phenomenal detachability from petri dish mould. Almost similar physical appearance parameter outcomes were observed in the films of levocitrizine, in which ODF formed with low viscous polymer grades and ODF with low polymer percentage content were difficult to be peeled from mould, hence it can be established that ODFs with low polymer content lacks in detachability. Moreover, in levocitrizine ODFs, films with higher pullulan content were translucent in appearance.[40]

Weight variation and thickness

Weight variation and thickness test were performed on five ODFs of all retrieved batches. TF1, TF2, TF3 and TF9 batches were unable to be detached and retrieved from mould. Hence, these batches were not included in both tests. All ODF batches qualified the % weight variation according to USP pharmacopeial limit of ± 10 % for dosage form with weight of 130 mg or less. Weight variation was determined to be within the range of 72.67mg ± 0.12 to 102.42mg ± 1.41 (Table 3). Thickness of ODFs was recorded to be within the range of 0.11 mm ± 0.0089 to 0.63 mm ± 0.0549. These findings were in accordance with the findings of Nair et al. (2013),[28] where it was suggested that thickness range of the typical film must be within the range of 50µm-1000µm. Optimum and homogenous thickness of film is requisite for its uniform drug distribution which will ultimately have profound effect on its content uniformity.[41, 42] Uniform drying of ODF is very crucial stage in providing the uniform thickness of ODF batch. The recorded thickness values were almost uniform in all trials suggesting the homogenous distribution of all ingredients in the ODF. In addition to this, findings also highlight the validity of uniform drying in hot air oven at 45 °C. It cannot be ignored that ODF with higher thickness values contribute towards diminished pliability and consequently low values in folding fortitude evaluation.[43]

Folding Fortitude

Folding fortitude was observed by rotating the ODF at single plane of 180º until it broke. Plasticizer is supposed to impart major pliability property along with main polymers. In this context, plasticizer plays its role by entrapping itself into the polymer matrix and consequently rupturing and weakening the polymer-polymer linkages and augmenting the motility of polymer strands.[44] Folding fortitude of all retrieved ODF trial formulations of value remained within the scale of 81.66 ± 7.63 to 372.33 ± 1.57 (Table 3). It was deduced that ODF with relatively high content of pullulan tend to be more pliable and record higher folding fortitude value. Whereas ODF with relatively higher HPMC E15 had the tendency to show diminished flexibility and ultimately exhibited lowered folding endurance. This deduction was supported by analysing the recorded folding endurance values of TF5, TF13, TF14

and TF15. All mentioned trial formulations were formulated with relatively higher content of HPMC E15 than that of pullulan, which imparted the diminished pliability to ODFs and consequently poor folding endurance. This conclusion is also corroborated El Meshad and El Hagrasy (2011), who inscribed in their findings that mosapride ODFs formed with HPMC are stiff and lack pliability.[45]

Influence of plasticizer concentration can also be observed in research project of clobazam ODFs formation, where increase in plasticizer concentration imparts enhanced pliability to ODF.[46] These findings give credence to our results. There is no authentic official pharmacopeial value range for folding endurance, hence ODF with more than 250 folding fortitude value were regarded ODF with good folding fortitude attribute.[31]

Content Uniformity

Drug content homogeneity was examined to ascertain the homogenous and precise distribution of fluoxetine in all successfully retrieved ODF trial batches. Three ODFs out of each trial formulation batch were inspected on UV spectrophotometer. Drug content must be within the range of 85 % to 115% to be regarded as successful batch.[20] Drug load of 10 mg per ODF of 4 cm^2, which corresponds to 2.5 mg /cm^2 was targeted to be achieved in all ODF trial batches, whereas the ranges of drug content in fluoxetine ODFs were found out to be from 73.28 % ± 0.15 to 118.82 % ± 0.57 (Table 3).

Disintegration time

As European pharmacopoeia publishes that ODF must disintegrate as placed in buccal cavity; however, it does not declare any authentic method and maximal acceptable time for disintegration. Centre of drug evaluation and research (CDER) states that disintegration time range ought to be within the limits of 0-30 sec so same criterion was opted for ODF.[47, 48]

PVP was employed as the super-disintegrant in concentration of 160 mg per batch of the ODF. PVP performs rapid disintegration by absorbing water by capillary action and expands, ultimately increasing hydrostatic pressure which is required to disintegrate ODF readily.[43] It was notable that disintegration time ascended with the aggravation of polymer content in the ODF trials. Moreover, constant concentration of super- disintegrant in all ODFs was sparse to induce the disintegration in ODF of such high polymer content. Hence, it can be assumed that concentration of super-disintegrant must be commensurate with polymer content in ODF and its higher concentration will lead to faster disintegration. Moreover, high polymer content could also be the cause to seal the capillary pores and ultimately blocking the influx of liquid into ODF which eventuate in delayed disintegration time.[49]

ODF trial batches, which recorded the disintegration time equal to or less than 30 seconds, were regarded as the successful ODF in terms of disintegration time characterization (Table 3). TF7 manifested itself with exceptional and phenomenal disintegration time of just 10.66 seconds. It was inferred after keen analysis of disintegration time with correlation to polymer percentage that ODFs formulated with 45 % of polymer content revealed themselves with exceptionally short disintegration time up to 19 seconds. It was deduced from the recorded data that PVP proved itself as competent super-disintegrant for the fluoxetine ODF formulation, although its efficacy is contingent on polymer concentration being incorporated.

***In-vitro* dissolution studies**

No official method of drug release of ODF is prescribed in pharmacopoeias to be followed for *in-vitro* drug release characterization. For drug release, large volumes of

media are used whereas it does not conform to limited saliva volume capacity of buccal cavity.[23]

Moreover, one major predicament arose whilst research project which was inappropriateness of dissolution media. Because media used is not bio-relevant medium and do not conform to physiological conditions of buccal cavity. Due to unavailability of artificial saliva in research lab, phosphate buffer of pH 6.8 was used in dissolution apparatus type II and absorbance recorded at 263 nm. Dissolution apparatus used only permits the sampling to be taken at the minimum intervals of 30 seconds and it is not possible to withdraw the samples less than brief interval of 30 seconds. All the ODF batches exhibited the gradual increase in percentage drug release over the 11-minute assay runtime. Percentage drug release of ODF also varied along the consecutive 11 minutes of assay runtime. It was due to various concentration combinations of polymers pullulan and HPMC. Fastest drug dissolution was observed in TF7 which almost completely released 99.37 % of fluoxetine within 3 minutes (detailed results shown in Figure 1). It was deduced from the recorded data that ODF with lower polymer content tended to exhibit the faster drug release. ODF formulated with total polymer content between 35 and 45 % were faster in releasing the fluoxetine than other ODF batches, reaching their maximum drug release in 5 minutes (Figure 1a).

ODFs formulated with higher polymer concentration (50-60%) combination of pullulan and HPMC E15 showed the slow drug release pattern (Figure 1b). Similar outcomes were observed in the levothyroxine ODF formulation project, where films formed with higher percentage of polymer content tended to slow down the levothyroxine release.[26] It was concluded that CPDR slowed down in ODFs with higher polymer content. This was presumably owing to higher polymer quantity which could cause the generation of robust matrix layer by close and in-depth contact among the molecular structures of swollen matrix which possibly participated in slow drug release phenomenon.[42]

Analysis and selection of optimized formulation

The most optimized formulation was selected by scrutinizing the characterization data of all ODF batches and opted on the criteria of ODF with instant detachability/peel ability from petri dish mould, rapid maximum drug release in minimum period, the briefest disintegration time, acceptable folding endurance, and content uniformity. After meticulous scrutiny of data, TF7 emanated as the ODF with phenomenal traits. TF7 was formulated with same concentration and procedure and subjected to further evaluation techniques of UTM for mechanical properties evaluation, SEM, XRD and TGA.

Tensile strength, percent elongation and Young's modulus

The main objective of tensile test was to evaluate the fortitude and plasticity of TF7. TF7 of 30 x 16 mm^2 area was tested in UTM by mounting it between two tensioning clamps and motile clamp was set at the speed of 1.0 mm/min. Then load at break was observed, which ruptured the ODF at 0.1200 N. It was noted that sample was ruptured at the middle of ODF in lieu of ODF at clamps.

It is essential for the finished product to meet the requisite parameter criteria for its required competent functioning. Hence, to achieve this aspect, critical quality attributes (CQA) are supposed to be specified.[50] Classical ODF must be physically robust and pliable. These traits can be interpreted as classical ODF must possess high tensile strength and high percent elongation at rupture and lowered value of Young's modulus. According to Critical quality attributes of mechanical properties of ODF, corresponding values should be as Tensile strength >2 N/mm^2, % Elongation >10 %,

Young's modulus <550 N/mm^2.[51] Tensile strength was found to be 5.76 N/mm^2. Percentage elongation of TF7 was determined to be 38.85%. And resultant value of Young's modulus was 280.37 N/mm^2. Our results indicate the robustness of TF7 structure (see detailed results in Table 5).

Ultimately, it was concluded from resultant figures that TF7 is robust, flexible, and tough. Concentration of incorporated plasticizer (PG) has positive effects on tensile strength and % elongation, which presumably could be due to bonds formation between PG (plasticizer), and polymer (pullulan & HPMC E15), thereby imparting adequate flexibility and fortitude to ODF to endure and resist the rupture. However, it was also found that plasticizer concentration has negative effect on disintegration time.[26] It is also to be considered that much higher elongation is also not desirable because it could generate the problem of elongation at edges while cutting the ODF batches which could yield inhomogeneous ODFs and diversified drug load. Therefore, optimal incorporation of appropriate plasticizer concentration holds key importance in the formation of classical ODF with adequate physical attributes.[52]

X-ray diffractometry

The XRD patterns investigation of pure fluoxetine powder manifested the clear and sharp peaks which implied that it is pure and crystalline in nature. Peak signals were distinctively manifested at the 2 theta (Θ) = 20.30º, 21.94º, 23.79º, 27.94º, which substantiate the high crystallinity of fluoxetine. Findings of Childs et al. (2004)[53] also corroborate the XRD pattern of current investigation. XRD patterns of placebo formulation TF0 manifest no signal of fluoxetine peak as it was devoid of fluoxetine. Placebo formulation TF0 gave no distinct peak in its XRD analysis pattern which attested to its incorporated excipients' amorphous nature and lack of crystallinity. XRD investigation of optimized formulation TF7 manifested the peak signals of fluoxetine in it which substantiated the efficient loading of fluoxetine into the TF7 and indicated the fluoxetine recrystallization phenomena (Figure 2). However, peak signal intensities of TF7 were less pronounced and showed minor aberration when they were compared to peak intensities of pure fluoxetine. Due to already detected 98.23 % content uniformity of TF7, it can be conclusively affirmed that fluoxetine did not decompose, but rather fluoxetine presumably recrystallized in another refitting. ODF technology is typically focused on water soluble drugs and the ideal case dictates that after solvent evaporation, drug retain its dissolved form in ODF matrix and does not crystallize. Whereas, during experimentation and it usually differs from ideal situation.[54] As fluoxetine is white powder drug with crystalline form, which exists in multiple polymorph crystalline form. As our results indicate that fluoxetine stays in crystalline form in ODFs which could exert its multi-faceted effects. On one hand, this crystallinity refers to the enhanced inherent stability of drug in dosage form. On the other hand, stable crystal form of drug may display inadequate solubility, dissolution rate and effects on pharmacokinetics.[55] Here it is noteworthy that recrystallization of fluoxetine in TF7 can exert its excessive influence on the disintegration properties, and dissolution which may lead to problematic bioavailability.[23] Though these influences need to be explored further in future studies, especially in relation to its *in-vivo* effects.

Scanning electron microscopy

Scanning electron microscopy was performed for the morphological inspection comparison of ODF TF7 formulated with drug and placebo ODF formulation TF0. Naked eye visual inspection of TF7 and TF0 ostensibly reveal not much difference in their surface morphology, both ODFs exhibit relatively smooth surface. However, it can be observed that surface structure of TF7 and TF0 varied from each other. Both

samples showed coarse surface on higher resolution images of SEM. TF7 showed drug particles on its surface where as TF0 had no crystal-like drug particles presented on it (Figure 3).

It was observed in SEM images that fluoxetine recrystallized and formed needle like structure in TF7 whereas, placebo formulation TF0 was devoid of such needle like crystal structures. Recrystallization phenomena of fluoxetine in SEM of TF7 can also be validated by the XRD pattern of TF7. Fluoxetine recrystallization phenomenon could be the contributing factor towards the coarseness or roughness of TF7 surface observed under high resolution. Previous studies suggest that crystalline nature of drugs may severely influence the mechanical characteristics of ODF by imparting more brittleness and less transparency.[56] However, as per our data, recrystallization of fluoxetine in TF7 could not negatively display its impact on final dosage from, presumably owing to excellent polymer selection and plasticizer role.

Thermogravimetric analysis

Optimized formulation TF7 and pure drug fluoxetine were subjected to TGA. It was spotted that fluoxetine showed initial weight loss at 165 °C and ensued by frequent weight loss around 208°C which elucidated the fact of initiation of fluoxetine decomposition. As temperature reached 228 °C, abrupt and massive plummet in the mass of fluoxetine was spotted which conspicuously correspond to the decomposition of fluoxetine.

Commencement of decline in the mass of TF7 can be observed in the initial stage of heating exposure. This mass decline can be presumably attributed to evaporation of its entrapped water molecules and not the degradation of polymers in ODF. Degradation profile of TF7 is also attributed to the incorporated excipients. As ODF are highly susceptible to moisture uptake and regarded hygroscopic in nature, it is crucial to attribute the initial weight loss up to 100 °C due to evaporation of water molecules. According to previously reported data, TGA profile of propylene glycol suggested that PG degradation initiated at low temperature.[57]

It can be inferred from the data that as optimized formulation TF7 was comprised of higher percentage of polymers and ability of both polymers to retain water molecules in their matrices cannot be ignored while inspecting the TGA profile of formulation. Initial weight loss can be attributed to drying and water evaporation which is followed by the early degradation tendency of propylene glycol. In addition, considerable mass decomposition spotted after 220 °C can be certainly ascribed to fluoxetine decomposition as elucidated in TGA of fluoxetine (Figure 4).

Conclusion and future prospect

ODFs fabricated with cumulative percentage content of hydrophilic film forming polymers (pullulan and HPMC E15) within the range of 35 to 45 %, generated the results of shorter disintegration time and faster percentage drug release. Propylene glycol exert excellent as plasticizing characteristics in formulating ODFs and it imparted satisfactory tenacity and flexibility to ODFs. Conclusively, as the formulation of fluoxetine ODF was successful and has been thoroughly characterized with unobjectionable results, this dosage form sets the precedent and future prospect for further uptake of its *in-vivo* evaluation by scientific community and ensuing compliance studies in paediatrics patients of selective mutism and OCD. Because it is hypothesized that paediatric psychiatric patients in the need of fluoxetine will be persuaded by the convenience of ODF. There is also imperative necessity of standardized methods and official guidelines for the evaluation techniques of ODF for efficient quality analysis.

Conflict of interest
The authors declare no conflict of interest.

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Tables

Table 1 Experimental trials design and composition

Trials	Pullulan	HPMC E15	Fluoxetine	PG	PVP	Citric acid	Fructose	Water
TF1	15 %	15 %	10 %	10 %	10 %	4 %	4 %	q.s
TF2	20 %	15 %	10 %	10 %	10 %	4 %	4 %	q.s
TF3	25 %	15 %	10 %	10 %	10 %	4 %	4 %	q.s
TF4	30 %	15 %	10 %	10 %	10 %	4 %	4 %	q.s
TF5	15 %	20 %	10 %	10 %	10 %	4 %	4 %	q.s
TF6	20 %	20 %	10 %	10 %	10 %	4 %	4 %	q.s
TF7	25 %	20 %	10 %	10 %	10 %	4 %	4 %	q.s
TF8	30 %	20 %	10 %	10 %	10 %	4 %	4 %	q.s
TF9	15 %	25 %	10 %	10 %	10 %	4 %	4 %	q.s
TF10	20 %	25 %	10 %	10 %	10 %	4 %	4 %	q.s
TF11	25 %	25 %	10 %	10 %	10 %	4 %	4 %	q.s
TF12	30 %	25 %	10 %	10 %	10 %	4 %	4 %	q.s

TF13	15 %	30 %	10 %	10 %	10 %	4 %	4 %	q.s
TF14	20 %	30 %	10 %	10 %	10 %	4 %	4 %	q.s
TF15	25 %	30 %	10 %	10 %	10 %	4 %	4 %	q.s
TF16	30 %	30 %	10 %	10 %	10 %	4 %	4 %	q.s

*All quantities are expressed in % w/v

Table 2 Physical appearance of trial formulations

Trial No.	**Visibility**	**Surface Texture**	**Wrinkles around edges**	**Flexibility & Brittleness**	**Tackiness**	**Peelab-ility**
TF1	Semi-transparent	Coarse & punctured	---	---	Extremely tacky	0 + +
TF2	Semi-transparent	Bubbly, smooth, fragile, punctured	Wrinkled and bent edges	brittle	Extremely tacky	0 + +
TF3	Translucent	smooth, bubbly, thin fragile,punctured	Slightly wrinkled edges	brittle	Extremely tacky	0 +
TF4	Translucent	Smooth, intact surface	Wrinkleless straightened edges	flexible	Non tacky	1 +
TF5	Translucent	Smooth, bubbly and intact surface	inconspicuous wrinkles around edge	flexible	Tacky	1 +
TF6	Translucent	Coarse and intact surface	Wrinkleless straightened edges	flexible	Non tacky	1 +
TF7	Translucent	Extremely smooth and intact	Wrinkleless straightened edges	Flexible	Non tacky	1 + +
TF8	Translucent	Smooth and intact	Wrinkleless straightened edges	flexible	Slightly tacky	1 +
TF9	Translucent	Punctured surface	Wrinkleless straightened edges	flexible	Slightly tacky	0 +
TF10	Translucent	Smooth bubbly and intact	Wrinkleless straightened edges	flexible	Non tacky	1 +
TF11	Translucent	Very Smooth and intact	Wrinkleless straightened edges	flexible	Non tacky	1 + +

TF12	Translucent	Very smooth and intact	Wrinkleless straightened edges	flexible	Non tacky	1 + +
TF13	Translucent	Extremely bubby, coarse and intact	Wrinkleless straightened edges	flexible	tacky	0 +
TF14	Translucent	Smooth and intact	Wrinkleless straightened edges	flexible	Non tacky	1 + +
TF15	Translucent	Slightly coarse thick and intact	Wrinkleless straightened edges	partial brittleness	Slightly Tacky	0 +
TF16	Translucent	Coarse, thick and intact	Wrinkleless straightened edges	brittle	Slightly tacky	0 +

*Good = 1 +, Very good = 1 + +, Poor = 0 +, very poor = 0 + +

Table 3 Weight variation, thickness folding fortitude, content uniformity and disintegration time of trial formulations.

Sr. No.	**Trial No.**	**Weight Variation (mg) ± Standard Deviation (n=5)**	**Thickness mean (mm) ± Standard deviation (n=5)**	**Folding Fortitude mean ± Standard Deviation (n=3)**	**Drug Content uniformity (%) mean ± Standard deviation (n=3)**	**Mean Disintegration time (sec) ± standard deviation (n=3)**
1	TF4	82.55 ± 0.17	0.16 ± 0.0070	276.33 ± 1.52	80.09 ± 0.07	20.33 ± 0.57
2	TF5	72.67 ± 0.12	0.11 ± 0.0089	140.33 ± 4.16	81.33 ± 5.04	19.66 ± 0.53
3	TF6	76.68 ± 0.13	0.14 ± 0.0044	232.66 ± 3.05	113.58 ± 0.45	26.66 ± 1.15
4	TF7	83.66 ± 0.51	0.12 ± 0.0054	372.33 ± 1.57	98.23 ± 0.10	10.66 ± 1.15
5	TF8	88.84 ± 0.07	0.21 ± 0.0190	294.66 ± 1.63	73.28 ± 0.15	39 ± 2
6	TF10	83.97 ± 0.05	0.17 ± 0.0131	287.33 ± 2.30	90.73 ± 0.62	20.33 ± 0.57
7	TF11	88.27 ± 0.12	0.13 ± 0.0044	310.33 ± 1.57	96.68 ± 0.43	22 ± 1
8	TF12	92.85 ± 0.13	0.27 ± 0.0683	320.33 ± 0.57	82.47 ± 0.22	41.33 ± 0.57
9	TF13	82.23 ± 0.18	0.20 ± 0.0130	180.33 ± 1.52	106.85 ± 2.28	14 ± 2
10	TF14	88.39 ± 0.85	0.22 ± 0.0054	201.66 ± 2.08	118.82 ± 0.57	30.33 ± 1.52
11	TF15	95.05 ± 1.25	0.52 ± 0.0291	81.66 ± 7.63	89.41 ± 0.25	44.66 ± 2.08

12	TF16	102.42 ± 1.41	0.63 ± 0.0549	161.66 ± 10.40	84.39 ± 0.06	48.33 ± 2.57

Table 4 Cumulative percentage drug release of fluoxetine ODF batches.

Time (min)	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**5**	**7**	**9**	**11**
TF4	0	15.65	26.98	39.31	55.51	66.30	76.01	80.14	80.71		
TF5	0	13.71	30.15	42.15	50.01	59.81	72.15	83.91	84.42		
TF6	0	7.30	18.95	32.33	45.12	56.13	68.31	86.15	103.21		
TF7	**0**	**23.13**	**41.15**	**66.15**	**82.15**	**96.75**	**99.37**				
TF8	0	5.15	12.31	22.15	38.01	57.60	68.91	80.15	81.12	81.16	81.19
TF10	0	16.71	29.15	41.65	59.36	73.12	80.12	98.15			
TF11	0	9.16	18.15	25.79	38.29	52.76	65.90	83.15	97.61		
TF12	0	4.9	9.53	18.15	26.15	39.56	50.25	67.53	85.93	98.47	
TF13	0	19.45	37.26	54.57	71.77	86.89	98.35	102.4			
TF14	0	12.17	20.65	30.45	43.25	57.48	67.38	84.74	98.30	113.15	
TF15	0	7.80	14.16	22.15	33.67	49.56	63.21	75.5	84.56	87.75	87.81
TF16	0	5.90	9.40	12.45	18.45	22.56	32.76	49.65	62.43	78.57	89.35

Table 5 UTM test results of optimized formulation TF7

Area (mm^2)	16.000
Diameter (mm)	16.000
Elongation @ break (mm)	11.657
Elongation @ peak (mm)	0.5470
Elongation @ yield (mm)	0.4910
Energy @ break (N.m)	0.0016
Energy @ peak (N.m)	0.0024
Energy @ yield (N.m)	0.0020

Load @ break (N)	0.1200
Load @ peak (N)	7.1700
Load @ yield (N)	7.0100
Plastic strain @ break (%)	38.877
Strain @ break (%)	38.857
Strain @ peak (%)	1.8233
Strain @ yield (%)	1.6367
Stress @ break (N/mm^2)	0.0577
Stress @ peak (N/mm^2)	3.4471
Stress @ yield (N/mm^2)	3.3702
Young's Modulus (N/mm^2)	280.37

Figures:

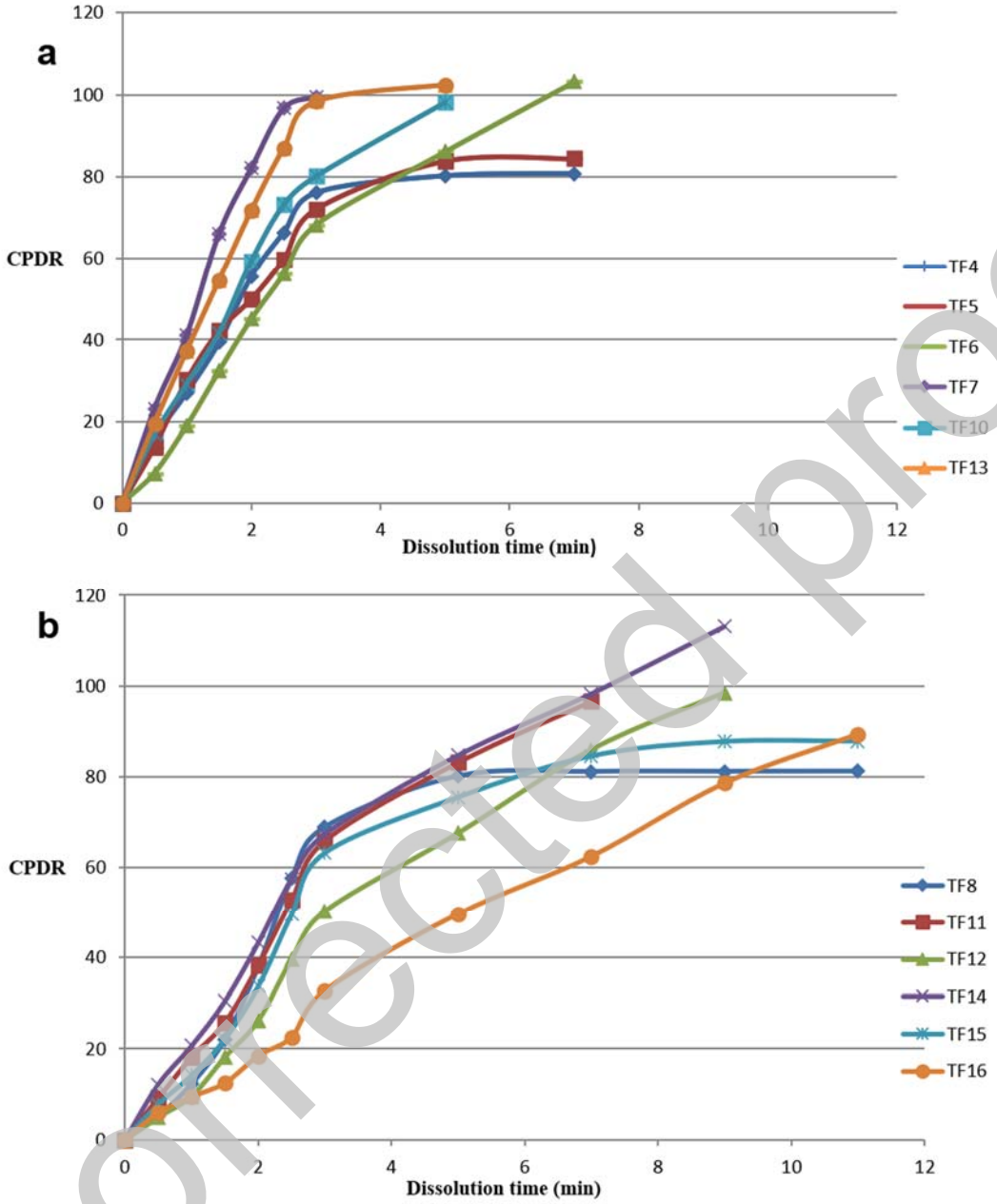

Figure 1 Dissolution profile of all trial ODFs (a) dissolution profile of ODFs with 35-45 % content of polymer (b) dissolution profile of ODFs with 50-60 % content of polymer.

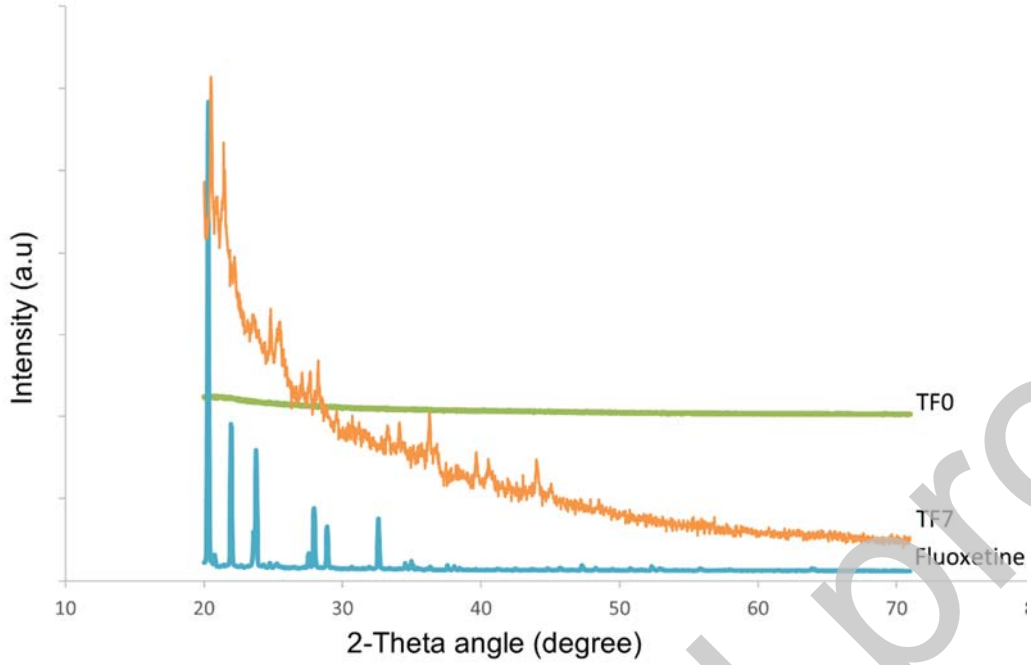

Figure 2 XRD patterns of fluoxetine, TF7 and TF0.

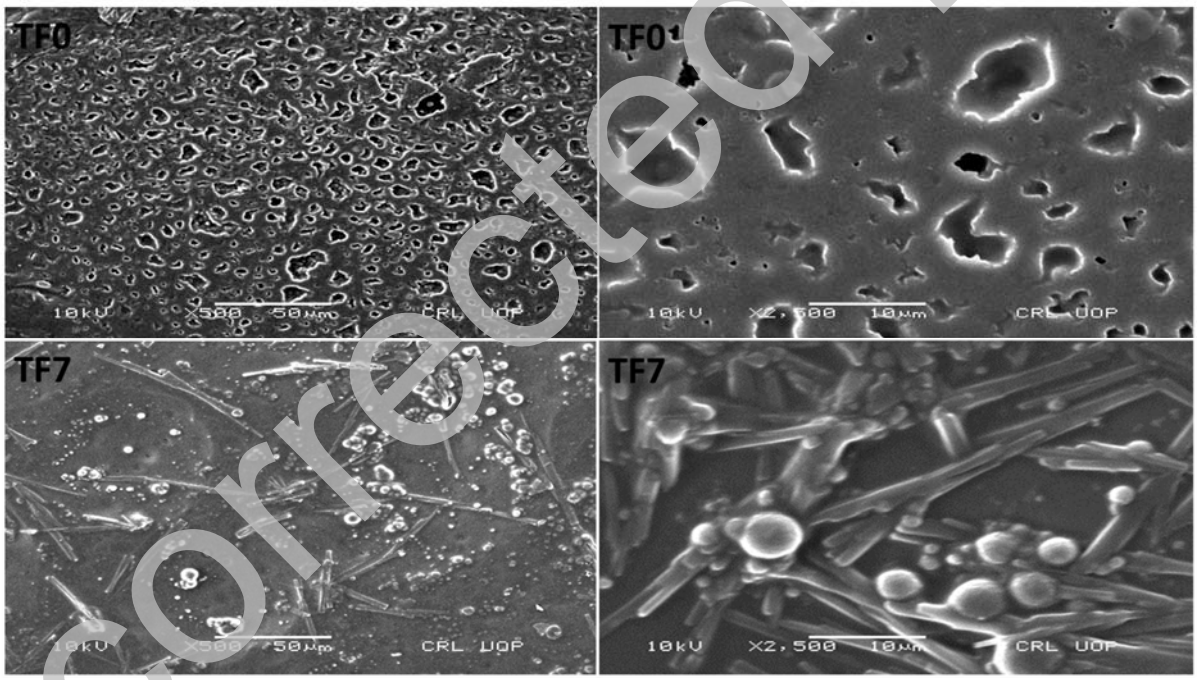

Figure 3 SEM images of TF0 and TF7.

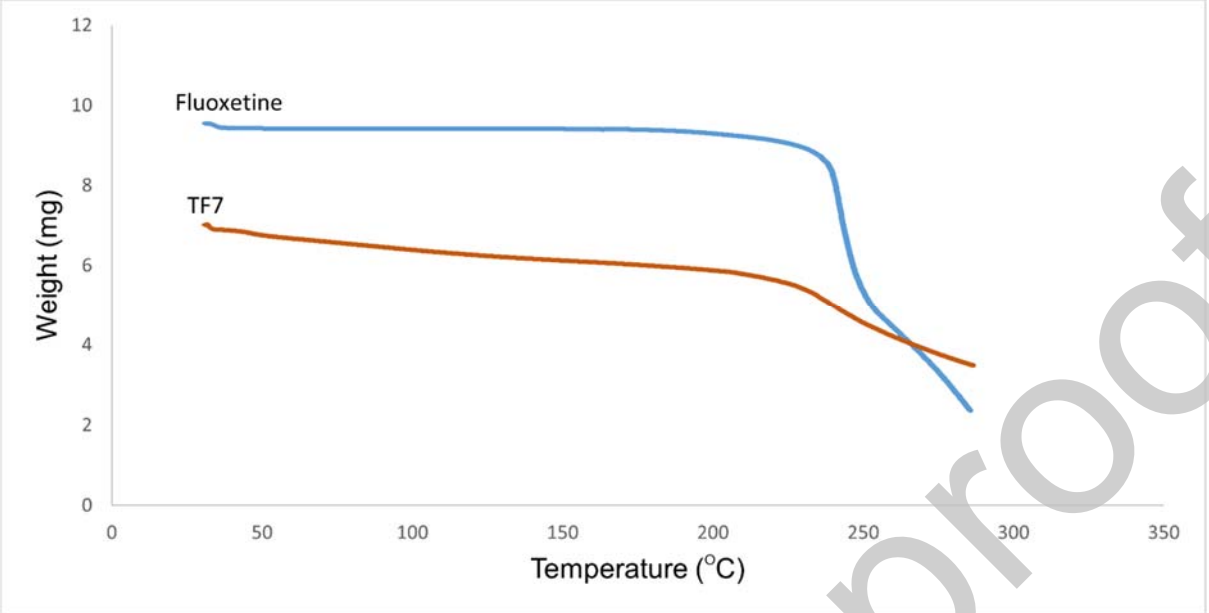

Figure 4 TGA curve of fluoxetine and TF7