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RESEARCH ARTICLE

Design, Optimization and In-vivo Characterization of Oral Fast Dissolving Films of Sertraline for Treatment of Postpartum Depression

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Abstract

Objectives: The main aim of the present study is to enhance solubility, oral bioavailability and minimize dose related side effects of Sertraline (STR) by using a novel approach. **Methods:** Different ratios of STR solid dispersions were prepared using PEG 4000 as a polymer. Evaluation studies were conducted to identify optimized formulation, and the selected optimized formulation was utilised for the preparation of oral fast dissolving films (OFDF). The OFDF formulations were fabricated using pullulan and PVA as a polymer by solvent casting method. **Findings:** Folding endurance, disintegration time, wetting time and in-vitro drug release studies were conducted to identify optimized formulation. It was found that OS_3 showed optimum characteristics with sufficient disintegration time (42.16 sec), wetting time (20 sec) and high drug release of 94.42%. **Novelty:** It is evident that OFDF enhanced the oral bioavailability as well as therapeutic efficacy of an extensive first pass metabolic drug with poor water solubility.

Keywords: Solvent casting method; Oral Bioavailability; Solubility; Folding Endurance; Therapeutic Efficacy

1 Introduction

Sertraline Hydrochloride (STR) is slightly water-soluble drug that belongs to category of selective serotonin reuptake inhibitor (SSRI) of antidepressants[(1)]. The minimum effective oral adult dose of Sertraline is 50mg/day in-case of depression. It has an oral bioavailability of about 45% because of extensive first pass metabolism in liver and gut wall to active metabolite (desmethyl sertraline). The therapeutic activity of desmethyl sertraline is 50 folds weaker than Sertraline due to which the dose is increased gradually to attain a therapeutic response. This enhancement in dose leads to dose related side effects.

To enhance oral bioavailability and to minimise dose related side effects oral fast dissolving system represents a novel approach for the oral release of active pharmaceutical ingredients (APIs). Oral fast dissolving film (OFDF) is a novel approach

to improve patient acceptance by enhancing dissolution. OFDF consists of thin oral strip, which when placed on the patient's tongue or on any mucosal tissue, hydrates and adheres rapidly onto the site of application when wet by the saliva[2,3]. After the oral fast dissolving films are dissolved or dispersed in the saliva, they are absorbed through the sublingual mucosa or they are ingested with the saliva, generating a systemic effect. This makes the film more bioavailable by bypassing the first pass metabolism.

Oral films contain 1-30% w/w of the active ingredient. Low doses of API are always incorporated in oral films. Micronized API can enhance the texture of film as well as the dissolution and uniformity of oral fast dissolving films. Numerous polymers are available for the preparation of oral films which are used in the concentration of about 40-45% w/w of the film content. Polymers are responsible for the film strength which can be obtained by using a single polymer or combination of polymers as per requirement. Different types of polymers are used in the preparation of OFDF[4,5] such as polyvinyl pyrrolidone (PVP), pullulan, hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA), sodium carboxy methyl cellulose, poly ethylene oxide (PEO), hydroxyl propyl cellulose (HPC), hydroxyl ethyl cellulose (HEC), methyl cellulose (MC).

The main objective of the work was to enhance the solubility as well as to bypass first pass metabolism of Sertraline.

2 Methodology

2.1 Materials:

Pure sample of STR was gifted by Aurobindo Pharma, Chittoor. Poly ethylene glycol 4000 was purchased from Yarrow Chem Products, Mumbai. Pullulan polymer was gifted by Kumar organics, Bangalore. Poly ethylene glycol 400, Poly vinyl alcohol was purchased from Yarrow Chem Products, Mumbai. Other chemicals used in the research were of analytical grade.

2.2 Development of oral fast dissolving film formulations

2.2.1 Preparation of Sertraline oral fast dissolving films

The OFDFs were prepared from solid dispersions by solvent casting method. The solubility of Sertraline was enhanced by conversion into solid dispersions using high molecular weight PEG 4000 as a polymer by solvent evaporation method[5,6]. Different formulations were prepared by changing the ratio of polymer (PEG 4000). Evaluation studies were conducted and optimized formulation of solid dispersions were selected for conversion into oral fast dissolving films. The OFDF films were formulated by using different ratios of polymers like pullulan and polyvinyl alcohol (PVA). Different trial formulations were prepared using different compositions of polymers. The trials with which films were not produced were ignored and the composition of 6 formulations (OS_1 to OS_6) producing good films was shown in Table 1. Weighed quantity of polymer was taken and allowed to swell (pullulan) or heat up to 60°C (PVA) in water in one beaker. In another beaker, STR solid dispersions and other ingredients were dissolved in smaller portions of water. Both the solutions were combined by using high shear mixer[7,8]. The solution formed was then casted on petri dish and dried at room temperature for 24hr. The films were wrapped first in butter paper to absorb moisture and then in aluminum foil. The films are stored in desiccator as shown in Figure 1.

Table 1. Formulation code of Sertraline oral films prepared by using pullulan and PVA polymers

Composition	OS_1	OS_2	OS_3	OS_4	OS_5	OS_6
Solid dispersions equivalent to 50 mg of Sertraline	50	50	50	50	50	50
Pullulan (mg)	200	300	400	-	-	-
PVA (mg)	-	-	-	200	300	400
PEG 400 (ml)	0.4	0.4	0.4	0.4	0.4	0.4
Citric acid (mg)	20	20	20	20	20	20
Mannitol (mg)	20	20	20	20	20	20
Water	q. s	q. s	q. s	q. s	q. s	q. s

2.3 Evaluation of Sertraline oral fast dissolving films

2.3.1. Thickness of the film

The thickness of every oral film was determined by using a screw gauge[8] at different places like corners and center of the film. From the average of three values standard deviation was calculated. Thickness of the film is important to determine the uniformity of the dose which is related directly to the dose accuracy.

Fig 1. Fast dissolving oral films of different formulations of Sertraline HCl

2.3.2. Weight uniformity

Three films of 2.5×2.5 cm^2 were taken randomly from each formulation. Films were weighed individually using electronic balance[9]. From the average of three values, mean weight was calculated for every batch.

2.3.3. Folding endurance

Folding endurance can be measured by continuously folding the film until it tears. The number of times the film was folded without breaking is considered as folding endurance value[10].

2.3.4. In-vitro disintegration time

A film of 2.5×2.5 cm^2 was taken and placed in a petri dish containing 2 ml of distilled water. The time within which the film dissolves completely was considered as disintegration time.

2.3.5. Scanning electron microscopy (SEM)

External and surface morphology of optimized Sertraline oral film formulation was evaluated by scanning electron microscopy.

2.3.6. FTIR analysis

Fourier transform infrared spectroscopic studies were used to check the chemical interaction between the drug and other polymers or excipients used in the formulation[11]. Oral films were scanned in 4000-400 cm^{-1} wavelength region using FTIR spectrophotometer.

2.3.7. In-vitro drug release studies

Dissolution studies were carried out in 500ml of 6.8 pH phosphate buffer using USP XXI dissolution apparatus (basket type) maintained at 50rpm[12,13] with a temperature of 37±0.2°C. A film of 2.5×2.5 cm^2 was taken and placed directly in 6.8 pH dissolution medium. At a specified time interval of 5min, samples were withdrawn and a similar amount of buffer was added to the dissolution medium to maintain sink condition. Samples withdrawn at 0, 1, 2, 4, 6, 8, 10, 12 and 14min and were assayed for drug release using UV-visible spectrophotometer by measuring absorbance at wavelength 275 nm.

2.3.8. X-ray diffraction studies

In this study, optimised formulations were analysed at an angle of 2Θ over a range of 5-40^0 at 20kv with a scan rate of 2^0/min to determine the nature of drug[14]. X-ray patterns of optimised formulation (OS_3) were recorded on the X-ray diffractometer and compared with the X-ray pattern of Sertraline pure drug.

2.3.9. % Moisture loss

A film strip of 2.5 × 2.5 cm^2 was taken and placed in a desiccator containing fused anhydrous calcium chloride[15,16]. After 3 days the film strip was weighed immediately after being taken out from desiccator.

$$\%\ Moisture\ loss\ =\ Initial\ weight\ -\frac{Final\ weight}{Initial\ weight}\ \times 100$$

2.3.10. In-vitro wetting time

0.1% amaranth dye solution was prepared and 6ml of the dye solution was placed in a petri plate containing circular tissue paper. A film strip of 2.5 × 2.5 cm^2 was taken and placed in a petri dish containing circular paper. The time within which the dye appears on the surface is considered as wetting time.

2.4 Pharmacokinetic study of Sertraline oral fast dissolving films

2.4.1. Study protocol

New Zealand white rabbits weighing around 2 kg to 2.5 kg were used for pharmacokinetic study of promising formulations[17] like oral fast dissolving films of Sertraline (OS_3) and marketed product of Sertraline tablet. The protocol of animal studies was approved by the institutional animal ethics committee.

Rabbits were divided into 2 groups each containing 3 no.

Group 1: Marketed formulation of Sertraline equivalent to contain 20 mg/kg of rabbit weight given orally.

Group 2: Sertraline oral fast dissolving films prepared with solid dispersions of Sertraline HCl equivalent to contain 20 mg/kg of rabbit weight given orally.

2.4.2. Administration of Sertraline tablet to rabbits

Rabbits fasted overnight were taken and administered with G_1 (Sertraline marketed tablet) by using an oral dosing device. Sertraline tablets were placed into an empty gelatin capsule and then inserted into the dosing tube so that the short end of the capsule protrudes from the tip of the tube.

With one hand grasp the head of the rabbit firmly above the maxilla and then insert the dosing tube containing the tablet in the capsule behind the incisors and then slide slowly straight into the back of the mouth. By using plunger eject the capsule by pushing, remove the dosing tube and then close the rabbit's mouth[18]. To facilitate swallowing, stroke the neck of the rabbit gently. Throughout the experimental period, water was provided ad libitum and feed was provided approximately 3 to 4 h post dosing.

2.4.3. Administration of Sertraline oral films to rabbit

To overnight fastened rabbits G_2 (Sertraline oral film, OS_3) was administered by anesthetizing rabbits using Xylazine hydrochloride (10 mg/kg body weight) and Ketamine (40 mg/kg body weight). The oral film was placed above the tongue[19] of the anesthetized animal by slowly opening the mouth and adding approx. 0.25 ml of stimulated saliva to wet the film. Throughout the experimental period, water was provided ad libitum and feed was provided approximately 3 to 4 h post dosing.

2.4.4. Blood collection

Blood samples for pharmacokinetic analysis were taken at the specified time intervals[20] of (0.08, 0.16, 0.25, 0.50, 1.0, 2.0, 3.0, 6.0, 12.0, and 24.0 hours) from marginal ear vein of rabbit. The plasma samples (0.5ml) were collected in Eppendorf tubes containing K_2EDTA (approx.2 mg/mL) and then placed for centrifugation at 10000 rpm for 15min and then the upper organic layer is filtered through filter paper (0.45 μm Millipore). The filtered supernatant liquid is injected into Waters X bridge C_{18} (4.6 x 250mm, 5μ) column and the flow rate was adjusted to 1ml/min. The plasma concentration of Sertraline was estimated using (45:05:50, v/v/v) of Acetonitrile, methanol and Phosphate buffer(0.05M) was selected as the mobile phase for RP-HPLC method.

3 Results and Discussion

3.1 Optimization of oral fast dissolving films

3.1.1. Thickness of the film

Thickness of the film depends on the concentration of the polymer used in the preparation. Oral film thickness was measured using screw gauge at different places and the thickness varies between 0.322mm to 0.373mm as given in Table 2. The low S.D values indicate uniformity of thickness of prepared films which is directly related to the dose accuracy in the film.

Table 2. Evaluation data of Sertraline oral films

Formulation	Thickness (mm)	Folding endurance	Weight variation (mg)	Disintegration (seconds)
OS_1	0.322 ± 0.001	93 ± 0.81	287.4±0.329	28.02 ± 0.549
OS_2	0.340 ± 0.002	111.33 ± 1.24	312.06±0.169	33.74 ± 0.543
OS_3	0.363 ± 0.001	142.33 ± 2.05	328.05±0.147	42.16 ± 0.337
OS_4	0.335 ± 0.002	241.66 ± 1.24	274.68±4.024	32.07 ± 0.183
OS_5	0.35 ± 0.0016	266 ± 2.94	304.02±0.781	36.46 ± 0.410
OS_6	0.373± 0.002	290.66 ± 2.49	318.28±0.408	50 ± 0.816

*(n=3 ± SD)

3.1.2. Weight uniformity

Weight variation values of the Sertraline oral films as presented in Table 2 range in between 287- 328mg and the low S.D value indicates clearly that each formulation showed uniformity in the trial batches. Polymer plays a crucial role in the weight of the film.

3.1.3. Folding endurance

Film brittleness can be determined by continuously folding the film until it tears. All the formulations showed folding endurance in the range of 93-290 as shown in Table 2. The oral films formulated with PVA as polymer showed high folding endurance than the films formulated with pullulan. High folding endurance indicates high elasticity of the film during storage and handling.

3.1.4. In-vitro disintegration time

Oral films showed in-vitro disintegration time in the range of 28-50sec as indicated in Table 2. It was clear that disintegration time of the films increased with the increase in the polymer concentration. As the concentration of polymer increases thicker gel was formed upon contact with the dissolution medium prolonging the time for disintegration. Films formulated with pullulan showed less disintegration compared to PVA films.

3.1.5. Scanning electron microscopy (SEM)

Microphotographs of plain STR and OS_3 obtained by SEM analysis were shown in Figures 2 and 3. It was observed that the formulation is having smooth and even surface compared to the rough and irregular texture of plain drug.

3.1.6. FTIR analysis

FTIR spectrum of plain STR and Sertraline oral film formulation showed peak points of pure Sertraline HCl such as 3421 cm^{-1}, 1354 cm^{-1}, 1028 cm^{-1} were observed in the formulation (OS_3) clearly indicating that there is no incompatibility between drug and polymer.

3.1.7. In-vitro drug release studies

The in-vitro release data of oral films are shown in Figure 4. Dissolution was promoted by creating pores in the films for the diffusion of the drug thereby increasing the rate of drug release by hydrophilic polymers. From the in- vitro drug release data, it was observed that formulation OS_1 to OS_3 showed drug release from 89.9 to 94.42 in 12 min whereas OS_4 to OS_6 showed drug release from 89.2 to 94.86 in 14 min. The results revealed that the release of the drug was dependent on the amount of polymer. The drug release indicated that the films dissolved within minutes and the excipients didn't retain any drug.

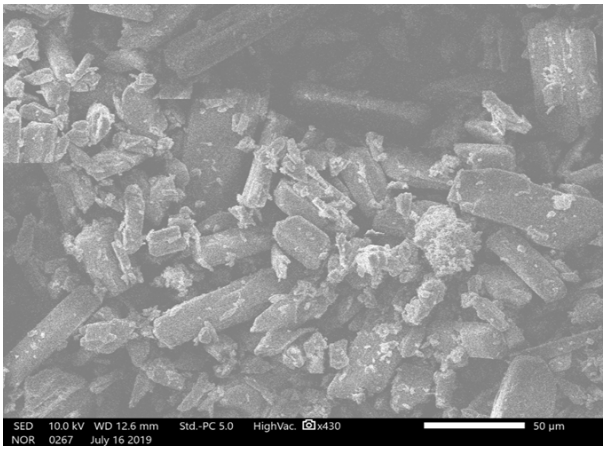

Fig 2. SEM image of Sertraline Plain drug

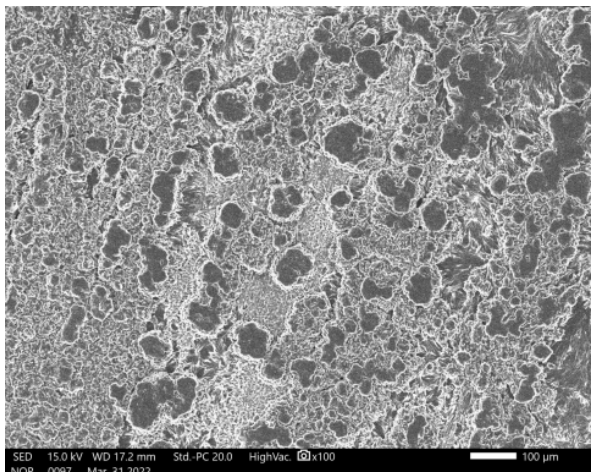

Fig 3. SEM image of OS_3 (Sertraline + Pullulan) oral film

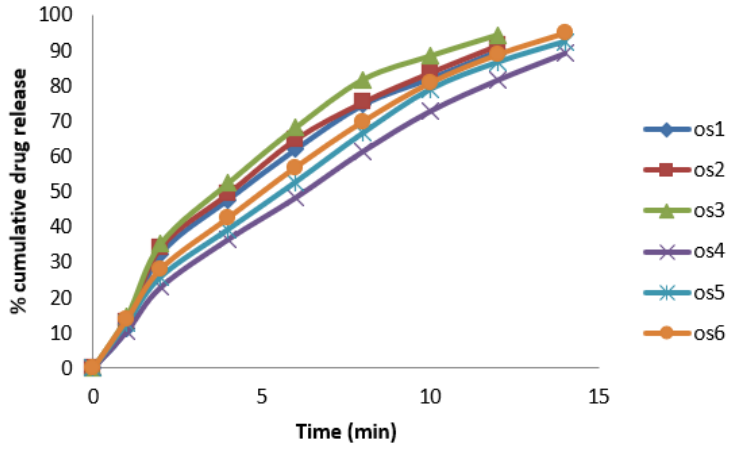

Fig 4. In-vitro drug release of different formulations of Sertraline oral films

3.1.8. X-ray diffraction studies

Reduction in the intensity of peaks and peak heights were observed at 13.0026, 17.663, 18.692, 21.1602, 22.4726, 23.39, 26.26 and 31.0754 indicating a decrease in crystallinity of drug. The absence of peaks of Sertraline pure drug in oral films, the presence of new diffraction peaks in oral films may be related to the change of crystallinity of the drug to amorphous nature as shown in Figures 5 and 6.

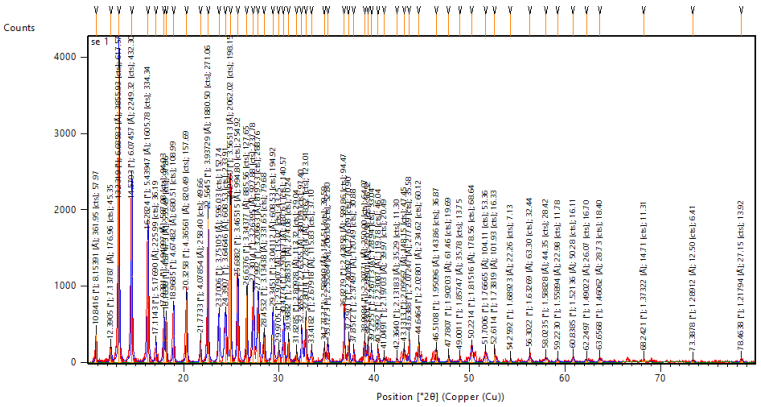

Fig 5. X-ray diffraction pattern of Sertraline HCl plain drug

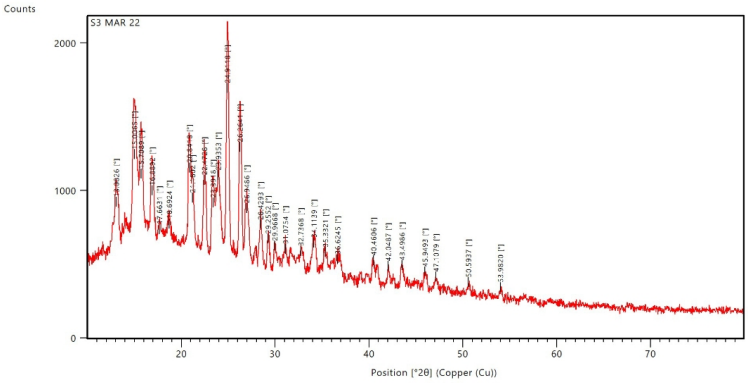

Fig 6. X-ray diffraction pattern of OS_3 oral film of Sertraline

3.1.9. % Moisture loss

The results of % moisture loss of prepared Sertraline oral films OS_1 to OS_6 are shown in Table 3. From the results obtained, it was clear that the percent moisture loss of all the formulations ranges between 0.38±0.05 to 1.8 ±0.03 clearly indicating an increase in moisture loss with increase in polymer.

Table 3. % Moisture loss of different formulations of Sertraline oral films

Formulation code	% Moisture loss
OS_1	0.38 ± 0.05
OS_2	0.66 ± 0.01
OS_3	1.8 ± 0.03
OS_4	0.43 ± 0.01
OS_5	0.79 ± 0.05
OS_6	1.03 ± 0.03

*(n=3 ± SD)

3.1.10. In-vitro wetting time

The wetting time of all formulations OS_1 to OS_6 were shown in Table 4. From the results wetting time of all the films was in the range of 20 to 42 sec clearly indicating with the increase in the concentration of polymer there was a decrease in wetting time. Disintegration behaviour of films was evaluated by wetting time.

Table 4. In-vitro wetting time data of Sertraline oral films

Formulation code	Wetting time (seconds)
OS_1	29 ± 0.1
OS_2	23 ± 0.57
OS_3	20 ± 1.15
OS_4	42 ± 1.00
OS_5	39 ± 0.1
OS_6	34 ± 0.57

*(n=3 $\pm$ SD)

3.2 Pharmacokinetic evaluation

3.2.1. Pharmacokinetic analysis of oral films

The mean Sertraline plasma concentration Vs time profile for the prepared oral fast dissolving films and the marketed tablets are shown in Table 5 and Figure 7. Pharmacokinetic parameters like elimination rate constant (K_e), elimination $t_{1/2}$, C_{max}, t_{max}, $t_{1/2}$, AUC $_{(0\rightarrow 24h)}$, AUC $_{(0\rightarrow\infty)}$, AUC $_{extra}$ was estimated using mean plasma concentration and time by non-compartmental analysis using **Phoenix 64 WinNonlin software (PHOENIX Version 8.1.0353, USA)**.

Table 5. Comparison of In-vivo pharmacokinetic parameters between marketed Sertraline tablet Vs Oral fast dissolving film of Sertraline (OS_3)

Pharmacokinetic parameters	Sertraline oral Commercial tablet	Sertraline oral film
Elimination rate constant (Ke) h^{-1}	0.052	0.081
$t_{1/2}$ (h)	15.150	9.934
C_{max} (μg/ml)	1.781	2.128
T_{max} (h)	2.67	1.33
$AUC_{(0-24h)}$ (μg/ml/h)	13.556	22.937
$AUC_{(0-\infty)}$ (μg/ml/h)	14.785	35.400

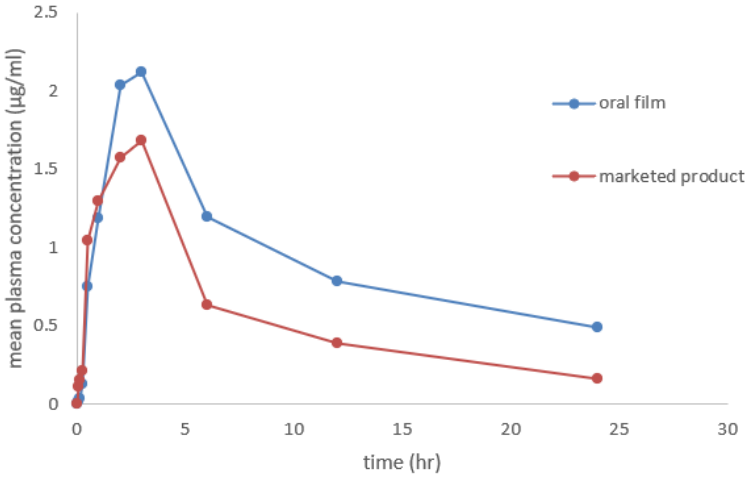

Fig 7. In-vivo bioavailability study between plasma concentration and time of marketed product of Sertraline HCl and oral fast dissolving film (OS_3)

3.2.2. In-vivo pharmacokinetic parameters

C_{max}, $t_{1/2}$ and AUC $_{(0-24)}$ of Sertraline oral tablet were found to be 1.781μg/ml, 15.150 hr,13.556 μg/ml/h respectively whereas C_{max}, $t_{1/2}$ and AUC $_{(0-24)}$ of oral fast dissolving film of Sertraline was 2.128 μg/ml, 9.934 h and 22.937 μg/ml/h respectively. T_{max} of Sertraline oral tablet was 2.67hrs whereas for the oral fast dissolving film of Sertraline was 1.33h. From the data, it is proved that the t_{max} of oral film decreased and C_{max} was increased compared to the marketed formulation as shown in the Table 5, Figure 7 which indicates fast dissolution of drug, maximum amount of drug is permeated through oral mucosa which directly enters into systemic circulation bypassing hepatic metabolism and thereby increasing the bioavailability of the drug.

4 Conclusion

Sertraline hydrochloride oral fast dissolving films prepared with pullulan (OS_3) by solvent casting method showed optimum characteristics with sufficient in-vitro disintegration (42.16 sec), wetting time (20 sec) and high drug release of 94.42% in 12 minutes indicating enhanced solubility and drug release of oral film compared to plain Sertraline. No physical and chemical interaction was observed between the drug and polymers used for the formulation of oral film and from XRD studies reduction in the intensity of peaks and peak heights was observed indicating the change in crystallinity of drug. Among the marketed tablet and optimized Sertraline oral film (OS_3), which were estimated for in-vivo pharmacokinetic study, oral film of Sertraline showed the highest C_{max} of 2.128 μg/ml compared to marketed tablet and decrease in t_{max} value indicating maximum drug is permeated into oral mucosa with fast onset of action respectively. Thus, the optimized formulation OS_3 showed a faster onset of action with improved drug permeability compared to the marketed product enhancing the bioavailability of the drug. Hence, the OFDF formulation of Sertraline can be considered as an effective, economical, and convenient way to enhance the bioavailability of Sertraline.

References

1) Dimcea DAM, Petca RC, Dumitrascu MC, Sandru F, Mehedintu C, Petca A. Postpartum depression: etiology, treatment, and consequences for maternal care. *Diagnostics*. 2024;14(9). Available from: https://doi.org/10.3390/diagnostics14090865.
2) Saxena A, Singh T. Oral Dissolving Films: A comprehensive review on recent perspectives and current approach to effective drug delivery. *J Drug Delivery Ther*. 2022;12(2):139–147. Available from: https://jddtonline.info/index.php/jddt/article/view/5244.
3) S KN, S WP, S IP, N DS. A Systemic review on oral drug delivery as a fast dissolving film to improve therapeutic effectiveness. *Research journal of pharmacy and technology*. 2021;14(3):1771–1778. Available from: https://doi.org/10.5958/0974-360X.2021.00315.2.
4) Qin ZY, Jia XW, Liu Q, Kong BH, Wang H. Fast dissolving oral films for drug delivery prepared from chitosan/pullulan electrospinning nanofibers. *International journal of biological macromolecules*. 2019;137:224–231. Available from: https://doi.org/10.1016/j.ijbiomac.2019.06.224.
5) Kumar RS, Yagnesh TNS. Oral dissolving films: an effective tool for fast therapeutic action. *Journal of drug delivery and therapeutics*. 2019;9(1):492–500. Available from: https://jddtonline.info/index.php/jddt/article/view/2395.
6) Dhande LB, Deshmukh MT, Khopade AN, Shete RV, Kunjir VV. A review on solubility enhancement by solid dispersion method. *Journal of drug delivery and therapeutics*. 2021;11(1):182–187. Available from: https://jddtonline.info/index.php/jddt/article/view/4489.
7) R KD, Keerthy HS, Yadav RP. A review on fast dissolving oral films. *Asian journal of pharmaceutical research and development*. 2021;9(3):122–128. Available from: http://dx.doi.org/10.22270/ajprd.v9i3.969.
8) TSB NB, T BS, K M, M SH, M LRP. Formulation and evaluation of fast dissolving films of repaglinide solid dispersion. *World journal of advanced research and reviews*. 2020;6(3):262–274. Available from: https://doi.org/10.30574/wjarr.2020.6.3.0214.
9) Priyanshi J, Ashish G, Gajanan D. A detailed overview on mouth dissolving film. *Journal of drug delivery and therapeutics*. 2023;13(7):172–176. Available from: https://jddtonline.info/index.php/jddt/article/view/6121.
10) A B, Murali S, Thomas TS, Vasanthkumar S, V PV. Formulation and evaluation of fast dissolving film of Losartan potassium. *International journal of pharmaceutical sciences review and research*. 2021;68(1):237–241. Available from: https://globalresearchonline.net/journalcontents/v68-1/36.pdf.
11) Raza SN, Kar AH, Wanii TU, Khan NA. Formulation and evaluation of mouth dissolving films of Loasrtan potassium using 32 factorial design. *International Journal of Pharmaceutical Sciences and Research*. 2019;10(3):1402–1411. Available from: https://ijpsr.com/bft-article/formulation-and-evaluation-of-mouth-dissolving-films-of-losartan-potassium-using-32-factorial-design/.
12) Singh S, Pawar R, Patidar S. A review on mouth dissolving film- a novel approach. *International journal of pharmaceutical sciences and medicine*. 2024;9(2):36–51. Available from: https://ijpsm.com/Publish/Feb2024/V9I206.pdf.
13) Kshirsagar T, Jaiswal N, Chavan G, Zambre K, Ramkrushna S, Dinesh D. Formulation and evaluation of fast dissolving oral film. *World journal of pharmaceutical research*. 2021;10(9):503–561. Available from: https://wjpr.s3.ap-south-1.amazonaws.com/article_issue/d9d130d83c4de059e408e281d43364d5.pdf.
14) Bhowmik S, Alam M, Pathan M. Preparation and evaluation of palonosetron hydrochloride oral thin film. *Bangladesh Pharmaceutical Journal*. 2019;22(2):228–234. Available from: https://www.mendeley.com/catalogue/53c8fc7b-a0d6-3d5e-86b4-9e94187b3b76/.
15) Ozakar RS, Ozakar E. Current overview of oral thin films. *Turkish journal of pharmaceutical sciences*. 2021;18(1):111–121. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7957312/#:~:text=In%20general%2C%20OTFs%20are%20characterized,flexible%20in%20their%20natural%20structure.
16) Singh S, Dixit S, Verma A, Faizan M, Jaiswal N. Fast dissolving oral films: A review. *International journal of medical, pharmacy and drug research*. 2024;8(2):69–77. Available from: https://www.academia.edu/121269083/Fast_Dissolving_Oral_Films_A_Review.
17) Zayed GM, Rasoul SAE, Ibrahim MA, Saddik MS, Alshora DH. In-vitro and in-vivo characterization of domperidone-loaded fast dissolving buccal films. *Saudi Pharmaceutical Journal*. 2020;28(3):266–273. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7078569/.

18) Mohamed MS, Abdelhafez WA, Zayed G, Samy AM. In vitro and in vivo characterization of fast dissolving tablets containing gliquidone pluronic solid dispersion. *Drug development and industrial pharmacy*. 2019;45(12):1973–1981. Available from: https://doi.org/10.1080/03639045.2019.1689993.
19) Habib BA, El-Samiae ASA, El-Houssieny BM, Tag R. Formulation, characterization, optimization and in-vivo performance of febuxostat self nano emulsifying system loaded sublingual films. *Drug delivery*. 2021;28:1321–1333. Available from: https://doi.org/10.1080/10717544.2021.1927247.
20) Mohan A, Sangeetha G. In vitro-in vivo evaluation of fast-dissolving tablets containing solid dispersion of oxcarbazepine. *International journal of pharmacy and pharmaceutical sciences*. 2016;8(8):124–131. Available from: https://journals.innovareacademics.in/index.php/ijpps/article/view/11874.